2023

IWGDF Guidelines on the prevention and management of diabetes-related foot disease

Practical Guidelines | 7 Guidelines | Development and methodology

IWGDF Guidelines

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Practical guidelines on the prevention and management of diabetes-related foot disease

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

Diabetes-related foot disease results in a major global burden for patients and the healthcare system. The International Working Group on the Diabetic Foot (IWGDF) has been producing evidence-based guidelines on the prevention and management of diabetes-related foot disease since 1999. In 2023, all IWGDF Guidelines have been updated, based on systematic reviews of the literature and formulation of recommendations by multidisciplinary experts from all over the world. In addition, a new guideline on acute Charcot neuro-osteoarthropathy was created.

In this document, the IWGDF Practical Guidelines, we describe the basic principles of prevention, classification and management of diabetes-related foot disease, based on the seven IWGDF Guidelines. We also describe the organizational levels to successfully prevent and treat diabetes-related foot disease according to these principles and provide addenda to assist with foot screening. The information in these practical guidelines is aimed at the global community of healthcare professionals who are involved in the care of persons with diabetes.

Many studies around the world support our belief that implementing these prevention and management principles is associated with a decrease in the frequency of diabetes-related lower-extremity amputations. The burden of foot disease and amputations is increasing at a rapid rate, and comparatively more so in middle to lower income countries. These guidelines also assist in defining standards of prevention and care in the these countries.

In conclusion, we hope that these updated practical guidelines continue to serve as a reference document to aid healthcare providers in reducing the global burden of diabetes-related foot disease.

1. INTRODUCTION

In these practical guidelines of the International Working Group on the Diabetic Foot (IWGDF) we describe the basic principles of prevention and management of diabetes-related foot disease. This document is a summary of the following evidence-based IWGDF Guidelines (2023 update):

- Prevention of foot ulcers in persons with diabetes (1)
- Classification of diabetes-related foot ulcers (2)
- Diagnosis and treatment of foot infection in persons with diabetes (3)
- Diagnosis and management of peripheral artery disease in persons with a foot ulcer and diabetes (4)
- Offloading foot ulcers in persons with diabetes (5)
- Interventions to enhance healing of foot ulcers in persons with diabetes (6)
- Acute Charcot neuro-osteoarthropathy (7)

The authors, as members of the editorial board of the IWGDF, have summarized the information from these seven guidelines, and also provide additional advice based on expert opinion in selected areas for which the guidelines were not able to provide evidence-based recommendations. These practical guidelines should be considered a shortened and simplified document to be used as a basic summary of the key management principles of prevention and treatment of diabetes-related foot disease. We refer the reader for details and background to the different guidelines (1-7) and their underlying systematic reviews (8-18). Should this summary text appear to differ from the information of any of these guidelines, we suggest the reader defers to that specific guideline. The seven evidence-based guidelines were developed following the GRADE methodology as described in a separate document (19). For readability, we did not include the strength of recommendations according to GRADE (i.e. strong or conditional) nor their detailed considerations in these practical guidelines. Because terminology in this multidisciplinary area can sometimes be unclear, we also refer the reader to our separate IWGDF Definitions and Criteria document (20).

Compared to the previous version of these practical guidelines (the 2019 update: (21)), the following is new in this 2023 update: several new recommendations in various sections based on the updated guidelines, re-ordering of the ulcer treatment principles, based on the order for clinical decision-making, and a summary of the IWGDF guidelines on the diagnosis and management of acute Charcot's neuro-osteoarthropathy. We now also included an appendix on measurement of ankle and toe blood pressures. This 2023 update supersedes any previous version of these practical guidelines.

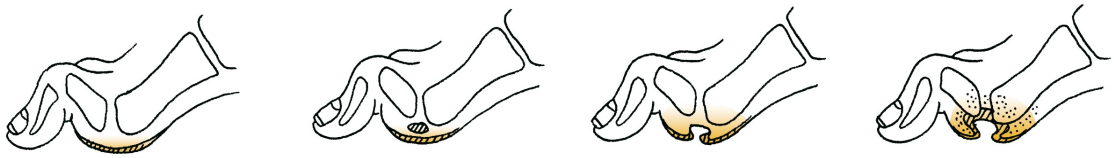
The information in these practical guidelines is aimed at the global community of healthcare professionals involved in the care of persons with diabetes and diabetes-related foot disease. The principles outlined may have to be adapted or modified based on local circumstances, taking into account regional differences in the socio-economic situation, accessibility to and sophistication of healthcare resources, and various cultural factors.

2. DIABETES-RELATED FOOT DISEASE AND ITS PATHOPHYSIOLOGY

Diabetes-related foot disease includes one or more of the following in the foot of a person with current or previously diagnosed diabetes mellitus: peripheral neuropathy, peripheral artery disease, infection, ulcer(s), neuro-osteoarthropathy, gangrene, or amputation. Foot ulceration is among the most serious complications of diabetes and is a source of reduced quality of life as well as financial costs for the person involved. Moreover, it places a considerable burden on the person's family, healthcare professionals and facilities, and society in general.

Although both the prevalence and spectrum of diabetes-related foot ulceration vary in different regions of the world, the pathways to ulceration are similar in most persons. These ulcers usually develop in a person with diabetes simultaneously having one or more risk factors, such as diabetes-related peripheral neuropathy and/or peripheral artery disease (PAD), in combination with a precipitating event. The neuropathy leads to an insensitive and sometimes deformed foot. Loss of protective sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot. This produces high mechanical stress in some areas, the response to which is usually thickened skin (callus). The callus then leads to a further increase in the loading of the foot, often with subcutaneous haemorrhage and eventually skin ulceration (see Figure 1). In addition, in people with neuropathy, minor trauma (e.g., from ill-fitting shoes, or an acute mechanical or thermal injury) can precipitate ulceration of the foot. Whatever the primary cause of ulceration, continued walking on the insensitive foot impairs healing of the ulcer.

Figure 1: Mechanism of ulcer developing from repetitive or excessive mechanical stress



The vast majority of persons with a diabetes-related foot ulcer will have neuropathy. PAD, generally caused by atherosclerosis, is present in up to 50% of these patients and is an important risk factor for impaired wound healing, gangrene and lower-extremity amputation. A small percentage of foot ulcers in patients with severe PAD are purely ischaemic; these are usually painful and may follow minor trauma. The majority of foot ulcers, however, are either purely neuropathic or neuro-ischaemic, i.e., the combination of neuropathy and ischaemia. In people with diabetes with neuro-ischaemic ulcers, symptoms may be absent because of the neuropathy, despite severe pedal ischaemia. Although diabetes-related microangiopathy can be observed in the foot, it does not appear to be the primary cause of either ulcers or of poor wound healing.

To reduce the burden of diabetes-related foot disease, strategies are required that include elements of prevention, patient and staff education, standardised assessment and classification, multi-disciplinary treatment, and close monitoring. The core of these strategies is described in the following sections of these practical guidelines.

3. FOOT ULCER PREVENTION

If a person with diabetes without a foot ulcer presents at your clinic, there are five key elements that underpin efforts to prevent foot ulcers, as described in the IWGDF Prevention Guideline (1):

1. Identify the person with an at-risk foot
2. Regularly inspect and examine the feet of a person at-risk for foot ulceration
3. Provide structured education for patients, their family and healthcare professionals
4. Encourage routine wearing of appropriate footwear
5. Treat risk factors for ulceration

3.1 IDENTIFYING THE PERSON WITH AN AT-RISK FOOT

Screen a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms of loss of protective sensation and PAD, to identify if they have become at-risk for foot ulceration. The absence of symptoms in a person with diabetes does not exclude foot disease; they may have asymptomatic neuropathy, PAD, pre-ulcerative signs, or even an ulcer. Yearly foot screening includes assessing or examining the following:

- Foot ulcer: assess if the foot is ulcer-free
- Loss of protective sensation (LOPS): assess with one of the following techniques (see Appendix 1 for details):
  - Pressure perception: Semmes-Weinstein 10 gram monofilament
  - Vibration perception: 128 Hz tuning fork
  - When monofilament or tuning fork are not available test tactile sensation: lightly touch the tips of the toes of the patient with the tip of your index finger for 1–2 seconds
- Vascular status: history of intermittent claudication, palpation of pedal pulses

If a person has LOPS or PAD, they are at-risk of ulceration (Table 1), and further examination is required. LOPS is usually caused by diabetes-related polyneuropathy. If diagnosed for the first time, it is usually necessary to elicit further history and conduct further examinations into its causes and consequences; however, these aspects are outside the scope of this guideline.

Prior to any surgical procedure on the foot in a person with diabetes, the presence of LOPS and PAD status should be established in order to assess the suitability for and risks of the procedure.

3.2 REGULARLY INSPECTING AND EXAMINING THE PERSON WITH AN AT-RISK FOOT (IWGDF RISK 1 OR HIGHER)

If the yearly foot screening identifies a person as "at-risk", perform a more comprehensive examination. This includes the following assessments or examinations in order to assess risk in more detail and to inform further management:

- Detailed history: determine foot ulcer and lower-extremity amputation history, diagnosis of end-stage renal disease, previous foot education, social isolation, poor access to healthcare and financial constraints, foot pain (with walking or at rest) or numbness, and mobility;
- Vascular status: in case of absent foot pulses or other signs of PAD, consider performing pedal Doppler waveforms in combination with measurement of the ankle pressure & ankle-brachial index and toe pressure & toe-brachial index (see Appendix 2);
- Skin: assess skin colour, temperature, presence of callus or oedema, fungal infection, pre-ulcerative signs such as haemorrhage or fissures;
- Bone/joint: check for deformities (e.g., claw or hammer toes), abnormally large bony prominences, or limited joint mobility. Examine the feet with the patient both lying down and standing up;
- Cognitive disorders
- Footwear: ill-fitting, inadequate, or lack of footwear;
- Poor foot self-care, e.g. improperly cut toenails, unwashed feet ;
- Physical limitations that may hinder foot self-care (e.g. visual acuity, obesity);
- Foot care knowledge.

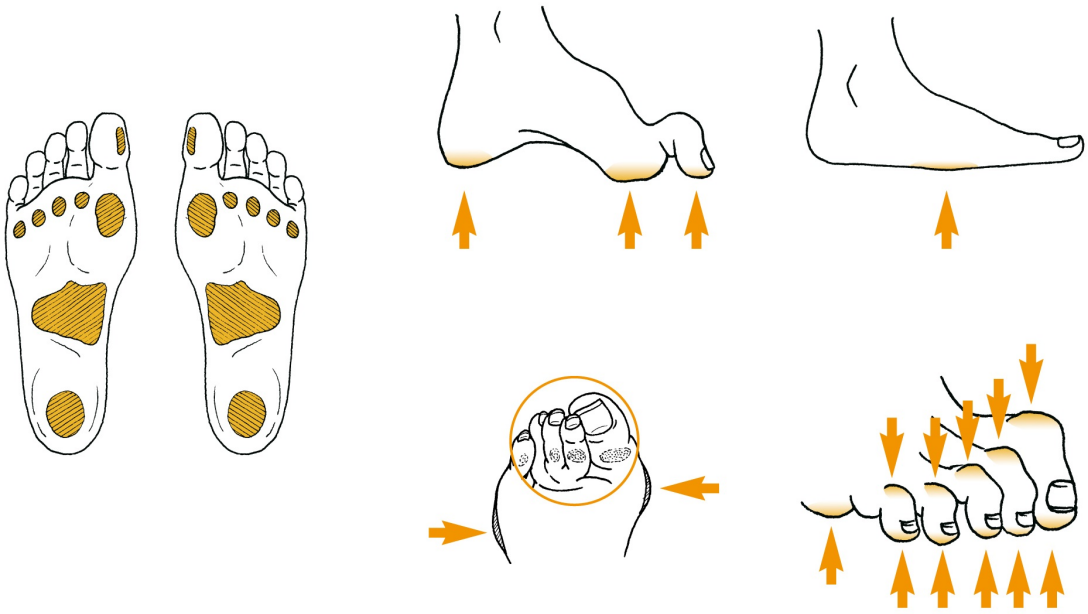
Following examination of the foot, stratify each patient using the IWGDF risk stratification category system shown in Table 1 to guide subsequent preventative screening frequencies and management. Areas of the foot most at-risk are shown in Figure 2. A person with a healed foot ulcer has the highest risk of ulceration and the foot should be considered in remission. This requires lifelong ulcer prevention strategies with an appropriately trained team of healthcare professionals that addresses all ulcer prevention cornerstones as part of integrated care. Any foot ulcer identified during screening should be treated according to the principles outlined in section 4.

Table 1: The IWGDF 2023 Risk Stratification System and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Frequency*
0	Very low	No LOPS and no signs of PAD	Once a year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity or PAD + foot deformity	Once every 3-6 months
3	High	LOPS or PAD, and one or more of the following: - history of a foot ulcer - a lower-extremity amputation (minor or major) - end-stage renal disease	Once every 1-3 months

Note: LOPS = Loss of Protective Sensation; PAD = Peripheral Artery Disease; * Screening frequency is based on expert opinion, since there is no published evidence to support these intervals

Figure 2: Areas of the foot at highest risk for ulceration



3.3 PROVIDING STRUCTURED EDUCATION FOR PATIENTS, THEIR FAMILY AND HEALTHCARE PROFESSIONALS ABOUT FOOT CARE AND SUPPORT TO PERFORM FOOT SELF-CARE

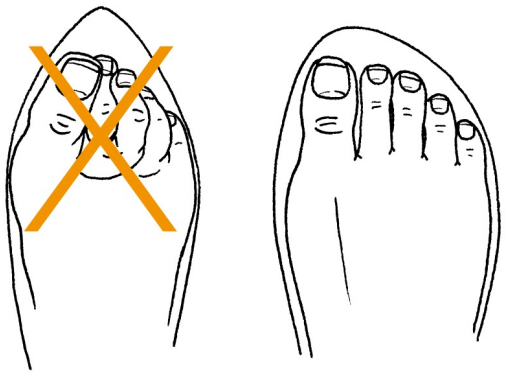
Education, presented in a structured, organized and repeated manner, is widely considered to play an important role in the prevention of diabetes-related foot ulcers. The aim is to improve a person's foot self-care knowledge and self-protective behaviour, and to enhance their motivation and skills to facilitate adherence to this behaviour. In particular those persons stratified as IWGDF risk 1 or higher, should be encouraged to wash and examine their feet daily and to learn how to recognize (pre-) ulcerative lesions. In case of such lesions, they should rapidly contact an appropriately trained health professional for further advice. They should be encouraged to use emollients to moisturize dry skin and to always walk with socks and shoes, whether indoors or outdoors. Specific emphasis should be placed on educating that only wearing socks indoors will not protect the feet, as both socks and shoes are needed. The educator should demonstrate specific skills to the person, such as how to cut toenails appropriately (straight across). A member of the healthcare team should provide structured education (see examples of instructions in Appendix 3) individually or in small groups of people, in multiple sessions, with periodical reinforcement, and preferably using a mixture of methods. This education should be culturally appropriate, account for gender differences, and align with a person's health literacy and personal circumstances. It is essential to assess whether the person with diabetes (and, optimally, any close family member or carer) has understood the messages, is motivated to act and adhere to the advice, and has sufficient self-care skills. Furthermore, healthcare professionals providing these instructions should receive periodic education to improve their own skills in the care of people at risk for foot ulceration.

3.4 ENCOURAGE ROUTINE WEARING OF APPROPRIATE FOOTWEAR

In persons with diabetes and IWGDF risk category 1 or higher, wearing inappropriate footwear or walking barefoot are major causes of foot trauma leading to foot ulceration. Persons with LOPS must have (and may need financial assistance to acquire) appropriate footwear, and should be encouraged to wear this at all times, both indoors and outdoors. All footwear should be adapted to conform to any alteration in foot structure or foot biomechanics affecting the person's foot.

For footwear to be considered appropriate, the inside length of the shoe should be 1-2 cm longer than the foot and should not be either too tight or too loose (see Figure 3). The internal width should equal the width of the foot at the metatarsal phalangeal joints (or the widest part of the foot), and the height should allow enough room for all the toes. Evaluate the fit with the patient in the standing position, preferably later in the day (when they may have foot swelling). If there is no off-the-shelf footwear that can accommodate the foot (e.g., if the fit is poor due to foot deformity) or if there are signs of abnormal loading of the foot (e.g., hyperaemia, callus, (previous) ulceration), prescribe therapeutic footwear, possibly including extra-depth shoes, custom-made footwear and custom-made insoles. This may also include the prescription and fabrication of (toe) orthoses.

Figure 3: Footwear should be sufficiently wide to accommodate the foot without excessive pressure on the skin



For people who have healed from a plantar foot ulcer, ensure that the therapeutic footwear has a demonstrated plantar pressure relieving effect during walking. When possible, demonstrate this plantar pressure relieving effect with appropriate equipment, as described in the prevention guidelines (1). Instruct the person to never again wear the same shoe that has caused an ulcer. Take protective measures to prevent heel ulceration in (temporarily) bedridden patients (either at home or admitted to an institution).

3.5 TREATING RISK FACTORS FOR ULCERATION AND PRE-ULCERATIVE SIGNS IN PERSONS WITH IWGDF RISK 1-3

Provide appropriate treatment of excess callus on the foot, for ingrown toe nails, and for fungal infections on the foot. Treat any (modifiable) pre-ulcerative sign on the foot including protecting blisters, or draining them if necessary. Consider coaching a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation and help prevent a foot ulcer. In case of an elevated temperature, ambulatory activity should be reduced and a member of the foot care team consulted. When excess callus or a pre-ulcerative lesion is present on the apex or distal part of a non-rigid hammertoe, consider digital flexor tendon tenotomy or consider prescribing orthotic interventions, such as toe silicone or (semi)rigid orthotic devices.

The risk for foot ulceration is not a barrier to participating in a physical training program as long as appropriate footwear is worn, with a gradual increase in activity to an additional 1000 steps/day. In addition, a foot-ankle exercise program may be considered.

4. ASSESSMENT AND TREATMENT OF FOOT ULCERS

If a person with diabetes presents with a foot ulcer, the ulcer should be assessed and treated immediately, with a consistent strategy and standardized protocol for assessment and treatment.

4.1 ASSESSMENT

4.1.1 Classification of the foot ulcer

As the first step, the foot ulcer should be classified following the assessment of the six items of the SINBAD system (2). These items serve as a basic guide for further treatment, and facilitate communication about the characteristics of an ulcer between health professionals. These six items of this acronym are:

- *"Site":* Describe where the ulcer is located on the foot. This includes description of forefoot, midfoot or hindfoot, but it is also suggested to differentiate between plantar, interdigital, medial, lateral or dorsal.
- *"Ischemia":* Assess if pedal blood flow is intact (at least one palpable pulse), or if there is clinical evidence of reduced blood flow. Further, examine the arterial pedal wave forms (with a Doppler instrument), measure the ankle and toe pressures, and calculate the ankle-brachial index (ABI) and toe-brachial index (TBI), as described in Appendix 2. PAD is less likely in the presence of triphasic or biphasic pedal Doppler waveforms, an ABI 0.9-1.3, and a TBI ≥0.70. In selected cases, transcutaneous pressure of oxygen ($TcpO_2$) can be useful. The level of perfusion deficit can help estimate the likelihood of healing and amputation (see below), but better risk estimation is obtained when wound depth and foot infection severity are also taken into account, as in the WIfI scoring system.
- *"Neuropathy":* Assess if protective sensation is intact or lost (see Appendix 1).
- *"Bacterial infection":* Assess if clinical infection is present. Diagnose infection by the presence of at least two clinical signs or symptoms of inflammation (redness, warmth, induration, pain/tenderness) or purulent secretions. Unfortunately, these signs may be blunted by neuropathy or ischaemia, and systemic findings (e.g., pain, fever, leucocytosis) are often absent in mild and moderate infections. Infections should be classified using the IWGDF/IDSA grading as mild (superficial ulcer with minimal cellulitis), moderate (ulcer deeper than skin or more extensive cellulitis, with or without abcess) or severe (accompanied by systemic signs of sepsis), with or without osteomyelitis.

  If not properly treated, infection can rapidly spread to underlying tissues and foot compartments, in particular in the presence of PAD. Therefore, explore the depth of the ulcer (see below). An abcess is more likely in case of fever, high CRP or ESR levels, but normal findings do not exclude a foot abcess; when in doubt, perform MRI. Determine if it is possible to visualise or touch bone with a sterile metal probe (probe-to-bone test). Obtain plain radiographs in persons with ulcers deeper than skin, tissue gas or foreign body. Osteomyelitis is likely in case of a positive probe-to-bone test in combination with abnormalities on plain X-ray; high levels of ESR, CRP, or procalcitonin further support this diagnosis. When in doubt perform an MRI or when this is not possible, consider other techniques (e.g., radionuclide or PET scans).

For clinically infected wounds obtain a tissue specimen for culture (and Gram-stained smear, if available) by curettage or biopsy, avoid using a swab; consider bone biopsy in case of osteomyelitis. The causative pathogens (and their antibiotic susceptibilities) vary by geographic, demographic and clinical situations, but Staphylococcus aureus (alone, or with other organisms) is the predominant pathogen in most cases of superficial infections. Chronic and more severe infections are often polymicrobial, with aerobic gram-negative rods especially in warmer climates and obligate anaerobes accompanying the gram-positive cocci.

- *"Area":* Measure ulcer area and express in cm^2.
- *"Depth":* Assess ulcer depth and classify as: confined to skin and subcutaneous tissue; reaching muscle or tendon; or reaching bone. Determining depth can be difficult, especially in the presence of overlying callus or necrotic tissue. To aid assessment, debride any neuropathic or neuro-ischemic ulcer that is surrounded by callus or contains necrotic soft tissue at initial presentation, or as soon as possible. Do not, however, debride a non-infected ulcer that has signs of severe ischaemia. Neuropathic ulcers can usually be debrided without the need for local anaesthesia.

Classification and Type
By following this standardised assessment, the ulcer can be classified according to the SINBAD system (2). The SINBAD system is simple and quick to use and contains the necessary information to allow for triage by a specialist team. In addition, infection severity should be classified according to the IWGDF/IDSA system and ischaemia as part of the WIfI system (2). It is important to describe the individual variables of each of these systems (2). In addition, the ulcer type can be described as neuropathic (LOPS, but no PAD), neuro-ischaemic (LOPS and PAD), or ischaemic (PAD, but no LOPS).

4.1.2 Determining the cause of the ulcer

Always try to determine the precipitating event that led to ulceration, this information is relevant both for treatment plans and for prevention of recurrence. Look for abnormal walking patterns, deformities, bony prominences and other foot abnormaities (supine and standing) that could have contributed to ulceration. Wearing ill-fitting shoes and walking barefoot are practices that frequently lead to foot ulceration, even in patients with exclusively ischaemic ulcers. Therefore, meticulously examine shoes and footwear behaviour in every patient with a foot ulcer as part of cause determination.

4.1.3 Assessment of person-related factors

Apart from a systematic evaluation of the ulcer, the foot and the leg, also consider person-related factors that can affect ulcer healing and affect treatment. These factors include kidney function/end-stage renal disease, oedema, malnutrition, poor metabolic control, depression or other psycho-social problems, and frailty.

4.2 TREATMENT OF A FOOT ULCER

Foot ulcers will heal in the majority of patients if the clinician bases treatment on the principles outlined below. When treating a person with a foot ulcer, always involve the person and their carer(s), by providing information on the treatments provided, and supporting the person to perform appropriate foot ulcer self-care and how to recognize and report signs and symptoms of new or worsening infection (e.g., onset of fever, changes in local wound conditions, worsening hyperglycaemia). This information should also involve how to prevent foot ulcers on unaffected parts of the foot or the contralateral foot (see section 3).

4.2.1 Treatment of foot infection

Infection of the foot in a person with diabetes presents an immediate threat to the affected foot and limb. If infection is diagnosed during initial assessment (see 4.1), prompt treatment is required. Depending on a person's social situation, local resources and infrastructure, hospitalization may be necessary. This hospitalization may also involve amputation of a part of the foot or lower-extremity. Based on the IWGDF/IDSA infection guidelines (3), the following recommendations for treatment are made:

In a person with deep or extensive (potentially limb-threatening) infection (moderate or severe infection):

- Urgently evaluate for need for immediate surgical intervention to remove necrotic tissue, including infected bone, release compartment pressure and drain abscesses;
- Assess for PAD; if present consider urgent treatment, including revascularisation once infection is under control;
- Initiate empiric, parenteral, broad-spectrum antibiotic therapy, aimed at common gram-positive and gram-negative bacteria, including obligate anaerobes;
- Adjust (constrain and target, if possible) the antibiotic regimen based on both the clinical response to empirical therapy and culture and sensitivity results;
- For soft-tissue infections antibiotic treatment during 1 to 2 weeks will frequently suffice, a longer duration may be required in case of a slowly resolving infection or severe PAD; and
- Consider conservative treatment for osteomyelitis with antibiotics when there is no need for incision and drainage to control infection.

In a person with a superficial ulcer with limited soft tissue (mild) infection:

- Cleanse, debride all necrotic tissue and surrounding callus; and
- Start empiric oral antibiotic therapy targeted at Staphylococcus aureus and β-haemolytic streptococci (unless there are reasons to consider other, or additional, likely pathogens).

4.2.2 Restoration of tissue perfusion

Ischemia in the lower-extremity affects healing potential of a foot ulcer. If ischaemia has been found during assessment (see 4.1), its treatment should always be considered. Based on the intersocietal IWGDF/ESVS/SVS guidelines (4), the following recommendations for treatment are made:

- In a person with either an ankle pressure <50mm Hg or an ABI <0.4 consider urgent vascular imaging, always with detailed visualization of below-the knee and pedal arteries, and revascularisation. Also consider urgent assessment for revascularisation if the toe pressure is <30mmHg or TcpO2 is <25 mmHg. However, clinicians might also consider revascularisation at higher pressure levels in patients with extensive tissue loss or infection, i.e. with higher WIfI scores.
- When an ulcer fails to show signs of healing within 4-6 weeks, despite optimal management, consider angiography and revascularisation, irrespective of the results of the vascular diagnostic tests described above.
- If contemplating a major (i.e., above the ankle) amputation, first consider the option of revascularization.
- The aim of revascularisation is to restore in-line flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound. But, avoid revascularisation in patients in whom the risk-benefit ratio for the probability of success is unfavourable.
- Select a revascularisation technique based on both individual factors (such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities) and local operator expertise.
- After a revascularisation procedure, its effectiveness should be evaluated with an objective measurement of perfusion.
- Pharmacological treatments to improve perfusion have not been proven to be beneficial.
- Emphasise efforts to reduce the very high cardiovascular risk associated with PAD in the individual with diabetes (cessation of smoking, control of hypertension and dyslipidaemia, use of anti-platelet drugs, SGLT2-inhibitor or GLP1-agonist).

4.2.3A Pressure offloading and ulcer protection

Offloading is a cornerstone in treatment of foot ulcers that are caused by increased mechanical stress. Based on the IWGDF Offloading guidelines (5), the following recommendations for treatment can be made:

- The preferred offloading treatment for a neuropathic plantar ulcer is a non-removable knee-high offloading device, i.e, either a total contact cast (TCC) or removable walker rendered (by the provider fitting it) irremovable.
- When a non-removable knee-high offloading device is contraindicated or not tolerated by the patient, consider using a removable knee-high or ankle-high offloading device. Always provide informationon the benefits of adherence to wearing the removable device.

- If other forms of biomechanical relief are not available, consider using felted foam, but only in combination with appropriate footwear.
- If the ulcer is on digits 2-5 secondary to a flexible toe deformity, perform a digital flexor tenotomy if not contra-indicated (e.g. severe ischamia, infection).
- When infection or ischaemia are present, offloading is still important, but be more cautious, as discussed in the IWGDF Offloading guidelines (5).
- For non-plantar ulcers, use a removable offloading device, footwear modifications, toe spacers, orthoses, or digital flexor tenotomy, depending on the type and location of the foot ulcer.
- If the ulcer fails to heal with non-surgical offloading treatment, for a metatarsal head ulcer consider Achilles tendon lengthening, metatarsal head resection, or metatarsal osteotomy, and for a hallux ulcer, a joint arthroplasty, all in combination with an offloading device.

4.2.3B Local ulcer care

Local ulcer care is important to create an environment that increases the likelihood of ulcer healing. However, even optimum local wound care cannot compensate for inadequately treated infection or ischaemia, or continuing trauma to the wound bed, as described in the sections above. Based on the IWGDF Wound Healing Guidelines (6), the following recommendations for local ulcer care can be made:

- Regular inspection of the ulcer by a trained health care provider is essential, its frequency depends on the severity of the ulcer and underlying pathology, the presence of infection, the amount of exudation and wound treatment provided.
- Debride the ulcer and remove surrounding callus (preferably with sharp surgical instruments), and repeat as needed.
- Select dressings to control excess exudation and maintain a moist environment.
- Wash but do not soak the feet, as this may induce skin maceration.
- Consider negative pressure wound therapy to help heal post-operative wounds.

Consider any of the following adjunctive treatments in non-infected ulcers that fail to heal after 4-6 weeks despite optimal clinical care and where resources exist to support these interventions:

- A sucrose octasulfate impregnated dressing in neuro-ischemic ulcers (without severe ischaemia).
- A multi-layered patch of autologous leucocytes, platelets and fibrin in ulcers with or without moderate ischaemia.
- Placental membrane allografts in ulcers with or without moderate ischaemia.
- Topical oxygen therapy.
- Systemic hyperbaric oxygen therapy as an adjunctive treatment in ischaemic ulcers.

The following treatments are not well-supported for routine ulcer management:

- Biologically active products (collagen, growth factors, bio- engineered tissue) in neuropathic ulcers;
- Topical antiseptics and antimicrobial dressings or applications.

4.2.4 Person-centred care

In addition to the aforementioned recommendations, the person-related factors as assessed in section 4.1.3 should also be treated where possible. This includes:

- Optimise glycaemic control, if necessary, with insulin.
- Treat oedema or malnutrition, if present.
- Treat cardiovascular risk factors.
- Treat depression or other psycho-social difficulties.

5. ACTIVE CHARCOT NEURO-OSTEOARTHROPATHY (CNO)

In any person with diabetes mellitus and with a red, hot, swollen foot, the diagnosis of active CNO should be considered. As described in our Charcot guidelines, CNO is a sterile inflammatory process in persons with neuropathy that results in injury to bones, joints and soft tissues (7). If not treated adequately, it can result in progressive fracturing and dislocations resulting in a deformed foot. The diagnosis is based on the aforementioned clinical findings of inflammation after exclusion of other causes and abnormalities on imaging. If these abnormalities are not seen on plain X-ray, an MRI should be performed; if an MRI is not possible, perform a CT-scan and/or a radionucleotide scan. When such advanced imaging is not possible the person should be treated as having a probable active CNO.

In order to promote remission of the disease and to prevent (progressive) deformity, the affected extremity should be offloaded and immobilized. The first choice is a non-removable knee-high total contact cast, the second choice a knee-high walker rendered non-removable. A removable knee-high device worn at all times is a third choice, but probably less effective. Below-the-ankle offloading devices are not recommended. Assistive devices (e.g. crutches) can help to reduce weight-bearing on the affected limb. Treatment should start once the diagnosis is considered and continue until clinical remission with consolidation of fractures is achieved. As long as there are clinical signs of inflammation the offloading should be continued. This can take many months. Such long-term treatment is associated with the risk of complications (e.g. ulceration) and adverse effects (e.g. muscle atrophy or excessive loading of the contra-lateral limb), and treated persons must be followed closely. Currently there is no medical therapy that can shorten the duration of disease or prevent deformities, such interventions are therefore not recommended. Vitamin D and calcium should be supplemented according to local guidelines for persons with an elevated risk of inadequate vitamin D levels.

Measuring skin temperature with infrared thermometry in both feet according to a standardised protocol is an easy and objective technique to monitor disease activity. In unilateral disease the left-right temperature difference can be calculated at each visit. Unfortunately, there is currently no absolute cut-off value to define remission of CNO. Therefore, temperature, oedema, and imaging should all be considered when concluding that active CNO is in remission. The knee-high cast can be stopped when there are no clinical signs of inflammation with radiographic consolidation of fractures (if present) on plain X-ray. The person should have custom made footwear and/or orthoses that best accommodate and support the shape of the foot and ankle to help prevent re-activation of the CNO, and to help optimize plantar pressure distribution. When deformity and/or joint instability is present, below-the-knee customized devices should be considered for additional protection. After remission is achieved, ambulation and loading of the foot should be gradually increased because of the risk of reactivation. If signs of recurrence do arise, a member of the team should be contacted promptly.

6. ORGANIZATION OF CARE FOR DIABETES-RELATED FOOT DISEASE

Successful efforts to prevent and treat diabetes-related foot disease depend upon a well-organised team, that uses a holistic approach in which a foot ulcer is seen as a sign of multi-organ disease, and that integrates the various disciplines involved. Effective organisation requires systems and guidelines for all aspects of standard care as outlined in these practical guidelines. Local variations in resources and staffing often dictate how to provide care, but ideally organized diabetes-related foot care should provide the following:

- Education for persons with diabetes and their carers, for healthcare staff in hospitals and for primary healthcare professionals;
- Systems to detect all people who are at risk, including annual foot examination of all persons with diabetes;
- Access to measures for reducing risk of foot ulceration, such as podiatric care and provision of appropriate footwear and insoles;
- Ready access to prompt and effective treatment of any foot ulcer or infection;
- Rapid access to, or expertise in, endovascular and surgical bypass revascularisation procedures;
- Access to modalities to off-load the ulcer as described in this guideline;
- Access to wound care that includes, as a minimum, regular inspection, debridement, non-adherent dressings and, if indicated, dressings to control excess exudation;
- Auditing of all aspects of services to identify and address problems and ensure that local practice meets accepted standards of care;
- An overall structure designed to meet the needs of persons requiring chronic care, rather than simply responding to acute problems when they occur.

In all countries, there should optimally be at least three levels of foot-care management with interdisciplinary specialists like those listed in Table 2.

Table 2: Levels of care for diabetes-related foot disease

Level 1	General practitioner, podiatrist, and diabetes nurse
Level 2	Diabetologist, surgeon (general, orthopaedic, or foot/ podiatric), vascular specialist (endovascular and open revascularisation), infectious disease specialist or clinical microbiologist, podiatrist and diabetes nurse, in collaboration with a pedorthist, orthotist or prosthetist
Level 3	A level 2 foot centre that is specialized in care for diabetes-related foot disease, with multiple experts from several disciplines each specialised in this area working together, and that acts as a tertiary reference centre

7. CONCLUDING REMARKS

Studies around the world have shown that setting up an interdisciplinary foot care team and implementing prevention and management of diabetic foot disease according to the principles outlined in these practical guidelines, is associated with a decrease in the frequency of diabetes related lower-extremity amputations. If it is not possible to create a full team from the outset, aim to build one step-by-step, introducing the various disciplines as possible. This team must first and foremost act with mutual respect and understanding, work in both primary and secondary care settings, and have at least one member available for consultation or assessment at all times. We hope that these updated practical guidelines and the underlying seven evidence-based guidelines continue to serve as reference document to reduce the global burden of diabetes-related foot disease.

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CONFLICT OF INTEREST STATEMENTS

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All individual conflict of interest statement of authors of this guideline can be found at:
www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies

REFERENCES

(1) Bus SA, Sacco ICN, Monteiro-Soares M, Raspovic A, Paton J, Rasmussen A, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3651.

(2) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3648.

(3) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(4) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023;in press.

(5) Bus SA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3647.

(6) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3644.

(7) Wukich DK, Schaper NC, Gooday C, Bal A, Bem R, Chabra A, et al. Guidelines on the diagnosis and treatment of active charcot neuro-osteoarthropathy in persons with diabetes mellitus (IWGDF 2023). Diab Metab Res Rev. 2023;e3646.

(8) Van Netten JJ, Sacco ICN, Raspovic A, Lavery LA, Monteiro-Soares M, Paton J, et al. Clinical and biomechanical effectiveness of foot-ankle exercise programs and weight-bearing activity in people with diabetes and neuropathy: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;e3649.

(9) Van Netten JJ, Raspovic A, Lavery LA, Monteiro-Soares M, Paton J, Rasmussen A, et al. Prevention of foot ulcers people with diabetes at risk of ulceration: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;e3652.

(10) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Classification of foot ulcers in people with diabetes: a systematic review. Diab Metab Res Rev. 2023;e3645.

(11) Lazzarini PA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Effectiveness of offloading interventions for people with diabetes-related foot ulcers: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;e3650.

(12) Chuter VH, Schaper NC, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review. Diab Metab Res Rev. 2023;in press.

(13) Chuter VH, Schaper NC, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: A systematic review. Diab Metab Res Rev. 2023;in press.

(14) Chuter VH, Schaper NC, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. Effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral artery disease: A systematic review. Diab Metab Res Rev. 2023;in press.

(15) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Diagnosis of infection in the foot in diabetes: a systematic review. Diab Metab Res Rev. 2023;in press.

(16) Peters EJG, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. Diab Metab Res Rev. 2023;in press.

(17) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diab Metab Res Rev. 2023;in press.

(18) Raspovic KM, Schaper NC, Gooday C, Bal A, Bem R, Chabra A, et al. Diagnosis and Treatment of Active Charcot Neuro-osteoarthropathy in Persons with Diabetes Mellitus: A Systematic Review Diab Metab Res Rev. 2023;e3653.

(19) Bus SA, Van Netten JJ, Apelqvist J, Fitridge R, Game F, Monteiro-Soares M, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;e3656.

(20) Van Netten JJ, Bus SA, Apelqvist J, Chen P, Chuter VH, Fitridge R, et al. Definitions and criteria for diabetes-related foot disease (2023 update). Diab Metab Res Rev. 2023;e3654.

(21) Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3266.

(22) Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890-909.

(23) Tehan PE, Fox M, Mill JL. Measurement of toe systolic pressures: a technique paper. Wound Practice and Research. 2021;29(3).

(24) Kim ES, Sharma AM, Scissons R, Dawson D, Eberhardt RT, Gerhard-Herman M, et al. Interpretation of peripheral arterial and venous Doppler waveforms: A consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. Vasc Med. 2020;25(5):484-506.

APPENDIX 1

DOING A SENSORY FOOT EXAMINATION

Peripheral neuropathy can be detected using the 10g (5.07 Semmes-Weinstein) monofilament (detects loss of protective sensation) and a tuning fork (128 Hz, detects loss of vibratory sensation).

10g (5.07) Semmes-Weinstein monofilament

- First apply the monofilament on the patient's hands (or elbow or forehead) to demonstrate what the sensation feels like.
- Test three different sites on both feet, selecting from those shown in Figure 4.
- Ensure the patient cannot see whether or where the examiner applies the filament.
- Apply the monofilament perpendicular to the skin surface (Figure 5a) with sufficient force to cause the filament to bend or buckle (Figure 5b).
- The total duration of the approach -> skin contact -> and removal of the filament should be approximately 2 seconds.
- Do not apply the filament directly on an ulcer, callus, scar or necrotic tissue.
- Do not allow the filament to slide across the skin or make repetitive contact at the test site.
- Press the filament to the skin and ask the patient whether they feel the pressure applied ('yes'/'no') and next where they feel the pressure (e.g., 'ball of left foot'/'right heel).
- Repeat this application twice at the same site, but alternate this with at least one 'mock' application in which no filament is applied (a total of three questions per site).
- Protective sensation is: present at each site if the patient correctly answers on two out of three applications; absent with two out of three incorrect answers.
- Encourage the patients during testing by giving positive feedback.

Monofilaments tend to lose buckling force temporarily after being used several times on the same day, or permanently after long duration use. Depending on the type of monofilament, we suggest not using the monofilament for the next 24 hours after assessing 10-15 patients and replacing it after using it on 70-90 patients.

Figure 4: Sites that should be tested for loss of protective sensation with the 10g Semmes-Weinstein monofilament

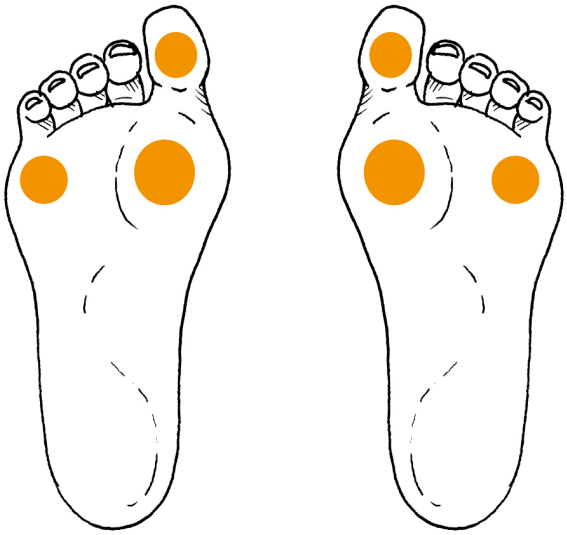
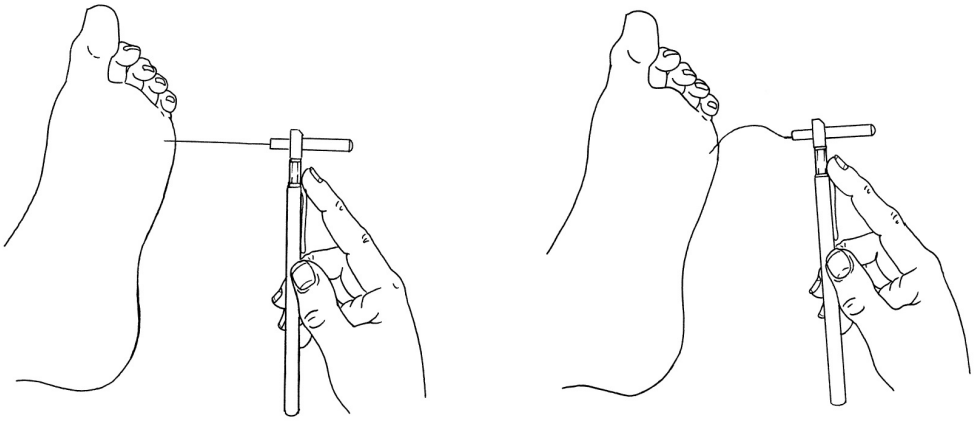


Figure 5: Proper method of using the 10g Semmes-Weinstein monofilament

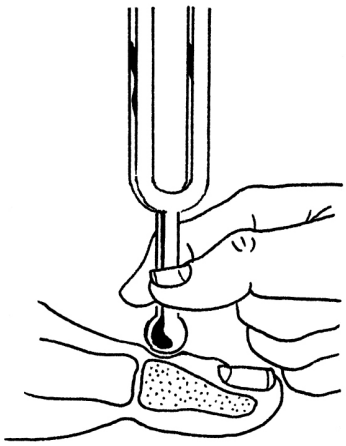


128 Hz Tuning fork

- First, apply the tuning fork on the patient's wrist (or elbow or clavicle) to demonstrate what the sensation feels like.
- Ensure the patient cannot see whether or where the examiner applies the tuning fork.

- Apply the tuning fork to a bony part on the dorsal side of the distal phalanx of the first toe (or another toe if the hallux is absent).
- Apply the tuning fork perpendicularly, with constant pressure (Figure 6).
- Repeat this application twice, but alternate this with at least one 'mock' application in which the tuning fork is not vibrating.
- The test is positive if the patient correctly answers at least two out of three applications, and negative if two out of three answers are incorrect.
- If the patient is unable to sense the vibrations on the toe, repeat the test more proximally (e.g., malleolus, tibial tuberosity).
- Encourage the patient during testing by giving positive feedback.

Figure 6: Proper method of using a 128 Hz tuning fork to check for vibratory sensation



Light touch test

This simple test (also called the Ipswich Touch test) can be used to screen for loss of protective sensation (LOPS), when the 10 gram monofilament or 128 HZ tuning fork is not available. The test has reasonable agreement with these tests to determine LOPS, but its accuracy in predicting foot ulcers has not been established.

- Explain the procedure and ensure that everything is understood
- Instruct the subject to close the eyes and to say yes when they feel the touch
- The examiner lightly sequentially touches with the tip of hers/his index finger the tips of the first, third, and fifth toes of both feet for 1–2 s
- When touching, do not push, tap, or poke
- LOPS is likely when light touch is not sensed in ≥ 2 sites

APPENDIX 2

MEASUREMENT OF ANKLE PRESSURES, ASSESSMENT DOPPLER WAVEFORMS AND CALCULATION OF THE ANKLE-BRACHIAL INDEX (ABI)

In persons with diabetes, the diagnostic accuracy of clinical examination for the presence of peripheral arterial disease (PAD) is low. Therefore, in any person with a foot ulcer, objective assessment of the perfusion in the foot is warranted with tests described below (22, 23). These test are also advised when PAD is suspected in a person without a foot ulcer.

Materials required

Hand-held 5-10 mHz Doppler device.
Transducer gel.
Sphygmomanometer.
Select blood pressure cuff of sufficient size to be placed around the upper arms and calves (approx. 40% extra to wrap around).

Measurement conditions

Quiet surroundings in room with comfortable temperature for the patient, such as 22–24 °C.
Alcohol, exercise and caffeine should be avoided for 2 hours prior to testing.
Patient in supine horizontal position, for 10 minutes prior to the measurement.
Both arms and lower legs should be bare.
No tight sleeves of shirts and trousers.
Always use the same sequence of measurements as described below.

Brachial & ankle pressures and Doppler waveforms

Brachial pressure
Place cuff around the upper arm.
Apply the gel over the area of the brachial artery (can be palpated first). Ensure that a clear audible signal is detected.
Inflate the cuff to supra-systolic values, i.e. about 30 mmHg above the pressure when the signal disappears completely.
Slowly deflate the cuff at a rate of 2–3mmHg per second until an audible signal re-appears, the cuff pressure at that moment equals the systolic pressure in the artery. Record the result.
Repeat this procedure in the other arm.

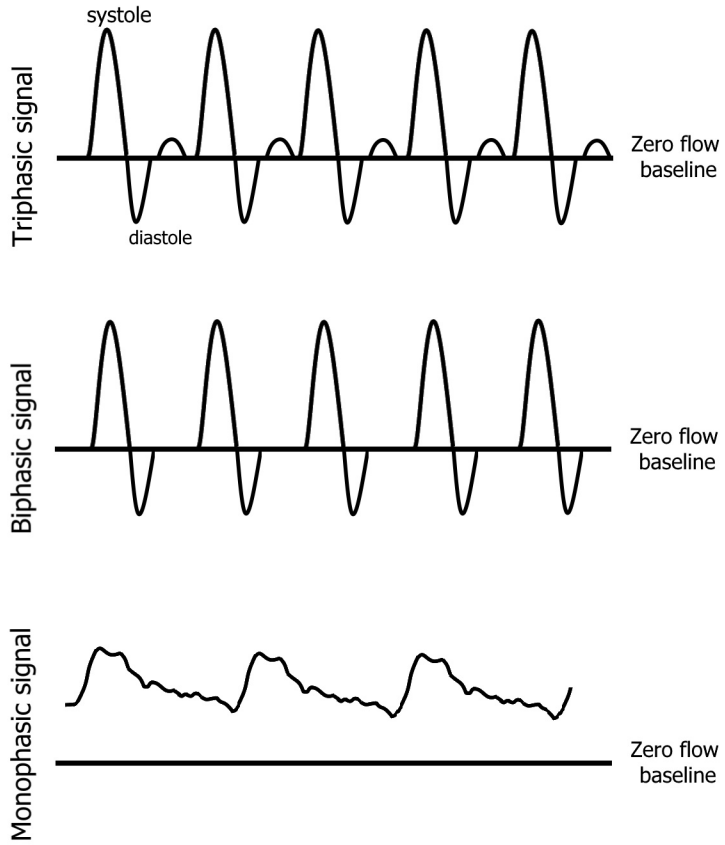
Ankle pressure and assessment of the Doppler waveform
Place the calf cuff approximately 2 cm above the malleolus, with the tubes pointing upwards
Apply the gel in the areas of the dorsalis pedis and posterior tibial arteries (see figure below)
Place the Doppler probe with an angle of 40-60° pointing upstream in the area of each artery
Slowly move the probe to select the area with the best signal.
Ideally print/ review waveform on screen of doppler machine. If the waveform is not displayed by the machine used, audibly assess the Doppler waveform and sound.
An absent signal or a monophasic signal is abnormal (see Figure 7) and is indicative of the presence of

peripheral artery disease (Figure 7).
Inflate the cuff to 30 mmHg above the pressure where the pulsatile sound is lost/the visual waveform disappears.
Slowly deflate the cuff at a rate of 2–3mmHg per second, the systolic pressure should be taken as soon an audible waveform returns or there is a small regular upstroke of a visual waveform (which occurs before the full waveform returns). Record the result.
After a minute rest, perform the measurement on the other artery of the same foot or if the signal was lost during the first measurement (do not reinflate the cuff during the procedure)
Repeat these measurements on the other leg.

Calculation of ABI in persons with diabetes

To diagnose peripheral artery disease, calculate the ankle-brachial index (ABI) for each limb by dividing the lower value of the dorsalis pedis or posterior tibial pressures of that foot by the highest of the left or right brachial pressures. This is particularly in those people with diabetes who have below knee arterial disease, which may affecti only one of the tibial arteries.
The ABI has traditionally been calculated using the higher of the dorsalis pedis or posterior tibial pressures. This gives a best-case scenario of blood flow to the foot.
An ABI above 1.3 or below 0.9 is abnormal, i.e. indicative of PAD (4, 12).

Figure 7: triphasic (A), biphasic (B) and monophasic Doppler (C) signals. Based on (24).



TOE PRESSURE AND TOE-BRACHIAL INDEX (TBI) MEASUREMENT USING PHOTOPLETHYSMOGRAPHY (PPG)

Equipment

Several different types of equipment can be used such as mercury strain gauge, laser Doppler, and continuous wave Doppler. PPG is commonly used; with an infra-red probe. Changes in opacity and blood volume are measured in the toe, resulting in a waveform. Here we describe the use of PPG.

Preparation

Sphygmomanometer.
Cuff for digital pressure measurements; cuff size approximately 1.5 times the diameter of the digit
PPG probe.
PPG unit or hand-held Doppler that can be connected to PPG probe.

Measurement conditions

As in ABI measurements, see above.

Toe-pressure measurement

Place the digital cuff at the base of the hallux and the PPG probe against distal toe pulp, sufficiently firmly to keep it in place but ensure there is no excess pressure on the digit whilst not inflated.
Where the hallux cannot be used, the second digit can be used (if a smaller cuff can be placed around the base of the toe).
Fixate the probe with tape ensuring contact of its entire flat surface against the skin (no external light should enter the underside of the probe) and preventing small movements which will disrupt the waveform.
Wait until a cyclical signal of the probe appears on the unit's screen.
Once a consistent waveform is seen, inflate the cuff to approximately 30 mmHg higher than the point at which the waveform flatlines.
Deflate the cuff slowly deflated at a rate of 2–3mmHg per second.
The cuff pressure at the first sign of reappearance of a regular upstroke is equal to the systolic pressure in the artery. Record the result.
In case of a suboptimal measurement repeat the measurement after a 3 minute waiting period.
Note: when the resting toe pressure is low (indicating reduced peripheral blood flow), the returning waveform is typically smaller and less clearly distinguishable from baseline.

Brachial artery systolic pressure

Measure the brachial artery systolic pressure in both arms as per ABI (above).

Calculation of TBI

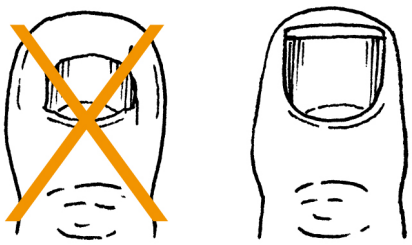
The Toe-Brachial Index is calculated for each limb by dividing the toe pressure by the highest of the left and right brachial pressures.
A TBI below 0.7 is considered to be abnormal, i.e. indicative for PAD (4, 12).

APPENDIX 3

ITEMS TO COVER WHEN PROVIDING EDUCATION FOR A PERSON AT-RISK FOR FOOT ULCERATION (IWGDF RISK 1 OR HIGHER)

- Determine if the person is able to perform a foot inspection. If not, discuss who can assist the person in this task. Persons who have substantial visual impairment or physical inability to visualise their feet cannot adequately do the inspection
- Explain the need to perform daily foot inspection of the entire surface of both feet, including areas between the toes
- Ensure the patient knows how to notify the appropriate healthcare professional if measured foot temperature is perceptibly increased, or if a blister, cut, scratch or ulcer has developed
- Review the following practices with the patient:
    - Avoid walking barefoot, in socks without footwear, or in thin-soled slippers, whether at home or outside
    - Do not wear shoes that are too tight, have rough edges or uneven seams
    - Visually inspect and manually feel inside all shoes before you put them on
    - Wear socks/stocking without seams (or with the seams inside out); do not wear tight or knee-high socks (compressive stocking should only be prescribed in collaboration with the foot care team), and change socks daily
    - Wash feet daily (with water temperature always below 37°C), and dry them carefully, especially between the toes
    - Do not use any kind of heater or a hot-water bottle to warm feet
    - Do not use chemical agents or plasters to remove corns and calluses; see the appropriate healthcare professional for these problems
    - Use emollients to lubricate dry skin, but not between the toes
    - Cut toenails straight across (see Figure 8)
    - Have your feet examined regularly by a healthcare professional

Figure 8: The proper way to cut toe nails



Guidelines on the prevention of foot ulcers in persons with diabetes

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

This is the 2023 International Working Group on the Diabetic Foot (IWGDF) guideline on the prevention of foot ulcers in persons with diabetes, which updates the 2019 guideline. This guideline is targeted at clinicians and other healthcare professionals.

We followed the GRADE methodology to devise clinical questions and critically important outcomes in the PICO format, to conduct a systematic review of the medical-scientific literature including, where appropriate, meta-analyses, and to write recommendations and their rationale. The recommendations are based on the quality of evidence found in the systematic review, expert opinion where (sufficient) evidence was not available, and a weighing of the desirable and undesirable effects of an intervention, as well as patient preferences, costs, equity, feasibility and applicability.

We recommend screening a person with diabetes at very low risk for foot ulceration annually for loss of protective sensation and peripheral artery disease, and screening persons at higher risk at higher frequencies for additional risk factors. For preventing a foot ulcer, educate persons at-risk about appropriate foot self-care, educate not to walk without suitable foot protection, and treat any pre-ulcerative lesion on the foot. Educate moderate-to-high risk people with diabetes to wear properly fitting, accommodative, therapeutic footwear, and consider coaching them to monitor foot skin temperature. Prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking, to help prevent plantar foot ulcer recurrence. Consider advising people at low-to-moderate risk to undertake a, preferably supervised, foot-ankle exercise program to reduce ulcer risk factors, and consider communicating that a total increase in weight-bearing activity of 1000 steps/day is likely safe with regards to risk of ulceration. In people with non-rigid hammertoe with pre-ulcerative lesion, consider flexor tendon tenotomy. We suggest not to use a nerve decompression procedure to help prevent foot ulcers. Provide integrated foot care for moderate-to-high-risk people with diabetes to help prevent (recurrence of) ulceration.

These recommendations should help healthcare professionals to provide better care for persons with diabetes at risk of foot ulceration, to increase the number of ulcer-free days and reduce the patient and healthcare burden of diabetes-related foot disease.

LIST OF RECOMMENDATIONS

1. Screen a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms of peripheral neuropathy and peripheral artery disease, to determine if the person is at increased risk for foot ulceration, using the IWGDF risk stratification system. (GRADE recommendation: Strong; Certainty of evidence: High)
2. If a person with diabetes has loss of protective sensation or peripheral artery disease, extend the screening using clinical history and further foot examinations to assess for
    - a history of foot ulceration or lower-extremity amputation;
    - diagnosis of end-stage renal disease;
    - presence or progression of foot deformity;
    - limited foot and ankle joint mobility;
    - excess callus;
    - and any pre-ulcerative lesion or ulcer on the foot, to determine their risk for foot ulceration using the IWGDF risk stratification system and to inform treatment. Repeat this screening once every 6-12 months for those classified as IWGDF risk 1, once every 3-6 months for IWGDF risk 2, and once every 1-3 months for IWGDF risk 3. (Strong; High)
3. Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to protect their feet by not walking barefoot, not walking in socks without shoes, and not walking in thin-soled slippers, whether indoors or outdoors. (Strong; Low)
4. Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to wash their feet daily (with careful drying, particularly between the toes), use emollients to moisturize dry skin, and cut toenails straight across. (Strong; Low)
5. Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to examine their feet daily and with the presence or suspicion of having a (pre-)ulcerative lesion, to rapidly contact an appropriately-trained healthcare professional for further advice. (Strong; Low)
6. Provide structured education to a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) about appropriate foot self-care for preventing a foot ulcer. (Strong; Low)
7. Consider coaching a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation and help prevent a first or recurrent plantar foot ulcer. If the temperature difference between corresponding regions of the left and right foot is above a temperature threshold of 2.2 °C (or 4.0 °F) on two consecutive days, coach the patient to reduce ambulatory activity and consult an adequately trained healthcare professional for further diagnosis and treatment. (Conditional; Moderate)
8. In a person with diabetes who is at risk of foot ulceration
    a. and with no or limited foot deformity, no pre-ulcerative lesions and no plantar ulcer history (IWGDF risk 1-3), educate to wear footwear that accommodates the shape of the feet and that fits properly. (Strong; Low)

   b. and with a foot deformity that significantly increases pressure or a pre-ulcerative lesion (IWGDF risk 2 or 3), consider prescribing extra-depth shoes, custom-made footwear, custom-made insoles, and/or toe orthoses. (Conditional; Low)
   c. and with a healed plantar foot ulcer (IWGDF risk 3), prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking, to help prevent a recurrent plantar foot ulcer; furthermore, encourage the person to consistently wear this prescribed footwear, both indoors and outdoors. (Strong; Moderate)

9. Provide appropriate treatment for any pre-ulcerative lesion or excess callus on the foot, for ingrown toe nails, and for fungal infections on the foot, to help prevent a foot ulcer in a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3). (Strong; Very low)
10. In a person with diabetes at risk of foot ulceration (IWGDF risk 1-3) and a non-rigid hammertoe with nail changes, excess callus or a pre-ulcerative lesion on the apex or distal part of this toe:
    a. consider digital flexor tendon tenotomy for treating these outcomes and to help prevent a first or recurrent foot ulcer (Conditional; Moderate), or
    b. consider prescribing orthotic interventions, such as toe silicone or (semi-)rigid orthotic devices, to help reduce excess callus on the toe. (Conditional; Low)
11. In a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3), we suggest not to use a nerve decompression procedure to help prevent a foot ulcer. (Conditional; Very low)
12. Consider advising and referring a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) to participate in an 8-12-weeks foot-ankle exercise program, preferably under the supervision of an appropriately trained healthcare professional, and to continue performing foot-ankle exercises afterwards, with the aim of reducing risk factors for ulceration. (Conditional; Low)
13. Consider communicating to a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) that an increase in the level of walking-related weight-bearing daily activity by an extra 1000 steps/day is likely to be safe regarding risk of foot ulceration. Advise this person to wear appropriate footwear when undertaking weight-bearing activities, and to frequently monitor the skin for (pre-)ulcerative lesions. (Conditional; Low)
14. Provide integrated foot care for a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2 and 3) to help prevent a first or recurrent foot ulcer. This integrated foot care should include at least professional foot care, adequate footwear and structured education about self-care. Repeat this foot care or re-evaluate the need for it once every one to three months for a person at high risk, and once every three to six months for a person at moderate risk, as necessary. (Strong; Low)

INTRODUCTION

Foot ulceration is a major complication of diabetes mellitus and is associated with high levels of morbidity and mortality, as well as significant financial costs (1-4). The lifetime incidence rate of diabetes-related foot ulceration is 19-34%, with a yearly incidence rate of 2% (5). After successful healing the recurrence rate of diabetes-related foot ulceration is 40% within a year and 65% within 3 years (5). Therefore, the prevention of diabetes-related foot ulceration is paramount to reduce the risk to the patient and the resultant economic and social burden to society.

Not all people with diabetes are at-risk for ulceration. Key risk factors include: a loss of protective sensation (LOPS), peripheral artery disease (PAD) and foot deformity (5-7). Additionally, a history of foot ulceration and any level of lower extremity amputation, further increases the risk for ulceration up to 40% in one year after healing (5-7). In general, people with diabetes without any of these risk factors do not appear to be at an increased risk of foot ulceration in comparison to people without diabetes (5-7). For the current guideline, we define a person at risk of foot ulceration as one currently or previously diagnosed with diabetes who does not have a foot ulcer, but who has at least LOPS or PAD. Table 1 shows the International Working Group on the Diabetic Foot (IWGDF) system for stratifying risk for foot ulceration.

Considering the above, only interventions aimed specifically at the prevention of foot ulcers in at-risk persons are included in this guideline. Within this group, those persons with a history of diabetes-related foot ulceration or amputation are considered at higher risk for ulceration when compared to those without such a history (7). Thus, we consider the first incidence of diabetes-related foot ulceration and recurrent incidences as separate outcomes of interest. Apart from ulceration as a key clinical outcome, other outcomes are also important for the prevention of foot ulcers and are considered in this guideline, following Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology. These include pre-ulcerative lesions, quality of life, costs, foot-related mechanical stress, and adherence, among others.

Various interventions for the prevention of foot ulcers are either used in clinical practice or have been studied in scientific research (8, 9). We identify five key elements of prevention: 1) Identifying the at-risk foot; 2) Regularly inspecting and examining the at-risk foot; 3) Educating the person with diabetes, family and healthcare providers (this update newly including psychological interventions); 4) Ensuring routine use of appropriate footwear; 5) Treating risk factors for ulceration. Integrated foot care is a combination of these elements, and concerns the 6th element covered in this guideline.

The aim of this guideline is to provide evidence-based state-of-the-art recommendations for the prevention of foot ulcers in people with diabetes and includes a rationale of how we came to each recommendation. This guideline is targeted at clinicians and other healthcare professionals in the field. This guideline is part of the IWGDF Guidelines on the prevention and management of diabetes-related foot disease (10-15), and updates and replaces our previous guideline (16). The rationale provided is based on two systematic reviews of the literature (8, 9), together with a consideration of the desirable and undesirable effects of each intervention, as well as patients' values and preferences, costs related to

the intervention, equity, feasibility and acceptability, again using GRADE methodology. We also provide general considerations and propose an agenda for future research.

WHAT'S NEW IN THIS 2023 UPDATE

We have made several changes to the recommendations included in this updated 2023 guideline on foot ulcer prevention when compared to the previous 2019 guideline. The main changes are the following:

- Used a more thorough GRADE methodological approach to the guideline and the systematic review supporting it, by performing meta-analyses, grading effect sizes, grading certainty(quality) of evidence with 'very low' as an option, and developing summary of judgement tables;
- Added new clinical question on psychological intervention for ulcer prevention;
- Added new important outcomes, including health-related quality of life, costs, mortality, self-efficacy, well-being and adverse events;
- Split the recommendation on the use of footwear according to the severity of foot deformity present;
- Reorganized the recommendations for a person with diabetes at risk of foot ulceration and a non-rigid hammertoe to contain both a surgical and orthotic intervention recommendation; and
- Updated the strength of recommendation and the certainty of evidence underlying the recommendation where appropriate based on new available evidence and on using the more thorough GRADE approach.

METHODS

In this guideline we have followed the key steps of the GRADE evidence-to-decision framework, including: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes in the PICO-format (Patient-Intervention-Comparison-Outcome), iii) performing systematic reviews and rigorous appraisals of all available evidence that addresses the questions, iv) assessing summary of judgements items for each question, v) developing recommendations and their rationale based on these summary of judgements, and vi) consulting external stakeholders on each step (17, 18). The methodology for this guideline is summarised below; we refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (19).

First, a multidisciplinary working group of independent international experts in preventing diabetes-related foot ulcers (the authors of this guideline) was invited by the IWGDF Editorial Board to develop and write this guideline. International experts were defined as those having significant experience in clinical practice and/or studying the prevention of diabetes-related foot ulcers and published on the topic in the previous four years. The working group comprised members from exercise and human movement science, podiatry, podiatric surgery, and physical therapy disciplines from Europe, North America, South America and Australia.

Second, the working group devised important clinical questions and associated outcomes, building on the last version of the guideline, to be answered using the GRADE approach. The questions and outcomes were reviewed and prioritised with the help of 18 external clinical experts and two persons with lived diabetes-related foot ulcer experience from various geographical regions, and the IWGDF Editorial Board. The aim was to ensure the questions and outcomes were of relevance to a wide range of healthcare professionals and people with the disease so as to provide the most useful clinical information on the prevention of foot ulcers in people with diabetes. The working group classified the outcomes as critically important or important, aligning with international diabetes-related foot ulcer standards (20, 21) or the expert opinion of the working group if standards did not exist.

Third, we systematically reviewed the literature and appraised all studies addressing the above agreed upon clinical questions. Each assessable outcome for each question was meta-analysed if appropriate, and had effect sizes and certainty of evidence assessed using the Cochrane and GRADE Handbooks. Finally, we developed evidence statements for each assessable outcome for each question which we presented in full in the systematic review. The systematic reviews supporting this guideline are published separately (8, 9).

Fourth, based on the systematic review, summary of findings tables and expert opinion, teams of two members of the working group developed summary of judgements tables for each question following GRADE (see supplemental information). The summary of judgement items assessed included desirable and undesirable effects, balance of effects, certainty of evidence, values, costs, cost-effectiveness, equity, acceptability and feasibility. Definitions for these items can be found in the Summary of Judgements tables in the supplemental information. After careful weighing of the summary of judgements, the team proposed to the working group a direction, strength, certainty of evidence and wording of recommendation(s) and rationale to address the question concerned. Certainty of evidence was rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Rationale for each recommendation was also provided and based on the summary of judgements tables (17, 18).

Fifth, summary of judgements tables and recommendations for each question were extensively discussed in online meetings with the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention, and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the supplemental information.

Finally, all recommendations, with their rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same clinical experts and persons with lived experience who reviewed the clinical questions, as well as by members of the IWGDF Editorial Board. The working group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline.

CONFLICT OF INTEREST STATEMENT

The prevention guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and these can be found at *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*. No company was involved in the development or review of the guideline. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting on-site.

RESULTS

Overall, 14 clinical questions, each with up to 13 (critically) important outcomes, were finalised and addressed by this guideline. The accompanying systematic reviews identified 172 eligible studies, performed 10 meta-analyses and developed 33 evidence statements to collectively address these questions (8,9). Based on the systematic reviews and expert opinion of the group, 9 summary of judgements tables were completed (see supplemental material) with 14 recommendations developed that addressed the clinical questions.

The different interventions for ulcer prevention are organized and discussed according to five key categories of prevention: 1) Identifying the at-risk foot; 2) Regularly inspecting and examining the at-risk foot; 3) Educating the person with diabetes, family and healthcare providers (this update newly including psychological interventions); 4) Ensuring routine use of appropriate footwear; 5) Treating risk factors for ulceration. Integrated foot care is a combination of these elements, and concerns the 6th element covered in this guideline.

We refer readers to the glossary at the end of this guideline for the definitions of the interventions discussed. Furthermore, many of the interventions recommended require specific training, skills, materials and equipment to apply properly. These aspects are discussed to only a limited extent in this guideline as they are often not described in the studies performed and may differ between centres and countries, and are beyond the scope of the guideline. We suggest that the person applying the intervention should be a properly trained healthcare professional who according to their national or regional standards has the knowledge, expertise, and skills necessary to treat people with diabetes who are at risk of foot ulceration.

RECOMMENDATIONS

1. IDENTIFYING THE AT-RISK FOOT

Clinical questions:

- In people with diabetes what structure and frequency of screening for risk factors of foot ulceration is indicated?
- In people with diabetes what risk factors for foot ulceration should be screened for?
- In people with diabetes how should one screen for peripheral sensory neuropathy and foot deformities?
- In people with diabetes how should ulcer risk be defined?

Recommendation 1: Screen a person with diabetes at very low risk of foot ulceration (IWGDF risk 0) annually for signs or symptoms of peripheral neuropathy and peripheral artery disease, to determine if the person is at increased risk for foot ulceration, using the IWGDF risk stratification system. (GRADE recommendation: Strong; Certainty of evidence: High).

Rationale: Targeting people with diabetes for foot ulcer prevention treatment, first requires identification of those at-risk. We found no evidence in the literature on the direct effect of screening for preventing a diabetes-related foot ulceration. However, we recommend an annual foot screening for all adult persons with diabetes with no additional risk factors (IWGDF risk 0). Foot screening identifies those at risk and should specifically include screening for LOPS caused by peripheral neuropathy, and for signs or symptoms of PAD. Foot screening should also include assessment for presence of a foot ulcer, excess callus, or pre-ulcerative lesion, such as blisters, fissures and haemorrhage. Foot screening should be performed by an adequately trained healthcare professional (see glossary for definition). We do not aim to provide an exhaustive description of the assessment techniques or methods, as they have been detailed elsewhere, including in the IWGDF practical guidelines (22). LOPS can be assessed with a 10-gram Semmes Weinstein monofilament (22): a meta-analysis of individual patient data found consistent results using this assessment to predict risk of foot ulcer (7). If a 10-gram monofilament is unavailable, use the Ipswich Touch Test (23). While outcomes of this test were not included in the aforementioned meta-analysis, the Ipswich Touch Test has shown results similar to testing with the 10-gram monofilament (24). Because limited vibratory sensation may also predict risk of foot ulceration (5), we suggest to screen for this with a tuning fork or biothesiometer/neurothesiometer, if outcomes from monofilament testing do not show LOPS. Screening for PAD is discussed in the IWGDF Guidelines on PAD (13). In short, this includes taking a cardiovascular history, palpating for foot pulses, and obtaining pedal Doppler arterial waveforms and ankle-brachial pressure index and toe-brachial pressure index measurements. Although evidence for a screening interval is non-existent, we recommend an annual screening for a person with diabetes in whom LOPS or PAD have not yet been identified.

Based on a meta-analysis (7), the quality of the evidence that LOPS and PAD are predictive of foot ulceration is high. We suggest there are no undesirable effects associated with yearly foot screenings, the desirable effects of foot screening outweigh the undesirable effects. We also suggest persons with diabetes will value such yearly screenings as part of their regular diabetes check-ups. While foot

screening is generally feasible, acceptable and inexpensive on the individual level, it can be more complex and costlier to organize on the societal level, given the growing number of people with diabetes and the limited time allotted for primary care visits. However, early identifying persons at risk of foot ulceration is important and is needed to target those who require preventative treatment. Therefore, the recommendation for annual foot screening is strong.

Because we found no evidence in the literature on the effect of screening for preventing a diabetes-related foot ulceration, we did not complete summary of judgement tables for this question.

2. REGULARLY INSPECTING AND EXAMINING THE AT-RISK FOOT

Clinical questions: see under 1. IDENTIFYING THE AT-RISK FOOT

Recommendation 2: If a person with diabetes has loss of protective sensation or peripheral artery disease, extend the screening using clinical history and further foot examinations, to include:

- a history of foot ulceration or lower-extremity amputation;
- diagnosis of end-stage renal disease;
- presence or progression of foot deformity;
- limited foot and ankle joint mobility;
- excess callus;
- and any pre-ulcerative lesion or ulcer on the foot,

to determine their risk for foot ulceration using the IWGDF risk stratification system and to inform treatment. Repeat this screening once every 6-12 months for those classified as IWGDF risk 1, once every 3-6 months for IWGDF risk 2, and once every 1-3 months for IWGDF risk 3. (Strong; High)

Rationale: When either LOPS or PAD is identified in a person with diabetes, more extensive and more frequent foot examination is needed, as the ulcer risk is higher (5, 7). This examination should consist of taking a detailed history of foot ulceration, lower-extremity amputation, and determining a diagnosis of end-stage renal disease. Physically examine the foot for presence of deformities or progression thereof; excess callus and pre-ulcerative lesions, such as blisters, fissures and haemorrhage; and limited joint mobility of the foot and ankle (6, 7). A history of a previous foot ulcer or amputation are important predictive factors for a new ulceration, as identified in a meta-analysis of individual patient data (7). Foot deformities, excess callus, pre-ulcerative lesions, and limited joint mobility may increase the risk of foot ulceration (5, 25), and are important determinants of treatment in people with LOPS or PAD. Again, we do not aim to provide an exhaustive description of the assessment techniques or methods, as they have been detailed elsewhere, including in the IWGDF practical guidelines (22).

Notwithstanding the lack of evidence, other factors that we suggest taking a history of are: presence of social isolation, poor access to healthcare and financial constraints, depression or similar psychological comorbidities, frailty, foot pain (with walking or at rest) and numbness or claudication. We also suggest examining the presence of ill-fitting, inadequate, or lack of footwear; abnormal skin colour, temperature

or oedema; poor foot hygiene, e.g., improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks; physical limitations that may hinder foot self-care (e.g. visual acuity, obesity); and poor foot care knowledge (25-28). Lacking footwear, or having Ill-fitting or inadequate footwear can be a cause of ulceration (26), and poor hygiene may be reflective of an inability to self-care. Appropriate interventions can potentially improve these modifiable risk factors when they are identified.

Any foot ulcer identified during screening should be treated according to the principles outlined in the other IWGDF guidelines (10-15).

IWGDF Risk Stratification

Based on the findings of the screening, a person with diabetes can be stratified according to their risk for foot ulceration (Table 1). The risk categories defined are based on a meta-analysis and a systematic review of prospective risk factor studies on foot ulceration (7).

Table 1: The IWGDF Risk Stratification System and corresponding foot screening and examination frequency

Category	Ulcer risk	Characteristics	Frequency*
0	Very low	No LOPS and No PAD	once a year
1	Low	LOPS or PAD	once every 6-12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity or PAD + foot deformity	once every 3-6 months
3	High	LOPS or PAD, and one or more of the following: • history of a foot ulcer • a lower-extremity amputation (minor or major) • end-stage renal disease	once every 1-3 months

Note: LOPS = Loss of protective sensation; PAD = peripheral artery disease. *: Screening frequency is based on expert opinion, since no evidence is available to support these intervals. When the screening interval is close to a regular diabetes check-up, consider screening the foot at that check-up.

Someone without LOPS and without PAD is classified as IWGDF risk 0 and is at very low risk for ulceration. This person requires only annual screening. All other categories are considered "at-risk," and require more frequent foot screening, regular inspection and foot examination than in people who are not at-risk.

A person with either LOPS or PAD, but no additional risk factors, is stratified as IWGDF risk 1, and is considered at low risk. This person should be screened once every 6-12 months. When a combination of risk factors is present, a person is stratified as IWGDF risk 2 and is considered to be at moderate risk. As their risk is higher, this person should be screened every 3-6 months. All persons with either LOPS or PAD and a history of foot ulcer or lower-extremity amputation are stratified as IWGDF risk 3 and considered to be at high risk of ulceration. These persons should be screened once every 1-3 months. We also regard persons with LOPS or PAD in combination with end-stage renal disease (29-31) as

being at high risk, irrespective of their ulcer history, and have therefore added these to IWGDF risk 3. We have not extended the high-risk level in the risk stratification system with new layers of sub-risk, nor have we included Charcot's neuro-osteoarthropathy as high risk or modifiable risk factors in our risk stratification system. These options were discussed in the working group and we concluded that there was not yet sufficient evidence to add these aspects to the risk stratification system.

A person's risk status should be made aware to the person and may change over time, thus requiring continuous monitoring. The screening frequencies we have provided help guide such monitoring. If findings lead to a change in risk status, screening frequency should be adjusted accordingly. As someone's diabetes course progresses, upgrading is the most likely change. Downgrading risk status might occur after (surgical) interventions that normalize foot structure or improve lower extremity blood flow. Further, in a person with LOPS, it is not required to repeat the assessment of LOPS at subsequent screenings. It should also be noted that only biological measures determine the risk level, not behavioural measures. However, behaviour plays a role in foot ulcer risk. When a person with diabetes and neuropathy does not follow recommendations for a person at low-risk, for example by not wearing shoes at all, the risk of developing an ulcer is likely much higher, despite the low-risk stratification. This should be considered when determining the right preventative treatments for the individual person.

In view of the lack of evidence for the effectiveness of a screening interval in at-risk people with diabetes we recommend these intervals based on expert opinion. The aim of more frequent screening is early identification of risk factors that can increase the chances of developing a foot ulcer. This should then be followed by providing appropriate preventative foot care. For example, early diagnosis and treatment of pre-ulcerative lesions on the foot may prevent foot ulcers, as well as more severe complications such as infection and hospitalization. Screening for all these factors should help increase awareness, while it might also raise concern or feelings of anxiety in some people. However, we think that in general the potential for harm is limited. All screening can be done without the need for intrusive interventions and may also provide an opportunity to provide patient education, counselling and support. We suggest that the benefits associated with targeted preventative treatment following screening likely outweigh potential harms, provided appropriate treatment is given by an adequately trained healthcare professional. Screening takes relatively little time, and while this is feasible, acceptable and inexpensive at the individual level, it may be harder to organize and costlier on a societal level. Taking all evidence together, we strongly recommend such screening.

Because we found no evidence in the literature on the effect of examining the foot and on screening interval for preventing a diabetes-related foot ulceration, we did not complete summary of judgement tables for this question.

3. EDUCATING THE PERSON WITH DIABETES, FAMILY AND HEALTHCARE PROVIDERS

3A. Education on foot self-care

Clinical question: In a person with diabetes at risk of foot ulceration, should foot self-care be recommended?

Recommendation 3: Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to protect their feet by not walking barefoot, not walking in socks without shoes, or not walking in thin-soled slippers, whether indoors or outdoors. (Strong; Low)

Rationale: The feet of an at-risk person with diabetes need to be protected against high mechanical stresses, as well as external physical trauma, as both may cause foot ulcers (22). To protect their feet, a person with diabetes should therefore not walk barefoot, not walk in socks without shoes, and not walk in thin-soled slippers, either at home or outside. This also includes any other open type of footwear that increases risk for direct skin damage by a foreign object. While no studies have been directly performed to assess the effect of walking barefoot, in socks without shoes, or in thin-soled standard slippers, on risk of foot ulceration, there are at least large prospective studies that show that at-risk people with diabetes have elevated levels of mechanical plantar pressure during walking barefoot, in socks without shoes and in thin-soled slippers (32, 33). These high pressures are a significant independent risk factor for foot ulceration and should therefore be avoided (5). In addition, walking barefoot, in socks without shoes, or in thin-soled standard slippers has other harmful effects in at-risk people with diabetes, such as lack of protection against thermal or external mechanical trauma. Thus, despite the lack of direct evidence for this recommendation, we strongly advocate that people should be educated to avoid these walking conditions to reduce risk of damaging the foot. Only when supervised by a qualified healthcare professional, limited barefoot walking may be part of foot and ankle exercise programs for low-to-moderate risk people with diabetes (see recommendation 12).

People with diabetes might prefer not to follow this recommendation, especially inside their house (34-36). However, given the potential harm of walking without shoes for foot protection outweighs any benefit to be gained from choosing this preference, we strongly recommend to educate at-risk people with diabetes not to walk barefoot, not to walk in socks without shoes, and not to walk in thin-soled standard slippers, whether at home or when outside. The education should be provided by a healthcare professional with disease-specific knowledge and skills in education.

Recommendation 4: Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to wash their feet daily (with careful drying, particularly between the toes), use emollients to moisturize dry skin, and cut toenails straight across. (Strong; Low)

Recommendation 5: Educate, and after that encourage and remind a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) to examine their feet daily and with the presence or suspicion of having a (pre-)ulcerative lesion, to rapidly contact an appropriately-trained healthcare professional for further advice. (Strong; Low)

Rationale: Although no direct evidence is available for the effect of these self-care interventions in preventing foot ulcers, they enable a person to detect and respond early to signs of diabetes-related foot ulceration and contribute to basic foot hygiene and escalation of care if indicated (i.e., if a pre-ulcerative lesion is suspected). This education is likely to help prevent a foot ulcer, although it may pose some burden to people with diabetes.

The education should be provided by a healthcare professional with disease-specific knowledge and skills in education. Specifically, for washing their feet daily, people should avoid soaking their feet in a bath. With rapidly contacting an appropriately trained healthcare professional we mean immediately calling when identifying the lesion during normal working hours, or at earliest possibility outside of working hours. Appropriately trained means qualified to diagnose, either treat or refer people with diabetes and (pre-)ulcerative lesions.

It can be expected that people will generally consider basic foot hygiene as accessible and feasible, and that the desirable effects will outweigh undesirable effects associated with either inappropriate or inadequate or no foot self-care at all. These foot self-care behaviours can be done at a low cost per person who is at risk for diabetes-related foot ulceration. Despite the limited evidence for the effect of these self-care activities on ulcer prevention, this is a strong recommendation.

The summary of judgements for this clinical question is shown in the supplemental information.

3B. Providing structured education about foot self-care

Clinical questions:

- In a person with diabetes at risk of foot ulceration, should structured education be offered or provided?
- In a person with diabetes at risk of foot ulceration, should psychological interventions be offered or provided?

Recommendation 6: Provide structured education to a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3) about appropriate foot self-care for preventing a foot ulcer. (Strong; Low)

Rationale: Structured education is considered an essential and integral part of foot ulcer prevention, as it is widely thought fundamental that people with diabetes at-risk of foot ulceration need to understand their disease, and what recommended foot self-care is, in order to engage in that care (37). Structured education is defined as any educational modality that is provided to people in a structured way, that is through a protocol or other defined set of sequential routines and content. This can take many forms, such as one-to-one verbal education, education which is integrated into motivational interviewing, educational group sessions, video education, booklets, software applications, quizzes, and pictorial education via animated drawing or descriptive images. Despite this myriad of forms available and education being ingrained in clinical practice all over the world, research on its specific effectiveness (i.e., its desirable effects) for prevention of diabetes-related foot ulceration is limited although education seems to improve knowledge and foot self-care behaviour (9). Our meta-analysis of 5 RCTs shows a relative risk (RR) for ulcer occurrence (either first-ever or recurrent) of 0.66 (95%CI: 0.37-1.19), a

statistically non-significant difference in favour of the intervention (9). Education seemed more effective in the subgroups with participants at lower risk of ulceration. Given its relative low cost, ease of provision and likely trivial undesirable effects, the use of this intervention is probably favoured on balance. Therefore, education should aim to improve the person's foot care knowledge and self-care behaviour, and encourage the person to adhere to the foot self-care education provided.

Structured foot care education should consist of information on:

- Foot ulcers and their consequences
- Prevention-focused foot self-care behaviours, such as: not walking barefoot or in socks without shoes or in thin-soled slippers
- Wearing adequate protective footwear
- Undergoing regular foot checks
- Practicing proper foot hygiene; and
- Seeking professional help in a timely manner after identifying a foot problem (see recommendations 4 and 5).

As there is evidence of the benefits of treatment adherence on ulcer outcomes (38, 39), encourage people at risk of diabetes-related foot ulceration to adhere to the foot self-care education provided. It is best if such education is integrated with regular foot screenings (see recommendations 1 and 2), is re-enforced and is part of integrated foot care (see recommendation 16). Structured education should be culturally appropriate, account for risk profile and gender differences, and align with a person's health literacy and personal circumstances. The education should be provided by a healthcare professional with disease-specific knowledge and skills in education. These steps are likely to further enhance the acceptability and feasibility of the intervention. It is not possible to provide globally applicable recommendations on the best form of education given the diversity of contexts in which education will be provided. We suggest that structured foot self-care education should be provided individually or in small groups of people with diabetes. It should be provided over several sessions and with periodical reinforcement, to maximise effect.

In summary, although the certainty of the evidence for the desirable effects of structured education is low, we strongly recommend providing structured education on foot self-care given undesirable effects are likely to be trivial, face value is high, education is considered by most to be an acceptable and feasible intervention, and we assess that on the balance of effects the benefits of education likely outweigh the potential harms. While education could potentially lead to harm such as an increased fear of complications (40), it may also provide an opportunity for people with diabetes to clarify misunderstandings and seek answers to questions they have (28). People with diabetes will probably prefer structured education when it is appropriate to their circumstances, feasible, and accessible. While structured education is inexpensive at the individual level, it may be harder to organize and costlier on a societal level. Taken together, we strongly recommend providing structured education.

The summary of judgements for this clinical question is shown in the supplemental information.

Psychological interventions: We are unable to make a specific recommendation about the use of psychological interventions for the prevention of diabetes-related foot ulceration in at risk people, due to a very low evidence base at this time. We believe this is an important avenue for future research and clinical guidance due to the success of psychological interventions in other health-related areas, using evidence-based approaches such as motivational interviewing, cognitive behavioural therapy (CBT) and health behaviour change strategies.

3C. Instructions about foot self-management

Clinical question: In a person with diabetes at risk of foot ulceration should instructions about foot self-management, including home foot temperature monitoring, be given?

Recommendation 7: Consider coaching a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2-3) to self-monitor foot skin temperatures once per day to identify any early signs of foot inflammation and help prevent a first or recurrent plantar foot ulcer. If the temperature difference between corresponding regions of the left and right foot is above a temperature threshold of 2.2 °C (or 4.0 °F) on two consecutive days, coach the person to reduce ambulatory activity and consult an adequately trained healthcare professional for further diagnosis and treatment. (Conditional; Moderate)

Rationale: Foot self-management differs from foot self-care as it involves more advanced interventions that are specifically designed for ulcer prevention, such as home-monitoring tools and telemedicine approaches. Self-management can include many interventions, but we found no evidence to support the use of any specific intervention, with the exception of home monitoring of foot skin temperature (9). We found evidence in our meta-analysis that home monitoring of plantar foot skin temperature at minimum once per day with an easy to use infrared thermometer, combined with subsequent preventative action when elevated temperatures were noted for two consecutive days, is statistically more effective than standard treatment for preventing foot ulcers in high-risk people with diabetes (IWGDF risk 2-3), with a relative risk of 0.51 (95%CI: 0.31-0.84) in favour of the intervention (9). These preventative actions include: reduction of ambulatory activity, consultation with an adequately trained healthcare professional to discuss the findings, and further preventative treatment as per the healthcare professional's assessment. For this recommendation to be effective a person needs to have ready access to and the ability to use an appropriate thermometer and be in communication with an adequately trained healthcare professional.

Professionals may value at-home foot temperature monitoring as an easy to use relatively affordable method (in comparison to therapeutic footwear or surgery) that may have high clinical value and helps empower people in their care of their own feet. However, people with diabetes may have difficulty using temperature monitoring because of necessity to measure daily, requirement to target locations on the foot, the risk of false alarms, the requirement for surrounding infrastructure, and costs (41). For both professionals and people with diabetes, the value of skin temperature measurement may be compromised because of the risk of missing an ulcer that develops without the skin heating up before ulceration (42). In addition, practicalities of scaling up the usage of foot temperature monitoring on a global scale raises questions about the implementation of this intervention in different settings worldwide, and therefore there is an uncertainty about the widespread global feasibility of such devices.

The available evidence shows that adherence to measuring foot temperatures was an important factor in its effectiveness, and people, in particular those who have not had a foot ulcer, may find the requirement for daily assessment a burden (43, 44). False-positive and false-negative outcomes of temperature measurements may unnecessarily concern people and affect their confidence in using this approach (42, 45-48).

To our knowledge, home monitoring of foot temperature is currently not routinely implemented in foot care of people with diabetes at moderate to high risk of diabetes-related foot ulceration. This may be due to how people value the need for and ease of use of daily temperature measurements, lack of easy access to calibrated equipment, lack of full-report information on cost-effectiveness and implementation feasibility. Although the desirable effects outweigh undesirable effects, given the potential limitations of this intervention regarding i) equity among different settings, as the tool needed may not be frequently available to be used; ii) patient acceptability, as it adds a burden to measure foot temperature daily; and iii) feasibility, we decided that this is a conditional recommendation.

The summary of judgements for this clinical question is shown in the supplemental information.

4. ENSURING ROUTINE WEARING OF APPROPRIATE FOOTWEAR

Clinical question: In a person with diabetes at risk of foot ulceration, what orthotic interventions, including therapeutic footwear, should be used?

Recommendation 8: In a person with diabetes who is at risk of foot ulceration

a. and with no or limited foot deformity, no pre-ulcerative lesion and no plantar ulcer history (IWGDF risk 1-3), educate to wear footwear that accommodates the shape of the feet and that fits properly. (Strong; Low)
b. and with a foot deformity that significantly increases pressure or a pre-ulcerative lesion (IWGDF risk 2 or 3), consider prescribing extra-depth shoes, custom-made footwear, custom-made insoles, and/or toe orthoses. (Conditional; Low)
c. and with a healed plantar foot ulcer (IWGDF risk 3), prescribe therapeutic footwear that has a demonstrated plantar pressure relieving effect during walking, to help prevent a recurrent plantar foot ulcer; furthermore, encourage the person to consistently wear this prescribed footwear, both indoors and outdoors. (Strong; Moderate)

Rationale: Appropriate footwear is considered an essential and integral part of foot ulcer prevention, as it is widely thought fundamental that people with diabetes at-risk of foot ulceration need to protect their feet from external stress, either through direct trauma or repetitive from weight-bearing activity, and from heat stress.

When educating about or prescribing footwear, also educate the person to check the inside of the shoe for any foreign objects each time before they don the footwear. Furthermore, the healthcare professional should be aware of cultural considerations around footwear and the impact this may have

on uptake of wearing appropriate footwear and the level of education and support that will be required for uptake.

Advise the person wearing footwear to wear socks of natural materials/threads, that are seamless and preferably of light colour so that stains from (pre-)ulcerative lesions may become visible.

Rationale for 8a and 8b: People at moderate or high risk for foot ulceration (IWGDF risk 2-3) have often lost their ability to feel pain or pressure, and may not adequately judge the fit of their footwear or the level of pressure on their foot. Being at increased risk for ulceration, it is important that their footwear fits, protects and accommodates the shape of their feet; this includes having adequate length, width and depth (49). When a foot deformity or pre-ulcerative lesion is present, it becomes even more important to change foot biomechanics and reduce plantar pressure on at-risk locations. This may require custom-made footwear, custom-made insoles or toe orthoses. For people who have healed from a plantar foot ulcer, therapeutic footwear needs to reduce plantar pressure at high-risk areas, including the previous ulcer location. Based on a meta-analysis of 3 RCTs and 3 cohort studies, therapeutic footwear, including shoes, insoles or orthoses may reduce the risk of a first-ever or recurrent foot ulcer over a person's own footwear in someone at moderate-to-high risk for diabetes-related foot ulceration (IWGDF risk 2 to 3), with a relative risk of 0.53 (95%CI: 0.24-1.17) (8). Additionally, such footwear can reduce the plantar pressure during walking (50). High plantar pressures are a significant independent risk factor for foot ulceration and should therefore be avoided (5, 51). Because people with diabetes with LOPS cannot adequately judge footwear fit, footwear should be evaluated by appropriately trained professionals. Evaluate the fit with the person in the standing position, preferably at the end of the day (49). People at moderate or high risk with a foot deformity that significantly increases pressure or a pre-ulcerative lesion may require extra-depth shoes, custom-made footwear, custom-made insoles, and/or toe orthoses. The evidence shows variable effects on ulcer recurrence for specific insoles compared to standard insoles worn in therapeutic footwear (9). These insoles have a positive effect on in-shoe plantar pressure.

People with diabetes may value the role of properly fitting footwear, extra-depth and more custom footwear when they have a deformity to prevent ulcers, but some still consider their footwear to be the cause of their problems, especially when the footwear does not fit properly. Properly fitting footwear, extra-depth or custom-made footwear may also not align with personal comfort and style preferences, while in some countries wearing footwear is not customary at all or may lead to inconvenience (e.g. in warmer or wet climates). However, we know little about the adherence of people with diabetes at moderate risk for ulceration to wearing properly fitting footwear. Therapeutic footwear or adequately trained professionals may also not be present in all countries, which limits access to orthotic interventions. With the additional benefit of protection against thermal and mechanical trauma, and the evidence of reducing ulcer risk, we judge the benefits to outweigh the harm and therefore assign a strong recommendation.

Rationale for 8c: For people with a healed plantar foot ulcer (IWGDF risk 3), therapeutic footwear needs to reduce plantar pressure at high-risk areas, including the previous ulcer location. A meta-analysis of two RCTs on footwear or custom-made insoles that were demonstrably optimised for pressure reduction showed a relative risk of 0.62 (95%CI: 0.26-1.47) (9). For other outcomes, no differences

were found between such pressure-optimized footwear and non-optimized footwear for pre-ulcer lesions, adverse events, health-related quality of life, adherence and mortality, while plantar pressure was lower in optimized footwear/insoles (3 RCTs and 3 non-controlled studies; (9)).

Demonstrated plantar pressure relieving effect means that at high pressure locations there should be a ≥30% reduction in the in-shoe peak pressure during walking (compared to the current therapeutic footwear), or an in-shoe peak pressure <200kPa (if measured with a validated, reliable, and calibrated in-shoe pressure measuring system with sensors sized 2cm^2) (52, 53). The way to achieve such a pressure relief or level is by applying available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot (54).

The desirable effects of continuously wearing optimised footwear or insoles with a proven offloading effect outweigh the undesirable effects, which are few based on the available trials (9). On the other hand, inappropriate footwear (inadequate length or width) increases the risk of ulceration (55), and we again stress the importance of ensuring adequate fit. Clinicians should also encourage people with diabetes to wear their prescribed footwear at all times. The costs of prescribing therapeutic footwear with demonstrated offloading effect may be quite high, as it requires the measurement of barefoot or in-shoe plantar pressure, which to date is relatively expensive for validated systems. However, these costs should always be considered in association with the benefit of ulcer prevention. Cost-effectiveness has not been reported to date. However, based on one unpublished cost-effectiveness analysis of pressure-optimized custom-made footwear as well as on the costs of foot ulceration, in our opinion, footwear designed or evaluated using plantar pressure measurement is likely to be cost-effective when it can reduce ulcer risk by 37% (the outcome from the meta-analysis), and even more when adherence is warranted (9). This is therefore a strong recommendation.

Note that this recommendation is predicated on the availability of both therapeutic footwear and accurate technology for pressure measurement. We acknowledge that the technology and expertise for such measurements are not yet widely available. For regions and settings where this can be made available, we encourage services to invest in regular plantar pressure measurements. For regions and clinical settings where this cannot yet be accommodated, we suggest to prescribe therapeutic footwear using available state-of-the-art scientific knowledge on footwear designs that effectively offload the foot (54).

The summary of judgements for this clinical question is shown in the supplemental information.

5. TREATING RISK FACTORS FOR ULCERATION

5A. Treatment of risk factors or pre-ulcerative lesions on the foot

Clinical question: In a person with diabetes at risk of foot ulceration, how should pre-ulcerative lesions and symptoms be treated?

Recommendation 9: Provide appropriate treatment for any pre-ulcerative lesion or excess callus on the foot, for ingrown toe nails, and for fungal infections on the foot, to help prevent a foot ulcer in a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3). (Strong; Very low)

Rationale: Pre-ulcerative lesions on the foot, such as blisters, fissures or haemorrhage appear to be strong predictors of future ulceration (5, 25, 27). Other risk factors that require treatment include excess callus, ingrown or thickened toe nails and fungal infections. These signs require immediate treatment by an appropriately trained healthcare professional. Appropriate treatment means: removing excess callus; protecting blisters and draining them when necessary; treating fissures; treating ingrown or thickened toe nails; treating cutaneous haemorrhage; and, prescribing antifungal treatment for fungal infections. The effectiveness of treating these signs on the prevention of a diabetes-related foot ulcer has not been directly investigated. Indirect evidence of benefit is that removal of callus reduces plantar pressure, an important risk factor for ulceration (9).

The benefit-harm ratio of treatment of pre-ulcerative lesions by an appropriately trained foot care professional will likely be positive, and come at relatively low costs. However, these treatments do have the potential to harm when improperly performed, and should therefore only be done by an appropriately trained healthcare professional and for the full length of time that the signs or lesions are present. It can be expected that people educated to the dangers of pre-ulcerative lesions prefer that they be treated. Despite a lack of evidence, we consider this standard practice and therefore the recommendation is strong.

The summary of judgements for this clinical question is shown in the supplemental information.

5B. Surgical interventions

Clinical question: In a person with diabetes at risk of foot ulceration, should surgical interventions be used?

Recommendation 10: In a person with diabetes at risk of foot ulceration (IWGDF risk 1-3) and a non-rigid hammertoe with nail changes, excess callus or a pre-ulcerative lesion on the apex or distal part of this toe:

a. consider digital flexor tendon tenotomy for treating these outcomes and to help prevent a first or recurrent foot ulcer. (Conditional; Moderate), or
b. consider prescribing orthotic interventions, such as toe silicone or (semi-)rigid orthotic devices, to help reduce excess callus on the toe. (Conditional; Low)

Rationale: Flexor tenotomy may reduce the risk of ulcer development in people with diabetes with excess callus on the tip of their toes or thickened nails (9). We consider flexor tenotomy a valuable procedure in a patient who has a pre-ulcerative lesion on the toe, that fails to respond to non-surgical treatment, and requires normalization of foot structure to prevent ulceration. Preventative surgery should only be considered after full evaluation of non-surgical treatment options by an appropriately trained healthcare professional.

The desirable effects of flexor tenotomy are moderate and likely outweigh the undesirable effects, as few complications have been reported (9), probably favouring the intervention. People with diabetes who have pre-ulcerative lesions for which they have frequent non-surgical treatment that does not improve outcomes may value and prefer treatment by flexor tenotomy. The procedure is easily performed in an outpatient setting, with no need for subsequent immobilization, and is not likely to negatively affect foot function. A flexor tenotomy is performed in a limited time and as an outpatient procedure and may prevent the use of non-surgical treatment options; thus, the added costs may be negligible, and the procedure may be cost-effective given the effect it has on ulcer prevention. Possible adverse effects of the surgery may include a transfer lesion or transfer pressure and should be discussed with the patient. In people with diabetes with poor arterial supply to the foot, this includes potential non-healing of the surgical incision or wound. Provided a surgeon is available, which seems the case in most settings, tendon tenotomy has little impact on equity, is acceptable and feasible. Due to the low number of controlled trials and low certainty of evidence, we consider the recommendation as conditional.

The summary of judgements for this clinical question is shown in the supplemental information.

To reduce excess callus and the associated increased foot pressure, people with diabetes at risk of ulceration (IWGDF risk 1-3) can be provided with toe silicone and (semi-)rigid orthoses or felted foam in addition to therapeutic footwear (9). The clinician should provide information on proper use of the orthosis, to avoid wrong placement that may even aggravate the situation.

Recommendation 11: In a person with diabetes who is at risk of foot ulceration (IWGDF risk 1-3), we suggest not to use a nerve decompression procedure to help prevent a foot ulcer. (Conditional; Very low)

Rationale: While observational studies on nerve decompression procedures have demonstrated low ulcer incidence rates over extended follow-up periods in people with diabetes with or without a prior foot ulcer experiencing neuropathic pain, there is no evidence to support an ulcer prevention effect of nerve decompression (9). Furthermore, if compared to standard of care in these studies, the standard of care was either poor according to current evidence-based guidelines or poorly described. Two RCTs are currently underway to assess the effect of nerve decompression, but primarily focus on quality of life and neuropathic symptoms, and secondarily on ulceration ((56) and NCT01762085). With various non-surgical or other surgical interventions available that are accepted standards of good quality care to prevent a foot ulcer in an at-risk patient (recommendations 1-10, 14), and given the inherent risk of the surgical procedure, we suggest not to use nerve decompression to help prevent a foot ulcer.

The summary of judgements for this clinical question is shown in the supplemental information.

5C. Foot-related exercises and weight-bearing activity

Clinical questions:

- In a person with diabetes at risk of foot ulceration, should foot-related exercises be done?

- In a person with diabetes at risk of foot ulceration, can the level of weight-bearing physical activity be increased?

Recommendation 12: Consider advising and referring a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) to participate in an 8-12-weeks foot-ankle exercise program, preferably under the supervision of an appropriately trained healthcare professional, and to continue performing foot-ankle exercises afterwards, with the aim of reducing risk factors of ulceration. (Conditional; Low)

Rationale: The risk of ulceration increases in the presence of risk factors. Interventions described in this guideline as part of education (section 3) and footwear (section 4) may help prevent foot ulcers, but do not mitigate the risk factors underlying them. While not all risk factors can be modified, some can. This includes plantar pressure distribution, neuropathy signs and symptoms, deficits in foot sensation, foot-ankle joint mobility and strength (8). Various forms of foot-related exercises are possible when aiming to improve these modifiable risk factors for foot ulceration. These exercises can include stretching and strengthening of the foot and ankle joints and musculature and functional exercises, such as balance and gait exercises (8). These exercises are generally provided in 8-12 weeks training programs, supervised by physical therapists or other qualified and trained professionals, face-to-face or home-based, individually or in groups. In our meta-analyses, we found that these exercise programs do not increase the risk of ulceration, while improving foot and ankle joint range of motion, neuropathy signs and symptoms and plantar pressure distribution (8). As such, the desirable effects outweigh the undesirable effects.

As people with diabetes who are at risk of foot ulceration will likely not be aware of appropriate exercises, we recommend them to undergo a foot assessment and exercise prescription by an adequately trained healthcare professional prior to commencing exercise. Weekly evaluation of progress with training and modification of the program in collaboration with the professional is recommended. While this involves moderate costs, we assessed the importance of involving a healthcare professional for supervision and support as being of value because of the nature of the intervention, and also found better results on some outcomes if supervision was incorporated. People with a pre-ulcerative lesion or with a foot ulcer should not partake in foot-related exercises in which the foot is mechanically loaded, as there is still no evidence if these exercises are safe.

Advising people with diabetes at low to moderate risk of foot ulceration (IWGDF risk 1 or 2) to perform foot-related exercises is based on low certainty of evidence (8). Any potential for harm is outweighed by both general health benefits of exercise and specific improvements to the complex musculoskeletal deficits that develop with diabetes. Foot-related exercises are relatively easy to perform autonomously, are acceptable to people with diabetes, and feasible to execute. Minimal exercise equipment is required, for example elastic bands or exercise balls. As adherence may be a challenge, we advise health practitioners to continue to motivate people with diabetes to complete the exercise program as prescribed. We recommend regularly evaluating the training and outcome progress and updating the program when required. However, lifelong continued support from a health trained professional is not feasible. We therefore recommend that people with diabetes continue after the program, without professional support, preferably with the support of booklets, videos or rehabilitation technology tools. Feasibility of this part of our recommendation has not been studied, and it is unknown

how people with diabetes assess such continuation. Because we expect the positive outcomes of the programs to continue if the exercises are continued, we do recommend people with diabetes to keep performing the exercise after the 8-12 weeks program.

We provide a conditional recommendation to this intervention. Although the benefits of performing foot-ankle exercises on health and foot-related outcomes outweigh the undesirable effects, it may require quite an effort to obtain the improvements in joint range of motion and neuropathy signs and symptoms, and the direct link between these improvements and ulcer prevention has not yet been proven. When implementation of foot-ankle exercises is considered as part of ulcer prevention programs, we stress the importance of first focusing on the strong recommendations in this guideline, such as the availability of adequate footwear. If these are met or at all unavailable in a given setting, implementation of foot-ankle exercises can be a relevant next step.

The summary of judgements for this clinical question is shown in the supplemental information.

Recommendation 13: Consider communicating to a person with diabetes who is at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) that an increase in the level of walking-related weight-bearing daily activity by an extra 1000 steps/day is likely to be safe regarding risk of foot ulceration. Advise this person to wear appropriate footwear when undertaking weight-bearing activities, and to frequently monitor the skin for (pre-)ulcerative lesions. (Conditional; Low)

Rationale: Exercise has general health benefits for people with diabetes, including specific improvements to the complex musculoskeletal deficits that develop with diabetes (57). However, when this exercise is weight-bearing, it increases the cumulative plantar tissue stress on the foot and should therefore be considered in the context of foot disease (58). Based on 4 studies where people with diabetes at risk of foot ulceration participated in a training program that increased their weight-bearing activity but where this did not result in increased incidence of ulceration (8), we suggest to consider advising people at low or moderate risk for ulceration (IWGDF 1 or 2) that a gradual increase in the level of walking-related weight-bearing activity is likely to be safe. We define an increase as a gradual increase in activity with an end goal of an additional 1000 steps/day, based on the increases seen in these 4 studies (8), and an RCT that showed such an increase to be beneficial for glycaemic control in people with diabetes (59). It is advisable to avoid sudden spikes in activity and to increase daily steps by a maximum of 10% per week, until a person reaches an overall increase of 1000 steps/day in comparison to baseline. This increase in daily steps may also be considered for those people with IWGDF risk 3 (60), as evidence showed that these people take on average the same number of daily steps compared to those at low or moderate risk (61). Thus it is probably safe, especially if they wear appropriate footwear when performing weight-bearing activities (see recommendations 8-11).

The certainty of the evidence to support this recommendation is low, as it is based on 4 RCTs, but with none of them powered to detect a difference in ulcer development (8). This uncertainty is a concern (and an important area for future research). However, we think the lack of differences in rates of ulceration between the groups in these trials and the known benefits of increasing weight-bearing exercises on general health and foot-related outcomes, outweighs the harms. Also, increasing weight-bearing activity is feasible for almost anyone, and as such this may increase equity to care. However, people with diabetes should remain cautious to avoid adverse outcomes such as falls and pre-ulcerative

lesions. To prevent adverse outcomes, advise people with diabetes to wear appropriate footwear when undertaking weight-bearing activities (see recommendations 8-11), and to monitor their skin for pre-ulcerative lesions or breakdown (see recommendations 4-6). Increasing the level of weight-bearing daily activity as recommended can be considered feasible and acceptable to people with diabetes. However, high drop-out rates in some trials show that this may not hold for all people with diabetes. Exercise programs are a relatively cheap intervention. Primarily because of the low quality of evidence in relation to ulcer prevention, this is a conditional recommendation.

The summary of judgements for this clinical question is shown in the supplemental information.

6. INTEGRATED FOOT CARE

Clinical question: In a person with diabetes at risk of foot ulceration, should integrated care be provided?

Recommendation 14: Provide integrated foot care for a person with diabetes who is at moderate or high risk of foot ulceration (IWGDF risk 2 and 3) to help prevent a first or recurrent foot ulcer. This integrated foot care should include at least professional foot care, adequate footwear and structured education about self-care. Repeat this foot care or re-evaluate the need for it once every one to three months for high risk, and once every three to six months for moderate risk, as necessary. (Strong; Low)

Rationale: We define integrated foot care as an intervention that at a minimum integrates regular foot care and examination by an adequately trained professional, structured education, and adequate footwear. In our meta-analysis of 3 RCTs, we found an RR of 0.78 (95%CI: 0.58-1.06), a statistically non-significant difference favouring integrated over non-integrated care (9). One cohort study and five non-controlled studies all reported a significantly lower percentage of recurrent ulcers in people with diabetes who received integrated foot care compared to those who did not, or in those people with diabetes who were adherent to an integrated foot care program compared to those who were not (9). None of the studies reported any complications from, or other harm related to, integrated care.

Professional foot care, by an adequately trained healthcare professional, consists of: treating risk factors and pre-ulcerative lesions as described in recommendation 9; structured education about foot self-care according to recommendations 3-6; and, providing adequate footwear following recommendation 8. The person's feet should be regularly examined (see recommendations 1 and 2). Integrated foot care may further include foot self-management (recommendation 7), access to surgery (recommendation 10), and foot-related exercises and weight-bearing activity (recommendations 12 and 13). Given the efficacy of several interventions in people with diabetes without a history of foot ulceration, we also recommend integrated foot care for those with moderate risk of foot ulceration, based on the same expected cumulative effects of the combined interventions as with high-risk people.

While integrated foot care programs have been directly investigated in the controlled and non-controlled studies found in our systematic review (9), none included all potential components of integrated foot care. The effect of a state-of-the-art integrated foot care program that combines all recommendations from this guideline is expected to be much stronger than that achieved by the

programs researched to date (5, 62). Our recommendation that integrated foot care as minimum, consists of professional foot care, structured patient education, and adequate footwear, with a regular examination of a person's feet, is based on this potential effect, shown by our systematic review and other analyses (5, 9, 62). However, the largest effect sizes in ulcer prevention can be found for self-management and surgical interventions (9). Therefore, a complete integrated foot care approach should include these as well. For all aspects of an integrated foot care program, adherence to what is recommended increases the benefits, and should be given adequate attention in communication with the person with diabetes. Taken together, state-of-the-art integrated foot care has been estimated to be able to prevent up to 75% of all diabetes-related foot ulcers (62).

We found no information on costs and cost-effectiveness of integrated foot care. However, a publication from the United States suggested that there was an increase in hospital admissions for a diabetes-related foot ulcer after Medicare cancelled financial coverage in one state for preventative treatment given by podiatrists (63). Two further studies suggested that there was a reduction in amputations following the introduction of integrated foot care that included both ulcer prevention and ulcer treatment (64, 65).

Integrated foot care should be provided by one or more adequately trained healthcare professionals. People with diabetes at risk for foot ulceration who are cared for by professionals without specific expertise on diabetes-related foot disease should refer them to integrated foot care services. Educational interventions targeting healthcare professionals to improve completion rates of yearly foot examinations and to improve diabetes-related foot disease specific knowledge of healthcare professionals not involved daily in diabetes-related foot care may be important, but the effectiveness of such education is unclear (66). Teams that provide integrated foot care may perform educational outreach activities for healthcare professionals in primary or secondary care. The teams should be aware, however, that the effect of such education is limited with respect to knowledge improvement and performance of yearly foot examination, and may have to be repeated frequently.

The benefits of integrated foot care by one or more adequately trained healthcare professionals outweigh the potential harm of such treatment. We think it is likely that people with diabetes prefer integrated foot care delivered by healthcare professionals working in partnership rather than undergoing uncoordinated care delivered by different healthcare professionals working in isolation. We consider the combined effect size of the various interventions that make up integrated foot care to be high. Despite the low quality of the evidence, given the other advantages described, we rate our recommendation as strong.

The summary of judgements for this clinical question is shown in the supplemental information.

CONSIDERATIONS

1. The recommendations in this guideline are aimed at healthcare professionals providing treatment to people with diabetes-related foot disease. However, these professionals treat people with diabetes within a healthcare system or organisation, which itself may have an effect on outcomes. Although direct evidence for this is not available, indirect evidence comes from the effect of increasing podiatry and multidisciplinary teams in the Netherlands (67), which resulted in a reduction of lower-extremity amputations. A study in the US showed that treatment by a podiatric physician reduced 2-year medical care costs compared to no podiatric treatment (68) and yet another study that the discontinuation of podiatry care from Medicare in the US (63) resulted in an increase in hospitalizations for diabetes-related foot disease. The incidence of ulceration and ulcer recurrence is also associated with the availability, implementation and organisation of prevention services. Each of the above studies point to the potential importance of healthcare organisation in diabetes-related foot care, including ulcer prevention. We suggest that a healthcare system includes the multiple levels of foot care as described in the IWGDF practical guidelines (22), that people with diabetes can be referred from primary care to secondary care without delay, and that evidence-based preventative interventions are reimbursed within the system. Also, all healthcare professionals should be adequately trained to triage people with diabetes to ensure they are treated by the right professional. Investment in these aspects of the healthcare system is important to provide adequate preventative foot care for at-risk people with diabetes. This guideline is not written for governments or other agencies investing in healthcare organisations, but we do urge politicians and managers responsible to invest in healthcare systems that facilitate these characteristics.
2. All recommendations in this guideline are targeted at just three strata within the IWGDF risk stratification system (Table 1). Some specifications are given in relation to the location of a previous ulcer (e.g. plantar vs. non-plantar; toes vs. forefoot) or the presence of foot deformities, when recommending orthotic or surgical interventions. However, many differences between people with diabetes in the same stratum exist, and may limit providing the right treatment for the right person at the right time. No research has been done on such personalised medicine and its effects on the prevention of diabetes-related foot ulcers, which means that specific personalised recommendations cannot be made. This may change in the near future, as the medical community is moving more and more towards personalised solutions for medical problems (69).
3. An important factor for most recommendations made is a person's adherence to the recommendations. As we noted in our previous guideline (16), adherence to an intervention has been shown to be crucial in preventing foot ulcers, and it is consistently reported that people with diabetes who do not adhere present with higher rates of ulceration (9). Several studies have investigated methods to improve adherence (36, 70, 71), but a stronger focus on the development, evaluation and implementation of methods that improve adherence to preventative foot treatment remains urgently needed. In turn, evaluating and optimizing feasibility and acceptability of treatments for people with diabetes, should be a key priority in the ongoing development and clinical research on the prevention of diabetes-related foot ulceration.
4. Probably the three most common preventative actions in daily clinical foot practice globally are foot screening (recommendations 1 and 2), foot self-care (recommendations 3 and 4), and (structured) education (recommendation 5). Despite the widespread application of these recommendations in

clinical foot practice, the evidence underlying these recommendations is still poor (9). Frequency of foot screening is based on expert opinion only, and foot self-care and structured education have not been studied adequately. Lack of effect shown does not imply that these interventions do not work, but more research is needed to provide a stronger evidence base.

5. Costs and cost-effectiveness have only to a very limited extent been investigated for any of the interventions described in this guidance, and more attention to cost aspects is warranted. While some interventions are relatively inexpensive at the individual level (such as foot screening), they can be costly at a societal level, considering the millions of people with diabetes. Other interventions are costly at the individual level (such as custom-made footwear and surgical intervention), but reduce ulcer recurrence risk to a level that they are expected to be cost-saving at a societal level. Furthermore, cost-effectiveness can be very dependent on the setting (e.g. high resource versus low resource). More research in this area is needed.
6. We acknowledge that several or maybe many of the recommendations in this guideline and the implementation thereof are subject to aspects such as cultural diversity, religion, socio-economic status, equity, climate, geography, ways of living, values, priorities etc. Identifying these factors is important for a given setting to assess how applicable these guidelines are in that setting. Translation of the guidelines to different languages and the use of them for the development of national guidelines may be helpful tools here.

FUTURE RESEARCH AGENDA

Based on the gaps in the evidence as identified in our systematic reviews (8, 9), and the recommendations and considerations made in this guideline, we consider the following topics as the most important for future research:

- A general increase in research on the prevention of diabetes-related foot ulceration, both in quantity and quality, as research on prevention is still not sufficiently prioritized by funding bodies, policy makers, healthcare settings and clinicians and other healthcare professionals themselves (9).
- A state-of-the-art integrated foot care approach that combines up-to-date interventions as recommended in this guideline has not been investigated to date on efficacy to prevent foot ulcers, while the effect sizes of various interventions found suggest that up to 75% of foot ulcers can be prevented (62). This needs to be investigated in well-designed randomized controlled trials, of which one is currently underway (NCT05236660).
- Current treatment recommendations are based on stratified healthcare. Research is needed to explore the potential of a more personalised medicine approach in diabetes-related foot ulcer prevention, in order to to deliver the right treatment, to the right person, at the right time (69). See also consideration 2.
- Organisation of healthcare and healthcare setting likely plays a significant role in ulcer prevention, but this has not yet been investigated. This includes podiatry services, but also nursing homes, from which little data is available. See also consideration 1.
- Structured education is by many considered a key aspect of a foot ulcer prevention program, but it remains unknown what the exact effect is and which educational approach works best. Future

research should assess the effectiveness of various educational interventions, as well as the frequency of education provided. This includes, but is not limited to, motivational, psychological, or other behavioural interventions, e-health applications and (online) social support systems by peers or healthcare professionals.

- Adherence to treatment is crucial to achieve the best possible outcome in ulcer prevention, but it is still largely unknown how adherence can be improved. Research to develop interventions that have the potential to improve adherence is needed. These interventions may include, among others, assistive technology, educational and behaviour change interventions or footwear solutions. Some proof-of-principle studies on some of these interventions have been conducted and are reported in these guidelines or the systematic review underlying the guideline (9). However, definitive randomized control studies are needed, to test the efficacy of interventions aimed at improving adherence to treatment to prevent ulcers. See also consideration 3.
- The costs and the cost-effectiveness of interventions that aim to prevent foot ulcers needs to be investigated more extensively. See also consideration 5.
- Peripheral neuropathy is the most important risk factor for the development of foot ulcers in people with diabetes, but there is little research on the prevention or treatment of neuropathy. A stronger research focus in this area is needed.
- Robust data are lacking on whom, how, and when to screen for the risk of foot ulceration. High quality data on the benefit of interventions to prevent a first foot ulcer are scarce. As the event rate (foot ulceration) is relatively low in a population without a previous ulcer, to have clinical impact on first foot ulcer occurrence, large numbers of people with diabetes would need to be targeted. It is unclear if the potential benefit for the relatively small number of first ulcers prevented, would outweigh the resource and cost burden of large-scale preventative treatment implementation. Studies should, however, better define the categories of people with diabetes that will benefit from preventative interventions and what specific types of interventions should be included.
- Foot-ankle exercise programs show some promising benefits on risk factors of ulceration, also in meta-analyses (8). However, these are primarily measured directly at the end of the program, mostly at 8 or 12 weeks. Future studies should investigate longer-term outcomes, including the acceptability and feasibility of continuing with the exercises beyond the supervised part of the program, and should also focus on ulceration as outcome.
- The development and evaluation of adjunctive psychological interventions, to support the psychosocial wellbeing of people with diabetes, their families, friends and supports, and help prevent diabetes-related foot ulceration and, are urgently needed. This is an undeveloped area in the prevention of diabetes-related foot ulceration, however, it presents strong promise and is an important focus for future research.

CONCLUDING REMARKS

The global patient and economic burden of diabetes-related foot disease can be considerably reduced when evidence-based preventative treatment is implemented in the foot care of people with diabetes who are at risk of developing a foot ulcer. Reducing the risk of ulceration also reduces the risk of infection, hospitalization, and lower-extremity amputation in these people with diabetes. Despite foot ulcer management still being regarded as the top priority by most clinicians and researchers, foot ulcer prevention should be considered the best way to prevent severe morbidity and mortality in people with diabetes. Following the recommendations for preventative treatment in this guideline will support healthcare professionals and teams to continuously improve the quality of care provided for people with diabetes who are at risk of ulceration.

As part of quality improvement, we encourage our colleagues, both those working in primary care and in diabetes-related foot clinics, to consider developing forms of surveillance (e.g., registries, pathways) to monitor and track the foot health outcomes of people with diabetes at risk of foot ulceration. We also encourage our research colleagues to consider our future research agenda to conduct properly-designed studies in collaboration with clinicians (20) to address the gaps identified in the evidence base to better guide policy and practice decisions on the most effective treatment to help prevent foot ulceration in people with diabetes who are at risk of ulceration.

GLOSSARY

Excess callus: Callus assessed by an appropriately trained healthcare professional as requiring debridement to reduce risk for ulceration.

Adherence: The extent to which a person's behaviour corresponds with agreed recommendations for treatment from a healthcare provider (72), expressed as quantitatively as possible; e.g. the proportion of time, steps or instances that the prescribed intervention (or comparator) is used.

Adequately trained healthcare professional: a person who according to national or regional standards has the knowledge, expertise, and skills to perform a specified task in screening, examining, or managing a person with diabetes who is at risk of foot ulceration.

Custom-made insole: An insole that is custom-made to the individual's foot using a 2D or 3D impression of the foot, and that is often built-up in a multi-layer construction. This may also incorporate other features, such as a metatarsal pad or metatarsal bar. The insole is designed to conform to the shape of the foot, providing cushioning and redistribution of plantar pressure. The term "insole" is also known as "insert" or "liner"

Custom-made (medical grade) footwear: Footwear uniquely manufactured for one person, when this person cannot be safely accommodated in pre-fabricated (medical grade) footwear. It is made to accommodate deformity and relieve pressure over at-risk sites on the plantar and dorsal surfaces of the foot. In-depth assessment, multiple measurements, impressions or a mould, and a positive model of a person's foot and ankle are generally required for manufacture. This footwear includes a custom-made insole. Also known as "bespoke footwear" or "orthopaedic footwear".

Diabetes-related foot ulcer (DFU): see IWGDF definitions and criteria document (21).

Extra-depth footwear: Footwear constructed with additional depth and volume in order to accommodate deformity such as claw/hammer toes and/or to allow for space for a thick insole. Usually a minimum of 5 millimetres (~3/16") depth is added compared to off-the-shelf footwear. Even greater depth is sometimes provided in footwear that is referred to as double depth or super extra-depth.

Foot deformity: Alterations or deviations from normal shape or size of the foot, such as hammer toes, mallet toes, claw toes, hallux valgus, prominent metatarsal heads, pes cavus, pes planus, pes equines, or results of Charcot neuro-osteoarthropathy, trauma, amputations, other foot surgery or other causes. Also includes limited joint mobility in the foot and/or ankle (21).

Foot-related exercises: Any physical exercise specifically targeting the foot or lower-extremity with the aim of changing foot function. These exercises can include stretching and strengthening of the foot and ankle musculature and functional exercises such as balance and gait training. These exercises are provided and/or supervised by a physical therapist or a similarly adequately trained healthcare professional.

Foot self-care: Foot care interventions the person with diabetes can do at home, consisting of but not limited to: foot inspection, washing of feet, careful drying between the toes, nail cutting, using emollients to lubricate skin, not using chemical agents or plasters to remove callus, footwear inspection, avoidance of walking barefoot or on socks only or in thin-soled slippers, avoidance of wearing tight socks, avoiding exposure to excessive cold and heat.

Foot self-management: Advanced assistive interventions the person with diabetes can use at home, consisting of but not limited to: home monitoring systems, lifestyle interventions, telemedicine, technological applications, peer support programs.

Footwear: defined broadly as any shoe-gear and including insoles.

Footwear modification: Modification to existing footwear with an intended therapeutic effect, e.g. pressure relief.

Hosiery: Stockings or socks of any kind. See further Stockings or Socks.

In-shoe (semi-)rigid orthosis: Term used for device put inside the shoe to achieve pressure reduction or alteration in the function of the foot. Can be pre-fabricated or custom-made.

Limited joint mobility: Reduced mobility of the joints of the foot, including the ankle, caused by changes in joints and associated soft tissues (21).

Medical grade footwear: Footwear that meets the specific needs of a person. Can be either pre-fabricated (see "Pre-fabricated medical grade footwear") or custom-made (see "Custom-made medical grade footwear"). Also known as pedorthic footwear

Off-the-shelf footwear: Readily available footwear that has not been modified and has no intended therapeutic functions. Preferred term is pre-fabricated footwear.

Pre-fabricated medical grade footwear: Pre-fabricated footwear that meets the specific needs of a person, on the basis of footwear that provides extra depth, multiple width fittings and features designed to accommodate a broader range of foot types. Other features may include modified soles, fastenings and smooth internal linings. This type of footwear is usually available at specialty shoe shops.

Pre-fabricated insole: An "off-the-shelf" flat or contoured insole made without reference to the shape of the patient's foot.

Shoe last: Last used to make footwear. The upper of the footwear is moulded or pulled over the last. The last shape defines the footwear shape including the outsole shape, heel pitch and toe spring. For off-the-shelf or pre-fabricated footwear generically generated lasts in different sizes are used.

Slipper: Low-cut, open type footwear that is easily slipped onto the foot. Includes thin-soled slippers and flip-flops (thongs).

Socks: Garment for the foot and lower part of the leg, typically knitted from wool, cotton, or nylon.

Stockings: Garment that fits closely over the foot and lower leg, typically elastic. Includes compression stockings for medical purposes.

Structured education: Any educational modality that is provided in a structured way. This can take many forms, such as one-to-one verbal education, motivational interviewing, educational group sessions, video education, booklets, software, quizzes, and pictorial education via animated drawing or descriptive images.

Therapeutic footwear: Generic term for footwear designed to have some therapeutic effect that cannot be provided by or in a conventional shoe. Custom-made shoes or sandals, custom-made insoles, extra-depth shoes, and custom-made or prefabricated medical grade footwear are examples of therapeutic footwear.

Toe orthosis: an in-shoe orthosis to achieve some alteration in the function of the toe.

Weight-bearing activity: Activity during which the foot is loaded by supporting the body weight of the person, and expressed as quantitatively as possible. Incudes walking and standing.

CONFLICT OF INTEREST STATEMENTS

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AUTHOR CONTRIBUTIONS

SAB performed qualitative assessments, completed summary of judgements, and wrote recommendations for interventions 5 and 6, and wrote the manuscript. AnitaR and MMS performed qualitative assessments, completed summary of judgements, and wrote recommendations for interventions 1-3, and critically reviewed and edited the manuscript. LL and JvN performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 5 and 8, and critically reviewed and edited the manuscript. JP performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 4, 6, and 8, and critically reviewed and edited the manuscript. IS performed qualitative assessments, completed summary of judgements, and wrote recommendations for intervention 4, and critically reviewed and edited the manuscript. AnneR performed qualitative assessments, completed summary of judgements, and wrote recommendations for interventions 5 and 6, and critically reviewed and edited the manuscript.

SAB acted as chair of the working group and JvN as secretary and they take full responsibility for the content of the manuscript.

REFERENCES

(1) Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964-74.

(2) Lazzarini PA, Pacella RE, Armstrong DG, van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabet Med. 2018.

(3) Jupiter DC, Thorud JC, Buckley CJ, Shibuya N. The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review. International wound journal. 2016;13(5):892-903.

(4) Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019;36(8):995-1002.

(5) Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376(24):2367-75.

(6) Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev. 2012;28(7):574-600.

(7) Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess. 2015;19(57):1-210.

(8) Van Netten JJ, Sacco ICN, Raspovic A, Lavery LA, Monteiro-Soares M, Paton J, et al. Clinical and biomechanical effectiveness of foot-ankle exercise programs and weight-bearing activity in people with diabetes and neuropathy: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;in press.

(9) Van Netten JJ, Raspovic A, Lavery LA, Monteiro-Soares M, Paton J, Rasmussen A, et al. Prevention of foot ulcers people with diabetes at risk of ulceration: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;in press.

(10) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;in press.

(11) Bus SA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;in press.

(12) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;in press.

(13) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on the diagnosis, prognosis and management of peripheral artery disease in patients with diabetes mellitus. Diab Metab Res Rev. 2023;in press.

(14) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(15) Wukich DK, Schaper NC, Gooday C, Bal A, Bem R, Chabra A, et al. Guidelines on the diagnosis and treatment of active charcot neuro-osteoarthropathy in persons with diabetes mellitus (IWGDF 2023). Diab Metab Res Rev. 2023;in press.

(16) Bus SA, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3269.

(17) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ (Clinical research ed). 2016;353:i2089.

(18) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(19) Bus SA, Game F, Monteiro-Soares M, Van Netten JJ, Apelqvist J, Fitridge R, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;in press.

(20) Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 2016;4(9):781-8.

(21) Van Netten JJ, Bus SA, Apelqvist J, Chen P, Chuter VH, Fitridge R, et al. Definitions and criteria for diabetes-related foot disease (2023 update). Diab Metab Res Rev. 2023;in press.

(22) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease. Diab Metab Res Rev. 2023;in press.

(23) Rayman G, Vas PR, Baker N, Taylor CG, Jr., Gooday C, Alder AI, et al. The Ipswich Touch Test: a simple and novel method to identify inpatients with diabetes at risk of foot ulceration. Diabetes care. 2011;34(7):1517-8.

(24) Sharma S, Kerry C, Atkins H, Rayman G. The Ipswich Touch Test: a simple and novel method to screen patients with diabetes at home for increased risk of foot ulceration. Diabetic medicine : a journal of the British Diabetic Association. 2014;31(9):1100-3.

(25) Waaijman R, de Haart M, Arts ML, Wever D, Verlouw AJ, Nollet F, et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care. 2014;37(6):1697-705.

(26) Apelqvist J, Larsson J, Agardh CD. The influence of external precipitating factors and peripheral neuropathy on the development and outcome of diabetic foot ulcers. J Diabet Complications. 1990;4(1):21-5.

(27) Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes care. 1999;22(1):157-62.

(28) Coffey L, Mahon C, Gallagher P. Perceptions and experiences of diabetic foot ulceration and foot care in people with diabetes: A qualitative meta-synthesis. Int Wound J. 2019;16(1):183-210.

(29) Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, Boulton AJ. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes care. 2010;33(11):2365-9.

(30) Otte J, van Netten JJ, Woittiez AJ. The association of chronic kidney disease and dialysis treatment with foot ulceration and major amputation. J Vasc Surg. 2015;62(2):406-11.

(31) Game FL, Chipchase SY, Hubbard R, Burden RP, Jeffcoate WJ. Temporal association between the incidence of foot ulceration and the start of dialysis in diabetes mellitus. Nephrol Dial Transplant. 2006;21(11):3207-10.

(32) Fernando ME, Crowther RG, Pappas E, Lazzarini PA, Cunningham M, Sangla KS, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. PLoS One. 2014;9(6):e99050.

(33) Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: A systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. Clinical biomechanics (Bristol, Avon). 2013;28(8):831-45.

(34) Barwick AL, van Netten JJ, Hurn SE, Reed LF, Lazzarini PA. Factors associated with type of footwear worn inside the house: a cross-sectional study. J Foot Ankle Res. 2019;12:45.

(35) Waaijman R, Keukenkamp R, de Haart M, Polomski WP, Nollet F, Bus SA. Adherence to wearing prescription custom-made footwear in patients with diabetes at high risk for plantar foot ulceration. Diabetes Care. 2013;36(6):1613-8.

(36) Keukenkamp R, Van Netten JJ, Busch-Westbroek TE, Bus SA. Custom-made footwear designed for indoor use increases short-term and long-term adherence in people with diabetes at high ulcer risk. BMJ Open Diabetes Research and Care. 2022;10(1).

(37) Price P. How can we improve adherence? Diabetes Metab Res Rev. 2016;32 Suppl 1:201-5.

(38) Calle-Pascual AL, Duran A, Benedi A, Calvo MI, Charro A, Diaz JA, et al. Reduction in foot ulcer incidence: relation to compliance with a prophylactic foot care program. Diabetes care. 2001;24(2):405-7.

(39) Viswanathan V, Madhavan S, Rajasekar S, Chamukuttan S, Ambady R. Amputation prevention initiative in South India: positive impact of foot care education. Diabetes care. 2005;28(5):1019-21.

(40) Wukich DK, Raspovic KM, Suder NC. Patients With Diabetic Foot Disease Fear Major Lower-Extremity Amputation More Than Death. Foot & ankle specialist. 2018;11(1):17-21.

(41) Rovers FJ, Van Netten JJ, Busch-Westbroek TE, Aan de Stegge WB, Bus SA. Adherence to at-Home Monitoring of Foot Temperatures in People with Diabetes at High Risk of Ulceration. Int J Low Extrem Wounds. 2022:15347346221114565.

(42) Stegge WBA, Van Netten JJ, Bus SA. Does the skin heat up before it breaks down in diabetic foot ulceration? Diabetes Metab Res Rev. 2023:e3621.

(43) Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Athanasiou KA, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. Diabetes Care. 2007;30(1):14-20.

(44) Bus SA, Aan de Stegge WB, van Baal JG, Busch-Westbroek TE, Nollet F, van Netten JJ. Effectiveness of at-home skin temperature monitoring in reducing the incidence of foot ulcer recurrence in people with diabetes: a multicenter randomized controlled trial (DIATEMP). BMJ Open Diabetes Res Care. 2021;9(1).

(45) Wijlens AM, Holloway S, Bus SA, van Netten JJ. An explorative study on the validity of various definitions of a 2·2°C temperature threshold as warning signal for impending diabetic foot ulceration. Int Wound J. 2017;14(6):1346-51.

(46) van Netten JJ, Prijs M, van Baal JG, Liu C, van der Heijden F, Bus SA. Diagnostic values for skin temperature assessment to detect diabetes-related foot complications. Diabetes technology & therapeutics. 2014;16(11):714-21.

(47) Featherston J, Wijlens AM, van Netten JJ. Is a Left-to-Right >2.2°C Difference a Valid Measurement to Predict Diabetic Foot Ulceration in People with Diabetes and a History of Diabetic Foot Ulceration? Int J Low Extrem Wounds. 2021:15347346211062719.

(48) Frykberg RG, Gordon IL, Reyzelman AM, Cazzell SM, Fitzgerald RH, Rothenberg GM, et al. Feasibility and Efficacy of a Smart Mat Technology to Predict Development of Diabetic Plantar Ulcers. Diabetes Care. 2017;40(7):973-80.

(49) van Netten JJ, Lazzarini PA, Armstrong DG, Bus SA, Fitridge R, Harding K, et al. Diabetic Foot Australia guideline on footwear for people with diabetes. J Foot Ankle Res. 2018;11:2.

(50) Arts ML, Waaijman R, de Haart M, Keukenkamp R, Nollet F, Bus SA. Offloading effect of therapeutic footwear in patients with diabetic neuropathy at high risk for plantar foot ulceration. Diabet Med. 2012;29(12):1534-41.

(51) Fernando ME, Crowther RG, Lazzarini PA, Sangla KS, Wearing S, Buttner P, et al. Plantar pressures are higher in cases with diabetic foot ulcers compared to controls despite a longer stance phase duration. BMC Endocr Disord. 2016;16(1):51.

(52) Bus SA, Waaijman R, Arts M, de Haart M, Busch-Westbroek T, van Baal J, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care. 2013;36(12):4109-16.

(53) Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of Recurrent Foot Ulcers With Plantar Pressure-Based In-Shoe Orthoses: The CareFUL Prevention Multicenter Randomized Controlled Trial. Diabetes Care. 2014;37(7):1982-9.

(54) Bus SA, Zwaferink JB, Dahmen R, Busch-Westbroek T. State of the art design protocol for custom made footwear for people with diabetes and peripheral neuropathy. Diabetes Metab Res Rev. 2020;36 Suppl 1(Suppl 1):e3237.

(55) Litzelman DK, Marriott DJ, Vinicor F. The role of footwear in the prevention of foot lesions in patients with NIDDM. Conventional wisdom or evidence-based practice? Diabetes Care. 1997;20(2):156-62.

(56) Rinkel WD, Fakkel TM, Castro Cabezas M, Birnie E, Coert JH. (Cost-)effectiveness of lower extremity nerve decompression surgery in subjects with diabetes: the DeCompression (DECO) trial-study protocol for a randomised controlled trial. BMJ Open. 2020;10(4):e035644.

(57) Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016;39(11):2065-79.

(58) Lazzarini PA, Crews RT, van Netten JJ, Bus SA, Fernando ME, Chadwick PJ, et al. Measuring Plantar Tissue Stress in People With Diabetic Peripheral Neuropathy: A Critical Concept in Diabetic Foot Management. Journal of diabetes science and technology. 2019;13(5):869-80.

(59) Kooiman TJM, de Groot M, Hoogenberg K, Krijnen WP, van der Schans CP, Kooy A. Self-tracking of Physical Activity in People With Type 2 Diabetes: A Randomized Controlled Trial. Computers, informatics, nursing : CIN. 2018;36(7):340-9.

(60) Fernando ME, Woelfel SL, Perry D, Najafi B, Khan T, DuBourdieu C, et al. Dosing Activity and Returning to Pre-Ulcer Function in Diabetic Foot Remission: Patient Recommendations and Guidance from the Limb Preservation Consortium at USC and The National Rehabilitation Center at Rancho Los Amigos. J Am Podiatr Med Assoc. 2021;111(5).

(61) van Netten JJ, Fijen VM, Bus SA. Weight-bearing physical activity in people with diabetes-related foot disease: A systematic review. Diabetes Metab Res Rev. 2022;38(6):e3552.

(62) Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab Res Rev. 2016;32 Suppl 1:195-200.

(63) Skrepnek GH, Mills JL, Armstrong DG. Foot-in-wallet disease: tripped up by "cost-saving" reductions? Diabetes Care. 2014;37(9):e196-7.

(64) Marn Pernat A, Persic V, Usvyat L, Saunders L, Rogus J, Maddux FW, et al. Implementation of routine foot check in patients with diabetes on hemodialysis: associations with outcomes. BMJ open diabetes research & care. 2016;4(1):e000158.

(65) Schmidt BM, Wrobel JS, Munson M, Rothenberg G, Holmes CM. Podiatry impact on high-low amputation ratio characteristics: A 16-year retrospective study. Diabetes research and clinical practice. 2017;126:272-7.

(66) van Netten JJ, Sacco ICN, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, et al. Treatment of modifiable risk factors for foot ulceration in persons with diabetes: a systematic review. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3271.

(67) van Houtum WH, Rauwerda JA, Ruwaard D, Schaper NC, Bakker K. Reduction in diabetes-related lower-extremity amputations in The Netherlands: 1991-2000. Diabetes Care. 2004;27(5):1042-6.

(68) Carls GS, Gibson TB, Driver VR, Wrobel JS, Garoufalis MG, Defrancis RR, et al. The economic value of specialized lower-extremity medical care by podiatric physicians in the treatment of diabetic foot ulcers. J Am Podiatr Med Assoc. 2011;101(2):93-115.

(69) Van Netten JJ, Woodburn J, Bus SA. The future for diabetic foot ulcer prevention: A paradigm shift from stratified healthcare towards personalized medicine. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3234.

(70) Keukenkamp R, Merkx MJ, Busch-Westbroek TE, Bus SA. An Explorative Study on the Efficacy and Feasibility of the Use of Motivational Interviewing to Improve Footwear Adherence in Persons with Diabetes at High Risk for Foot Ulceration. J Am Podiatr Med Assoc. 2018;108(2):90-9.

(71) McDonogh C, Nube VL, Frank G, Twigg SM, Penkala S, Holloway S, et al. Does in-shoe pressure analysis to assess and modify medical grade footwear improve patient adherence and understanding? A mixed methods study. J Foot Ankle Res. 2022;15(1):94.

(72) World Health Organization. Adherence to long-term therapies: evidence for action. Geneva, Switzerland 2003.

Guidelines on the classification of foot ulcers in people with diabetes

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

This publication represents a scheduled update of the 2019 guidelines of the International Working Group of the Diabetic Foot (IWGDF) addressing the use of systems to classify foot ulcers in people with diabetes in routine clinical practice. The guidelines are based on a systematic review of the available literature that identified 28 classifications addressed in 149 articles and, subsequently, expert opinion using the GRADE methodology. First, we have developed a list of classification systems considered as being potentially adequate for use in a clinical setting, through the summary of judgments for diagnostic tests, focusing on the usability, accuracy and reliability of each system to predict ulcer-related complications as well as use of resources. Second, we have determined, following group debate and consensus, which of them should be used in specific clinical scenarios. In conclusion of this process, in a person with diabetes and a foot ulcer we recommend:

1. for communication among healthcare professionals: to use the SINBAD (Site, Ischaemia, Bacterial infection, Area and Depth) classification (first option) or consider using WIfI (Wound, Ischaemia, foot Infection) system (alternative option, when the required equipment and level of expertise is available and it is considered feasible) and in each case the individual variables that compose the systems should be described rather than a total score;
2. for predicting the outcome of an ulcer in a specific individual: no existing system could be recommended;
3. for characterising a person with an infected ulcer: the use of the IDSA/IWGDF (first option) classification or consider using the WIfI system (alternative option, when the required equipment and level of expertise is available and it is considered as feasible);
4. for characterising a person with peripheral artery disease: consider using the WIfI system as a means to stratify healing likelihood and amputation risk;
5. for the audit of outcome(s) of populations: the use of the SINBAD score.

For all recommendations made using GRADE, the certainty of evidence was judged, at best, as being low. Nevertheless, based on rational application of current data this approach allowed the proposal of recommendations, which are likely to have clinical utility.

LIST OF RECOMMENDATIONS

1a. In a person with diabetes and a foot ulcer, use the SINBAD system for communication between healthcare professionals about the characteristics of an ulcer, and clearly state the presence or absence of each of the composing variables. (Strength of recommendation: Strong; Certainty of evidence: Low)

1b. In a person with diabetes and a foot ulcer, when resources exist in addition to an appropriate level of expertise and it is considered feasible, consider using the WIfI system for communication about the characteristics of an ulcer between healthcare professionals, but with characterisation of each of the composing variables. (Conditional; Low)

2. Do not use any of the currently available classification/scoring systems to offer an individual outcome prognosis for a person with diabetes and a foot ulcer. (Strong; Low)

3a. To classify a person with diabetes and an infected foot ulcer, use the IDSA/IWGDF (2015 version) system. (Strong; Low)

3b. To classify a person with diabetes and an infected foot ulcer, when resources exist in addition to an appropriate level of expertise and it is considered feasible, consider using the WIfI system. (Conditional; Low)

4. In a person with diabetes, peripheral artery disease and a foot ulcer, consider using the WIfI system as a means to stratify healing likelihood and amputation risk. (Conditional; Low)

5. Use the SINBAD system score for any regional/national/international audits, to allow comparisons between institutions on the outcomes of people with diabetes and a foot ulcer. (Strong; Low)

INTRODUCTION

It is estimated that diabetes affects 537 million people worldwide, 10.5% of the adult population, and the increase in prevalence is occurring at a faster rate in low- and middle-income countries (1). Up to one in three people with diabetes will develop a foot ulcer in their lifetime (2). The risk of developing a diabetes-related foot ulcer, and the factors associated with the development of complications (such as hospitalisation, lower extremity amputation, and mortality) may be patient-related, limb-related or ulcer-related. The impact of individual factors on the outcome of foot ulcers in people with diabetes will vary across communities and countries. For example, infection will more strongly influence the outcome in settings where antibiotics are not readily available, whereas ischaemia will have a greater impact in settings where peripheral artery disease is more prevalent. Of note, more than 80% of people with diabetes live in low- and middle-income countries, in which many diagnostic tools are not readily available and are not expected to become so in the near future (1).

A classification system may be defined as a descriptive tool that aims to divide patients into groups while not necessarily relating to the risk of adverse outcome(s), whereas a scoring system will attribute a scale by which the contribution of factors within the system is quantified and scores can be amalgamated to produce an overall (usually numerical) score with an increased score being associated with a higher risk of adverse outcome(s). In other words, classification systems tend to focus on discrimination (the ability to separate data/individuals into classes), while scoring systems tend to focus on calibration (a measure of the closeness of the estimated probability of a certain event to the underlying probability of the population under study) (3). With both types of tools, one can attempt to create more homogeneous groups of patients for which similar levels of care should be provided and also to standardize the modifiable factors that one should focus on to improve clinical outcomes. This does not mean that we should provide the same care to all patients within the same strata, but that the urgency and use of resources should be prioritised for those in most need. This approach does not invalidate clinical experience, knowledge, and the overall approach that we should provide for a person with an established diabetes-related foot ulcer but is designed to help us standardize communication among healthcare professionals and to facilitate more rational use of available resources (independently of their nature). On the other hand, the correct application of such systems is dependent on knowledge and experience of the required procedures to collect each of the variables that compose a system, and on how to apply the overall system.

Due to its frequency, complexity, and limited resources to treat diabetes-related foot ulcers, it is vital to accurately characterize them, understand their severity and to direct patients at most need to specialized care. To do so, healthcare providers should use the classification(s) that have evidence of their accuracy, reliability, and potential impact on clinical care.

In our systematic review (4), we found numerous proposed classification and scoring systems for foot ulcers in people with diabetes (n=28), and this suggests that none is ideal for routine use in populations worldwide. This also highlights the differing purposes of diabetes-related foot ulcer classification and scoring systems that can be used for: (a) communication among healthcare professionals (independent of the level of clinical care); (b) clinical prognostication of the outcome of an individual ulcer; (c) the

assessment of a person with infection; (d) the assessment of a person with peripheral artery disease; and (e) clinical audit of outcomes across units and populations.

The intended use of a classification or scoring system will influence its content. A system designed to assess the risk or prognosis for an individual with diabetes and an ulcer on their foot will necessarily require a certain level of detail. In contrast, a system seeking to compare outcomes between populations will need to minimise data input by busy clinicians and should have a less burdensome requirement for data collection and processing, if it is to be usable in clinical practice. While classifications used for communication among healthcare professionals should ideally be simple to memorise and use. This guideline aims to provide recommendations on the use of classifications of established foot ulcers in people with diabetes for the various purposes on behalf of the International Working Group of the Diabetic Foot (IWGDF).

WHAT'S NEW

We have made several changes to the recommendations included in this updated 2023 diabetes-related foot ulcer classification guideline when compared to the previous 2019 guideline (5). The main changes are the following:

- Used a systematic review instead of a critical review to support our recommendations;
- Used a more thorough GRADE methodology approach by grading effect sizes, grading certainty (quality) of evidence with 'very low' as an option, developing summary of findings tables and developing summary of judgement tables;
- Added new important outcomes, including hospitalization, health-related quality of life, diabetes-related foot ulcer and amputation free survival, and costs;
- Added the use of alternative options for communication between healthcare professionals and management of for complex cases (such as in the presence of infection or peripheral arterial disease) acknowledging the differences in access to equipment and detail needed according to the settings.

METHODS

In this guideline we have followed the key steps of the GRADE evidence-to-decision framework, including: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes in the PI/ECO-format (Patient-Intervention/Exposure-Comparison-Outcome), iii) performing systematic reviews and rigorous appraisals of all available evidence that address the questions, iv) assessing key summary of judgements items for each question, v) developing recommendations and their rationale based on these summary of judgements, and vi) consulting external stakeholders on each step (6, 7). The methodology for this guideline is summarised below; we refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (8).

First, a diverse multidisciplinary working group of independent international experts in developing, assessing, or disseminating classification or scoring systems for diabetes-related foot ulcers (the authors of this guideline) was invited by the IWGDF Editorial Board to develop and author this guideline. International experts were defined as those having significant experience in practising or studying classification or scoring systems to characterise diabetes-related foot ulcers and published on the topic in the previous four years. The working group comprised endocrinologists, internal medicine physicians, physiatrists, podiatrists and vascular surgeons from the United States of America, Europe, Asia and Australia.

Second, the working group devised important clinical questions and associated outcomes, building on the last version of the guideline, to be answered using the GRADE approach. The questions and outcomes were reviewed and prioritised with the help of nine external clinical experts and two persons with lived diabetes-related foot ulcer experience from various geographical regions, and the IWGDF Editorial Board. The aim was to ensure the questions and outcomes were of relevance to a wide range of healthcare professionals and people with the disease so as to provide the most useful clinical information on how to classify foot ulcers in people with diabetes. The working group classified the outcomes as critically important or important, aligning with international diabetes-related foot ulcer standards (9) or the expert opinion of the working group if definitions did not exist.

As stated in our systematic review (4), critically important outcomes were grouped and defined as

a. clinical outcomes
    - lower extremity amputation: resection of a segment of a limb through a bone or through a joint in the lower extremity,
    - wound healing: achieving intact skin, meaning complete epithelialization without any drainage of a previous foot ulcer site,
    - hospitalization: care in a hospital that requires admission as an inpatient and usually requires an overnight stay,
    - survival: the state or fact of continuing to be alive or exist,
    - health-related quality of life: a person's perceived physical and mental health,
b. post-baseline clinical outcomes
    - ulcer-free period: time that a person is alive and without a foot ulcer,
    - lower extremity amputation-free period: time that a person is alive and without amputation,
c. usability
    - facilitate referral and communication: the act of referring someone or something for consultation, review, or further action,
    - feasibility: the state or degree of being easily or conveniently done,
    - reliability: the extent that the instrument yields the same results over multiple trials,
    - audit: the ability to compare outcomes between institutions,
    - guide management/ interventions, and
d. use of resources: requirements of physical, personnel or financial costs.

The following outcomes were considered important but not critical and therefore not included: future infection, well-being, functionality/physical functioning, pain, acceptability, costs (direct/indirect) related to the implementation of the system, cost-effectiveness, and satisfaction/ patient preference.

Third, we systematically reviewed the literature and appraised all studies addressing the above agreed upon clinical questions (4). Due to the expected low number of validation studies per classification, along with high heterogeneity of the clinical settings, follow-up periods, and clinical outcome reporting and definition, the group decided not to perform a meta-analysis. Finally, we developed summary of findings tables, including evidence statements, for each assessable outcome for each question which we presented in full in the systematic review. The systematic review supporting this guideline is published separately (4).

Fourth, based on the systematic review, summary of findings tables and expert opinion, teams of two members of the working group developed summary of judgements tables for each question following GRADE (see supplemental information).

However, in comparison with the remaining guidelines developed by the IWGDF, this one is different in three main respects. First, we did not raise clinical questions relating to treatment/intervention, but prognostic questions, and this requires a major difference in the way that the clinical questions are formulated. Second, within the prognostic clinical questions, we focused on validity measures (namely, accuracy and reliability) creating a methodological approach between the diagnostic (discriminative properties) and prognostic (ability to estimate the likelihood of a specific event). Consequently, we have used the GRADE approach for diagnostic questions and respective "summary of judgments" (10). Third, although in our systematic review we have provided a summary of the available evidence and an evidence statement for each available classification and have therefore created a summary of judgments for each classification, we considered that it would not be beneficial to suggest recommendations for each of them. Instead, we have used this process to be able to recommend one classification as the first line and, whenever appropriate, a second line (alternative) classification to be used for each of the specified four clinical contexts. For one of the scenarios (assessment of a person with a foot ulcer and peripheral artery disease) we have determined that the "Peripheral Artery Disease" group should provide guidelines as to which system to recommend and so this was not addressed by our group (11). However, to provide readers with all the information about which classifications to use we have copied the information present on the "Peripheral Artery Disease" group guidelines.

The summary of judgments for diagnostic questions included the following items: problem priority, test accuracy, desirable effects, undesirable effects, the certainty of the evidence of test accuracy, the certainty of the evidence of the effects of the test, the certainty of the evidence of management's effect, certainty of the evidence of the link between the test result and management, the certainty of any effect on management, value, the balance of effects, resources required, the certainty of the evidence of required resources, cost-effectiveness, equity, acceptability to stakeholders and feasibility. All these items were assessed independently by two reviewers and then presented and discussed within the entire group.

The group determined that the diabetes-related foot ulcer problem has high priority, given the first step for our systematic review and creation of the guidelines was the selection of critical outcomes within

this field by the editorial board, experts, and patient representatives from several countries (further details in the acknowledgments section). For similar reasons, the group determined that there is probably no important uncertainty or variability in the way people value the main outcome(s).

The accuracy of each classification was based on the results of the systematic review, emphasising those studies in which direct comparison between classifications was conducted. The group considered direct improvement of care in any of the five clinical scenarios as desirable effects, and adverse events directly linked to the application of the classification as undesirable effects. For the certainty of test accuracy, the group used the information collected from the systematic review and mostly based their decision in the risk of bias of the retrieved studies, inconsistency of results, and indirectness and imprecision.

Most of the evidence found determined only the accuracy of classifications. Strong evidence that implementing the use of a specific classification in clinical practice could have a true impact on decision making, change a management plan and consequently the person's prognosis was lacking. Due to either lack of any evidence, or evidence that was limited to the availability of indirect evidence only, the certainty of the evidence of test's effects, management effect, or the link between test result and management were mainly based on expert opinion.

For the balance of effects, the group assessed all these items together and determined if, at this point, there was enough information in favour or against the use of each specific classification.

For the resources required, the group considered potential financial or human resources directly linked to the collection of the information required for each classification. As, however, there was no specific detail about these in the systematic review the available evidence was very low.

Taking into consideration the balance of effects and the resources required, the group reflected on the potential cost-effectiveness of each classification. However, we highlight that these outcomes were not considered as critically important and so were given less priority in our selection of the systems to recommend.

The group defined equity in this context as the ability of all people with diabetes and a foot ulcer (i.e. on a societal level) to have equitable access to the procedures required for the classification application.

Acceptability to stakeholders was based on expert opinion and consideration of whether there was balance in the classification between its completeness, simplicity, and objectivity.

Feasibility was determined based on the groups' experience and the ease of use of each classification.

After this entire process, having considered the available evidence, those systems that were considered to be unsuitable to be used in routine clinical practice were excluded from the list of systems that could be chosen as first or second line in each of the four specific scenarios. The reasons for recommending or not recommending a specific system are described in Appendix 1.

The summary of judgments for all the 28 systems are reported in Appendix 2 (Supplementary tables 1 to 28). In Table 1, we present the summary of judgments for each of the classifications that passed this first stage (6 of 28), meaning those we considered that, in face of the available evidence, could be

conditionally or strongly recommended: DIAFORA, Infectious Diseases Society of America (IDSA)/IWGDF, SINBAD, University of Texas Wound Classification System (UTWCS), (Meggitt-)Wagner and WIfI (Wound, Ischaemia, foot Infection).

All of these systems were considered to be accurate, to have moderate desirable effects, small to trivial undesirable effects, with a balance of effects that probably favours their use in clinical practice and is likely to be acceptable to stakeholders. The overall level of certainty of the evidence for the different aspects of the judgments made about these systems varied between very low and low.

Table 1: Summary of Judgments for the classifications considered as suitable for clinical use

Classification/ judgment	DIAFORA	IDSA/IWGDF	SINBAD	UTWCS	Wagner	WIfI
Problem priority	Yes	Yes	Yes	Yes	Yes	Yes
Test accuracy	Accurate	Accurate	Accurate	Accurate	Accurate	Accurate
Desirable effects	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Undesirable effects	Trivial	Small	Trivial	Trivial	Trivial	Trivial
Certainty of evidence of test accuracy	Low	Low	Low	Low	Low	Low
Certainty of evidence of test's effects	Very low	Very low	Very low	Very low	Low	Very low
Certainty of evidence of management's effect	Very low	Very low	Very low	Very low	Low	Very low
Certainty of the evidence of link between test result/management	Low	Low	Low	Low	Low	Low
Certainty of effects	Very low	Very low	Very low	Very low	Low	Very low
How much people value the main outcome	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention
Resources required	Negligible costs and savings	Moderate costs	Moderate savings	Moderate costs	Negligible costs and savings	Moderate savings
Certainty of evidence of required resources	Low	Low	Low	Low	Very low	Very low
Cost effectiveness	Does not favor either	Does not favor either	Probably favors the intervention	Does not favor either	Does not favor either	Probably favors the intervention
Equity	Probably no impact	Probably reduced	Probably increased	Probably reduced	Probably increased	Probably reduced
Acceptability (to stakeholders)	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes
Feasibility	Probably yes	Probably yes	Yes	Probably yes	Yes	Probably no

Note: For each colour a stronger shade implies a stronger assessment, Green filling represents a positive judgment (this is, supporting the use of the system), Blue filling represents a neutral judgment (this is, a balance between supporting or not the use of the system), and Red filling represents a negative judgment (this is, not favouring the use of the system). IDSA/IWGDF: Infectious Diseases Society of America/ International Working Group on the Diabetic Foot; UTWCS: University of Texas Wound Classification System.

After careful weighing of the summary of judgements, the team proposed to the working group a direction, strength, certainty of evidence and wording of recommendation(s) and rationale to address the question concerned. Certainty of evidence was rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Rationale for each recommendation was also provided and based on the summary of judgements tables (12, 13).

Fifth, summary of judgements tables and recommendations for each question were extensively discussed in online meetings with the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention, and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the supplementary material Appendix 2 and 3.

Finally, all recommendations, with the rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same clinical experts and persons with lived experience who reviewed the clinical questions, as well as by members of the IWGDF Editorial Board. The working group then collated, reviewed, and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline manuscript.

MANAGEMENT OF CONFLICT OF INTERESTS

The classification guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups, and these can be found at *www.iwgdfguidelines.org*. No company was involved in the development or review of the guideline. Nobody else involved in the guideline received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting on-site.

RESULTS

Overall, 5 clinical questions, each with up to 13 (critically) important outcomes, were finalised and addressed by this guideline. The accompanying systematic review identified 149 eligible studies, assessing 28 different systems. Based on the systematic review and expert opinion of the group, 28 summary of judgements tables were completed (see supplementary material Appendix 2) with 7 recommendations developed that address the clinical questions and have in consideration the existence of different clinical settings.

Furthermore, to guarantee the accuracy of most of the systems recommended to characterise foot ulcers, specific training, skills, and experience will be required. These specific skills and training are not described in the studies performed and may differ between centres and countries. Any recommendations, therefore, should be read in the understanding that the person applying the different systems should be an appropriately trained healthcare professional who, according to their national or regional standards, has the knowledge, expertise, and skills necessary to manage people with a diabetes-related foot ulcer following the IWGDF practical guidelines (14).

RECOMMENDATIONS

FOR COMMUNICATION AMONG HEALTHCARE PROFESSIONALS

Clinical question: In a person with diabetes and a foot ulcer, which classification system(s) is/ are the best for communication among healthcare professionals and to optimise the process of referral?

Recommendation 1a: In a person with diabetes and a foot ulcer, use the SINBAD system for communication about the characteristics of an ulcer between healthcare professionals, and clearly stating the presence or absence of each of the composing variables. (Strength of recommendation: Strong; Certainty of evidence: Low)

Recommendation 1b: In a person with diabetes and a foot ulcer, when resources exist in addition to an appropriate level of expertise and it is considered feasible, consider using the WIfI system for communication about the characteristics of an ulcer between healthcare professionals, but with characterisation of each of the composing variables. (Conditional; Low)

Rationale: Standardising communication between healthcare professionals about the severity of a foot ulcer could greatly improve the quality of any triage process, referral, or follow-up for a person with a diabetes-related foot ulcer. For a classification system to be used by all healthcare professionals managing people with a diabetes-related foot ulcer to make an adequate referral and or triage a referral to them, it should be quick and simple to apply and preferably require no complex or expensive equipment. On the other hand, for it to be useful to the receiving professional, it should contain appropriate information to allow triage of patients to ensure timely review and this may require more detailed information in some settings. Such a classification system should also be confirmed to have a high interobserver reliability. Although most people with diabetes and a foot ulcer may benefit from referral to a multidisciplinary team without delay, factors necessitating urgent review should at least include the dimensions of the ulcer (area and depth), presence of infection, and ischaemia. Any classification system for use as a triage tool will therefore need to include these criteria without the need for measurements that require specialist equipment (e.g., toe pressures, transcutaneous oxygen pressure ($TcPO_2$)). However, in settings where this equipment is available and there is a suspicion or confirmation of the presence of peripheral artery disease, more detailed information is extremely relevant for the receiving professional.

For these recommendations, the group focused on the organizational aspects of the six selected systems, mainly on accuracy measures (retrieved from our systematic review (4)), feasibility, equity, resources, etc.

The SINBAD system grades Site, Ischemia, Neuropathy, Bacterial infection, Area, and Depth as either 0 or 1 point (see below), creating an easy-to-use scoring system that can achieve a maximum of 6 points (15), as described in Table 2

Table 2: SINBAD system

Category	Definition	Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischemia	Pedal blood flow intact: at least one palpable pulse	0
	Clinical evidence of reduced pedal flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area Ulcer	Ulcer $<1 cm^2$	0
	Ulcer $\geq 1\ cm^2$	1
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon or deeper	1
Total possible score		0 – 6

The SINBAD system is simple and quick to use, requires no specialist equipment beyond clinical examination alone, and contains the necessary information to allow for triage by a specialist team. It would therefore be feasible to employ this classification system in localities where such equipment, including non-invasive measures of perfusion, are not readily available, which is the case for most geographic settings where diabetes-related foot ulcers occur. If used for the purpose of communication among healthcare professionals, it is important to use the individual clinical descriptors and not merely the total score. This scoring system has been validated in 12 studies for several foot ulcer-related clinical outcomes (including healing, amputation, hospitalisation, death, etc.) with somewhat consistent results and also substantial to good reliability (4). Therefore, we consider the description of the presence or absence of the variables included in this system to be the minimum information to be shared for an adequate communication among healthcare professionals about the characteristics of a foot ulcer. For this purpose, we consider that the use of the final score is insufficient.

The classification proposed by Meggitt and modified by Wagner (16) is the oldest classification and grades wounds into pre- or post-ulcerative site (grade 0), superficial ulcer (grade 1), ulcer penetrating to tendon or joint capsule (grade 2), lesion involving deeper tissues (grade 3), forefoot gangrene (grade 4) and whole foot gangrene involving more than two thirds of the foot (grade 5). In our systematic review it was the system with the highest number of articles validating it (n=74) (4). Most of the articles, however, were considered to be at high risk of bias and some inconsistency was observed, along with a predominance of studies reporting association measures instead of accuracy measures. Also, our group considered this classification to have a poor clinical discrimination, as it does not include area, neuropathy, infection and peripheral artery disease individually. It is also rendered blunt by the major impact of gangrene in this classification.

The DIAFORA score includes four foot-related and four ulcer-related variables: neuropathy, foot deformity, arteriopathy, previous foot ulcer or lower extremity amputation; and presence of multiple ulcers, infection, gangrene and/or bone involvement, respectively. This system, like Wagner, also includes

gangrene (17), but no external validation or reliability assessment was conducted (4) and therefore we could not recommend it for this purpose.

The UTWCS system was used in 30 articles (most at high risk of bias, using stage or grade separately and reported mostly association measures), while the WIfI system was used in 13 (with five being conducted in the same institution and with a larger population including previously reported participants plus additional participants) (4). For both systems the certainty of evidence was considered to be low. The WIfI system uses a combination of scores for wound (based on depth of ulcer or extent of gangrene), ischaemia (based on ankle pressure, toe pressure or $TcPO_2$), and foot infection (based on IDSA/IWGDF criteria), detailed in Table 3, to provide a 1-year risk for amputation and 1-year benefit for revascularisation, both stratified as very low, low, moderate, or high (18). This has benefit over perfusion pressures alone by including associated wound and infection criteria to provide a more holistic wound overview in revascularisation decision-making. UTWCS (19) and WIfI (18) both require equipment and clinical expertise to conduct the ankle-brachial index (ABI) as a minimum, which reduces equity and feasibility. In addition, false positives may lead to more anxiety, and thus we do not support the use of such tests without proper training. On the other hand, those individuals with previous signs and symptoms may already have a recent ABI test result or may be followed in settings in which vascular examination is possible and feasible. Neither UTWCS nor WIfI included loss of protective sensation (for which it is important to recommend offloading) as a variable.

In comparison with the WIfI system, the UTWCS system has less detail and classifies DFUs using a bidimensional 4 × 4 matrix, according to depth (Grades 0, 1, 2, and 3) and presence of infection (Stage B), ischaemia (Stage C), or both (Stage D) (19). The original publication (19) described a combination of clinical signs and symptoms, plus one or more non-invasive criteria (transcutaneous oxygen measurements, ABI, or toe systolic pressure) to assess perfusion. In addition,-size (area) is not included in this classification.

For these reasons, when resources exist in addition to an appropriate level of expertise and it is considered feasible, we recommend healthcare professional to also consider the use of the WIfI system for communication about the characteristics of an ulcer (see Table 3), focusing on the description of the grade of each composing variable.

Table 3: WIfI system

Wound

Grade	DFU	Gangrene
0	No ulcer	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
	Clinical description: major tissue loss salvageable with multiple (≥ 3) digital amputations or standard TMA ± skin coverage.	
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis ± calcaneal involvement
	Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect	

Ischaemia

Grade	ABI	Ankle systolic pressure (mmHg)	TP, $TcPO_2$ (mmHg)
0	≥ 0.80	> 100	≥ 60
1	0.6 – 0.79	70 – 100	40 – 59
2	0.4 – 0.59	50 – 70	30 – 39
3	≤ 0.39	< 50	< 30

Foot Infection

Grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least 2 of the following items: • Local swelling or induration • Erythema > 0.5 to ≤ 2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
2	Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: • Temperature > 38°C or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg • White blood cell count > 12,000 or < 4000 cu/mm or 10% immature (band) forms

ABI: Ankle-Brachial Index; $PaCO_2$: Partial Pressure of Carbon Dioxide; SIRS: Systemic Inflammatory Response Syndrome; $TcPO_2$: Transcutaneous Partial Oxygen Pressure; TMA: Transmetatarsal Amputation; TP: Toe Pressure

FOR PREDICTING THE OUTCOME OF AN ULCER IN A SPECIFIC INDIVIDUAL

Clinical question: In a person with diabetes and a foot ulcer, which classification system(s) is/ are the best to assess the prognosis of an individual person with diabetes and a foot ulcer?

Recommendation 2: Do not use any of the currently available classification/scoring systems to offer an individual outcome prognosis for a person with diabetes and a foot ulcer. (Strong; Low)

Rationale: We can use systems in a clinical setting to stratify people by a similar probability of developing a certain event and to create more homogenous groups that should receive similar healthcare or to estimate the individual probability of a specific person with a certain number of characteristics. A good example of the latter is the Framingham Risk Score for cardiovascular disease (20). This model uses six different variables and estimates the individual's risk at 10 years of developing or dying of cardiovascular disease.

To be used as a prognostic tool, a classification system needs to be complex enough to provide individualised outcome prediction yet quick to use within a busy clinical service, ideally not requiring measurements in addition to those performed for routine clinical care. The classification also needs to

be widely validated for the population in which its use is proposed, as the dominant factors for poor outcomes in foot ulcers in people with diabetes vary worldwide due to differences in the population, the local context and available resources for clinical care. This validation should include how well the classification system predicts both ulcer healing and risk of amputation. However, we found insufficient reporting of accuracy measures of the classifications and, even when they were described, they had wide confidence intervals, due to high variability, small sample sizes and low event rates (eg. for major amputation).

For this purpose we considered that likelihood ratios (both positive and negative) would be the more informative accuracy measures, as they summarise (in this context) how many times it is more (or less) likely for patients to develop the clinical outcome of interest than not developing it when they are classified to be at high risk (or low risk, respectively), and are not affected by the outcomes' prevalence (in contrast to the predictive values) (21).

In the rare cases in which positive likelihood ratios were reported (4) they were below 5, while negative likelihood ratios were around 0.2-0.4, indicating only small changes in the pre- to post-test probability of the clinical outcomes of interest would occur (22). A classification or scoring system should also have good inter- and intra- observer reliability to provide consistency of prognostic outcomes and allow for monitoring of progress with any intervention. None of the systems evaluated met these criteria, and so further research may be required, to either appropriately validate an existing classification, or to develop a classification/ scoring system according to these criteria.

The quality of evidence for the prediction of foot ulcer-related outcomes is weak (4) and thus the applicability of the accuracy of a classification system in predicting individual patient outcomes is poor. This has led to our current strong recommendation against the use of any system for prediction of individual patient outcomes.

FOR CLASSIFYING A PERSON WITH AN INFECTED ULCER

Clinical question: In a person with diabetes and an infected foot ulcer, which classification system(s) is/ are the best to predict clinical and health resources outcomes?

Recommendation 3a: To classify a person with diabetes and an infected foot ulcer, use the IDSA/IWGDF system (2015 version) (Strong; Low)

Recommendation 3b: To classify a person with diabetes and an infected foot ulcer, when resources exist in addition to an appropriate level of expertise and it is considered feasible, consider using the WIfI system. (Conditional; Low)

Rationale: The IDSA/IWGDF classification consists of four grades diabetic foot infection (see Table 4). It was originally developed as part of the PEDIS classification for research purposes (23) and is used as a guideline for management, in particular to identify which patients require hospital admission. Although the components of each grade may be considered complex, and a previous study has shown only moderate reliability (4), the criteria are widely used.

Table 4: IDSA/IWGDF system

Clinical manifestations	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥ 2 manifestations of inflammation (purulence, or erythema, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤ 2cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥ 1 of the following characteristics: cellulitis extending >2cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leucocytosis, acidosis, severe hyperglycaemia, or azotaemia)	Severe	4

In our systematic review, we found eight studies validating this system and, although most were at high risk of bias, they showed that an increase in the severity of the infection was associated with a lower incidence of ulcer healing, higher incidence of amputation, hospital admission(s) and having longer length of in-hospital stays (24).

In 2019, this classification underwent a modification during the process of developing the IWGDF guidelines (25). However, this updated version was derived from a study classified as being at high risk of bias (26) and so, at present, we cannot recommend its use.

Of note, whilst the IDSA/IWGDF is incorporated into WIfI (see Table 3), in situations where only infection is being assessed and equipment is not available to use WIfI, the IDSA/IWGDF infection classification can stand alone. On the other hand, in a case of suspected or confirmed infected ulcer complicated by ischaemia, meaning when in the presence of previously diagnosed peripheral artery disease or in a setting in which surgeons with vascular surgery expertise are available, the use of the WIfI classification could be considered.

The studies conducted to validate the UTWCS system have clearly shown that the concomitant presence of infection and peripheral artery disease in a person with diabetes and an ulcer has an incremental effect on the risk of poor clinical outcomes (such as non-healing, delay in healing, or amputation) as well as in costs (19, 27-36). For example, it is well known that oral antibiotic therapy is less effective in people with limited vascular supply. So, the group considered that, when resources and clinical expertise are available, vascular status should be ascertained.

As discussed for the first clinical scenario (communication between healthcare professionals), when comparing the WIfI with the UTWCS system we considered that the certainty of evidence is similar (low for both) (4), but the level of detail of the WIfI system and the direct link to clinical management

favors its use in comparison to UTWCS. In our opinion, the remaining classifications do not provide enough information to allow an accurate characterization of an infected foot ulcer.

We would like to emphasise that this recommendation is intended to classify the severity of infection in people with diabetes and an ulcer of the foot only, and not the severity of any lower limb infection overall. In addition, our focus was to base our recommendation on the available evidence of the accuracy of the systems to predict clinical outcomes and health resource use and not to direct health care professionals to clinical management decisions. We draw attention to this, as these differences may create disparities between our recommendations and the strength of these recommendations in comparison to the ones from the infection group (37).

FOR CLASSIFYING A PERSON WITH AN ULCER AND PERIPHERAL ARTERY DISEASE

Clinical question: In a person with diabetes, peripheral artery disease and a foot ulcer, which classification system(s) is/ are the best to predict clinical and health resources outcomes?

Recommendation 4: In a person with diabetes, peripheral artery disease and a foot ulcer, consider using the WIfI system as a means to stratify healing likelihood and amputation risk (Conditional; Low)

Rationale: Given that 1) there is a specific group to create recommendations on how to diagnose and treat peripheral artery disease in people with diabetes, 2) the importance of aligning the recommendations between groups within the IWGDF, and 3) the similarity of the population used (although the peripheral artery disease group included people with gangrene of the foot whereas our populations was restricted to ulcers of the foot alone) and the most important outcomes selected (prediction of healing and amputation), we have shared the results of our systematic review with the peripheral artery disease group and agreed that this group should make the recommendation on which system to use in this specific clinical context.

The peripheral artery disease working group has recommended the use of the WIfI classification to estimate the likelihood of healing and amputation (11). The choice of this system aligns with the classification working group's selection for the other purposes for which recommendations were made (see recommendation 2 and Table 3).

The peripheral artery disease working group applies this recommendation to both people with a foot ulcer or gangrene, focusing on tissue loss. By supporting the use of this system for both types of population we consider that it will also facilitate its implementation as, in people with diabetes and peripheral artery disease, gangrene without an open ulcer is often seen.

The peripheral artery disease working group also reinforces the importance of taking a relevant history for peripheral artery disease and examining the foot pulses, but also that pedal Doppler waveforms in combination with ankle brachial index (ABI) and toe brachial index (TBI) measurements are preferable as methods to diagnose peripheral artery disease in people with diabetes and with foot ulcers. For a population with suspected peripheral artery disease, we endorse the peripheral artery disease group's statements of the importance of access to these diagnostic procedures but highlight the need for the

clinical experts to perform them reliably and accurately. This method of grading ischaemia is included in the WIfI classification along with the ulcer depth and infection characterization, a system that is considered as relatively easy to apply and accurate when performed in settings where these resources are available.

FOR THE AUDIT OF OUTCOME(S) OF POPULATIONS

Clinical question: In a population of people with diabetes and foot ulcers and in which the purpose is to use for audit, which classification system(s) is/ are the best to predict clinical and health resources outcomes?

Recommendation 5: Use the SINBAD system for any regional/national/international audits to allow comparisons between institutions on the outcomes of people with diabetes and foot ulcers. (Strong; Low)

Rationale: The term "audit" refers to characterisation of all diabetes-related foot ulcers managed in a particular area or centre, to compare outcomes with a reference population or national standard and does not allude to the financial implications of care. Ideally, one classification system should be used internationally to allow comparisons of outcomes. In order to do this, such a classification system would need to accurately assess foot ulcer severity across the spectrum of aetiologies. Thus, healthcare systems where peripheral artery disease is a major contributor to nonhealing, and amputation can be compared with healthcare systems where infection is a major cause of amputation because of limited antibiotic availability. Further, the system should be simple to use, and require no specialist equipment, to allow the necessary clinical data to be collected routinely from all patients in all healthcare settings spanning the spectrum from low to high resource availability.

From the six pre-selected systems, only SINBAD and (Meggitt-)Wagner systems were considered to be clearly feasible. The Wagner classification, as stated previously, was the most frequently reported in the articles that we found in our systematic review (4). However, it is considered as having insufficient detail when compared with SINBAD.

Although none of the existing systems was designed, as far as we are aware, for audit, only the SINBAD score has actually been used for conducting a nationwide audit in the United Kingdom, within the National Diabetes Foot Care Audit (NDFA) of England and Wales. The 2021 annual report of the NDFA (38) reports the outcome of 76,310 people with diabetes with 108,450 ulcers at presentation and showed that a higher SINBAD score led to a lower chance of being alive and ulcer-free at 12 weeks and a higher chance of major amputation within 6 months. The group has determined that no other system should be suggested as an alternative option due to a lack of evidence of the remaining systems feasibility.

FURTHER CONSIDERATIONS / FUTURE RESEARCH / KEY CONTROVERSIES

This document represents the update of our 2019 recommendations on the classification of foot ulcers in people with diabetes (5). Rather than just including new evidence published since that time, in this round we have conducted a systematic as opposed to a critical review and we have used the full GRADE approach (39) for the evidence analysis and development of the recommendations. This led to a change in the certainty of evidence in several scenarios. In fact, for all recommendations the certainty of evidence was graded as low.

Another change was the proposal of first line and second line systems to be used for communication among professionals and for the management of infected foot ulcers, which we believe will lead to a more tailored use of these systems in the different contexts across the world. With this process we have developed six recommendations as well as including one from the "Peripheral Artery Disease" working group which is embedded in our document (11).

In our systematic review (4) we retrieved 149 articles that assessed 28 different systems used to characterize foot ulcers in people with diabetes. However, the current available evidence remains limited due to a lack of articles directly comparing existing systems, with small sample sizes being common; most studies being graded at high risk of bias, frequently reporting only association measures (without multivariable adjustment); and focusing largely on healing or amputation. All of these aspects should be considered before conducting the much-needed future research on this topic to support the use of existing systems, instead of creating new ones that tend to be merely derivative.

Due to the limitations in the available evidence, we were only able to recommend the use of six (21%) out of the 28 systems found (DIAFORA, IDSA/IWGDF, SINBAD, UTWCS, Wagner and WIfI). Moreover, when choosing the ones more indicated for specific scenarios, DIAFORA, UTWCS and Wagner were not selected to be applied for clinical use or audits.

The systems varied considerably in the number (ranging from 3 to more than 30) and type of variables included. Some require blood samples and biomarkers analysis, others specific equipment, while others only use readily available data. The population for its intended use also varied greatly, from infected diabetes-related foot ulcers to chronic wounds of any type. Some had a bi-dimensional structure, other require the use of an app to improve feasibility, others presented an easy to calculate score, and others are a linear grading system. All of this has an impact on complexity, detail, acceptability and feasibility. Some of the choices made by the group may be debatable, but were transparent, carefully discussed and agreed within this group, and the IWGDF editorial board. Questions will inevitably arise as there is much less information about the process to develop recommendations in the diagnostic and prognostic field than in areas that are about therapeutics or other interventions.

One of the debatable decisions is the use of the Summary of Judgments devised for diagnostic clinical questions when we were actually evaluating prognostic clinical questions. However, we believe that we should focus on the use of these systems to change clinical management and not just on their ability to predict the clinical course of any individual. This leads to the acknowledgement that several of the items

related to the assessment of the impact of implementing these systems in clinical practice had insufficient supporting evidence and were consequently graded mainly on expert opinion.

As expected, several members of the group had potential conflict of interest concerning some of the identified systems. By looking for experts in the field, it would be predictable that several of the members had any role in developing, validating, or discussing the existing classification systems. In such cases, those members that were authors or co-authors of an article developing a specific system were not able to score or grade any of the items in the risk of bias, summary of judgments, direction, or strength of recommendation in which such potential conflict of interest may have played a role. The group decided to not perform a meta-analysis, because we considered that the expected heterogeneity on the definition of outcomes, follow-up and clinical setting was too high to enable generation of a meaningful meta-analysis.

One of the scenarios for which we assign high priority for development is the potential for a classification to be used in the prognosis of clinical outcome in an individual. For this specific application we believe that a high level of detail would be required and that machine learning techniques (included in decision support systems) may be key. As an example, we have the models developed by Xie et al. (40), although their use may reduce equity, and further validation studies are required. Alternatively, there may be an option for refinement of existing systems. Also, SINBAD has not yet been assessed to improve stratification by including patient-related morbid factors such as the presence of end-stage renal failure or history of past amputation, and it is envisaged that such future determinations, potentially also combined with systemic validated biomarkers, may, at least at a group level, add clinical utility to such wound classification system alone in predicting foot ulcer outcomes.

As in the 2019 IWGDF classification guidelines, we continue to surmise that there may never be a single preferred foot ulcer classification system for people with diabetes, since the specification of any classification will depend heavily on its purpose and clinical setting. Furthermore, we stress the importance of assessing the impact of including the use of a system in clinical practice, such as that seen by the use of the SINBAD system within the UK-based NDFA, which has consistently found that faster referral to a specialist foot care service is associated with fewer severe ulcers and better 12 weeks outcomes (38). Consequently, being able to classify the severity of an ulcer easily and adequately and to communicate it quickly and in a standardized manner to the specialist foot care service is expected to have a positive impact on clinical outcomes.

CONCLUDING REMARKS

Classification of foot ulcers in people with diabetes is of paramount importance in daily practice. It aims to help in communication among healthcare professionals, assessment/ alignment of broad risk categories and choice of best treatment strategy, as well as audit of clinical outcomes across units and populations.

Based on evidence and consensus judgement using the GRADE methodology, this guideline recommends the use of SINBAD as the priority wound classification system to utilise in people with diabetes and a foot ulcer, for inter-professional communication (describing each composite variable), clinical audits (using the full score), but the use of other more specific assessment systems for infection (IDSA/IWGDF) and peripheral artery disease (WIfI) or when resources exist in addition to an appropriate level of expertise (WIfI).

We encourage clinicians to use the classifications described in this guideline. To do so, specific diagnostic tools are required, standardised definitions (41) should be used and training should be promoted.

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CONTRIBUTION OF AUTHORS

The guideline working group was chaired by FG and MM-S acted as scientific secretary. All members are well-recognised experts in the field with the aim to create an international, multidisciplinary expert guideline committee, including the disciplines endocrinology, internal medicine, physiatry, podiatry and vascular surgery from the United States of America, Europe, Asia and Australia. The working group consisted of eight members in total (the authors of this guideline). All members of the guideline working group were involved in the evidence-to-decision framework process, mostly working in teams (see Methods), from summarising the available evidence in the supporting systematic review (4) to writing the recommendations and rationales. MM-S wrote the draft guideline, and all co-authors reviewed the draft and provided feedback, in writing and during online meetings, during which the content was discussed. All authors reviewed the final draft guideline document and agreed with the content and presentation of the definitive document. All members of the working group undertook Level I GRADE training, and the chair and secretary undertook Level 2 Guideline Methodology training (InGuide program, McMaster University).

REFERENCES

(1) Federation ID. IDF Diabetes Atlas Tenth Edition. IDF Diabetes Atlas. 2021.

(2) Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. New England Journal of Medicine. 2017;376(24):2367-75.

(3) Walsh CG, Sharman K, Hripcsak G. Beyond discrimination: a comparison of calibration methods and clinical usefulness of predictive models of readmission risk. Journal of biomedical informatics. 2017;76:9-18.

(4) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Classification of foot ulcers in people with diabetes: a systematic review. Diab Metab Res Rev. 2023;e3645.

(5) Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, et al. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). Diabetes/metabolism research and reviews. 2020;36:e3273.

(6) Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. bmj. 2016;353.

(7) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(8) Bus SA, Van Netten JJ, Apelqvist J, Fitridge R, Game F, Monteiro-Soares M, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;e3656.

(9) van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, et al. Definitions and criteria for diabetic foot disease. Diabetes/metabolism research and reviews. 2020;36:e3268.

(10) Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Bossuyt P, Chang S, et al. GRADE: assessing the quality of evidence for diagnostic recommendations. BMJ Evidence-Based Medicine. 2008;13(6):162-3.

(11) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023.

(12) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. Bmj. 2016;353:i2089.

(13) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(14) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease. Diab Metab Res Rev. 2023;e3657.

(15) Ince P, Abbas ZG, Lutale JK, Basit A, Ali SM, Chohan F, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes care. 2008;31(5):964-7.

(16) Wagner F. A classification and treatment program for diabetic, neuropathic, and dysvascular foot problems. Instr Course Lect. 1979;28(1):143-65.

(17) Monteiro-Soares M, Dinis-Ribeiro M. A new diabetic foot risk assessment tool: DIAFORA. Diabetes/Metabolism Research and Reviews. 2016;32(4):429-35.

(18) Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischaemia, and foot infection (WIfI). Journal of vascular surgery. 2014;59(1):220-34. e2.

(19) Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischaemia to risk of amputation. Diabetes care. 1998;21(5):855-9.

(20) Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. The American journal of cardiology. 1976;38(1):46-51.

(21) Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. Bmj. 2004;329(7458):168-9.

(22) Jaeschke R, Guyatt GH, Sackett DL, Guyatt G, Bass E, Brill-Edwards P, et al. Users' guides to the medical literature: III. How to use an article about a diagnostic test B. What are the results and will they help me in caring for my patients? Jama. 1994;271(9):703-7.

(23) Schaper N. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes/Metabolism Research and Reviews. 2004;20(S1):S90-S5.

(24) Monteiro-Soares M, Hamilton EJ, Russell D, Srisawasdi G, Boyko EJ, Mills JL, et al. Classification of foot ulcers in people with diabetes: a systematic review. DMRR. 2023.

(25) Lipsky BA, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes/metabolism research and reviews. 2020;36:e3280.

(26) Lavery LA, Ryan EC, Ahn J, Crisologo PA, Oz OK, La Fontaine J, et al. The infected diabetic foot: re-evaluating the Infectious Diseases Society of America diabetic foot infection classification. Clinical Infectious Diseases. 2020;70(8):1573-9.

(27) Ali S, Fareed A, Humail S, Basit A, Ahmedani M, Fawwad A, et al. The personal cost of diabetic foot disease in the developing world—a study from Pakistan. Diabetic medicine. 2008;25(10):1231-3.

(28) Ali SM, Basit A, Fawwad A, Ahmedani MY, Miyan Z, Malik RA. Presentation and outcome of diabetic foot at a tertiary care unit. Pak J Med Sci. 2008;24(5):651-6.

(29) Gul A, Basit A, Ali SM, Ahmadani MY, Miyan Z. Role of wound classification in predicting the outcome of diabetic foot ulcer. JPMA The Journal of the Pakistan Medical Association. 2006;56(10):444.

(30) Habacher W, Rakovac I, Görzer E, Haas W, Gfrerer RJ, Wach P, et al. A model to analyse costs and benefit of intensified diabetic foot care in Austria. Journal of evaluation in clinical practice. 2007;13(6):906-12.

(31) Leese GP, Soto-Pedre E, Schofield C. Independent observational analysis of ulcer outcomes for SINBAD and university of Texas ulcer scoring systems. Diabetes Care. 2021;44(2):326-31.

(32) Monami M, Longo R, Desideri CM, Masotti G, Marchionni N, Mannucci E. The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. Journal of the American Podiatric Medical Association. 2008;98(2):130-6.

(33) Oyibo S, Jude E, Tarawneh I, Nguyen H, Armstrong D, Harkless L, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabetic Medicine. 2001;18(2):133-8.

(34) Parisi MCR, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. European Journal of Endocrinology. 2008;159(4):417.

(35) Prompers L, Huijberts M, Schaper N, Apelqvist J, Bakker K, Edmonds M, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia. 2008;51(10):1826-34.

(36) Smith-Strøm H, Iversen MM, Igland J, Østbye T, Graue M, Skeie S, et al. Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: a retrospective cohort study. PLoS One. 2017;12(5):e0177176.

(37) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(38) (NDFA) NDFCA. NDFA Interval Review: July 2014-March 2021. *www.hqip.org.uk/wp-content/uploads/2022/05/REF240_NDFA-Rep_FINAL-v1.1-20220511.pdf*; 2022.

(39) Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment org/handbook. 2019.

(40) Xie P, Li Y, Deng B, Du C, Rui S, Deng W, et al. An explainable machine learning model for predicting in-hospital amputation rate of patients with diabetic foot ulcer. International Wound Journal. 2022;19(4):910-8.

(41) Van Netten JJ, Bus SA, Apelqvist J, Chen P, Chuter VH, Fitridge R, et al. Definitions and criteria for diabetes-related foot disease (2023 update). Diab Metab Res Rev. 2023;e3654.

(42) Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Dinis-Ribeiro M. Lower-limb amputation following foot ulcers in patients with diabetes: classification systems, external validation and comparative analysis. Diabetes/metabolism research and reviews. 2015;31(5):515-29.

(43) Rigor J, Martins-Mendes D, Monteiro-Soares M. Risk factors for mortality in patients with a diabetic foot ulcer: a cohort study. European Journal of Internal Medicine. 2020;71:107-10.

(44) Chetpet A, DikShit B, Phalgune D. Evaluating a Risk Score for Lower Extremity Amputation in Patients with Diabetic Foot Infections. Journal of Clinical & Diagnostic Research. 2018;12(10).

(45) Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clinical infectious diseases. 2007;44(4):562-5.

(46) Pickwell K, Siersma V, Kars M, Apelqvist J, Bakker K, Edmonds M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. Diabetes care. 2015;38(5):852-7.

(47) Richard J-L, Sotto A, Jourdan N, Combescure C, Vannereau D, Rodier M, et al. Risk factors and healing impact of multidrug-resistant bacteria in diabetic foot ulcers. Diabetes & metabolism. 2008;34(4):363-9.

(48) Rubio JA, Jiménez S, Lázaro-Martínez JL. Mortality in patients with diabetic foot ulcers: Causes, risk factors, and their association with evolution and severity of ulcer. Journal of Clinical Medicine. 2020;9(9):3009.

(49) Ryan EC, Crisologo PA, Oz OK, La Fontaine J, Wukich DK, Lavery LA. Do SIRS Criteria Predict Clinical Outcomes in Diabetic Skin and Soft Tissue Infections? The Journal of Foot and Ankle Surgery. 2019;58(6):1055-7.

(50) Saltoglu N, Yemisen M, Ergonul O, Kadanali A, Karagoz G, Batirel A, et al. Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey. Clinical microbiology and infection. 2015;21(7):659-64.

(51) Seth A, Attri AK, Kataria H, Kochhar S, Seth SA, Gautam N. Clinical profile and outcome in patients of diabetic foot infection. International Journal of Applied and Basic Medical Research. 2019;9(1):14.

(52) Wukich DK, Hobizal KB, Brooks MM. Severity of diabetic foot infection and rate of limb salvage. Foot & ankle international. 2013;34(3):351-8.

(53) Bravo-Molina A, Linares-Palomino JP, Vera-Arroyo B, Salmerón-Febres LM, Ros-Díe E. Inter-observer agreement of the Wagner, University of Texas and PEDIS classification systems for the diabetic foot syndrome. Foot and Ankle Surgery. 2018;24(1):60-4.

(54) Alsabek MB, Abdul Aziz AR. Diabetic foot ulcer, the effect of resource-poor environments on healing time and direct cost: A cohort study during Syrian crisis. International Wound Journal. 2022;19(3):531-7.

(55) Chuan F, Tang K, Jiang P, Zhou B, He X. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. PloS one. 2015;10(4):e0124739.

(56) Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. International wound journal. 2017;14(3):537-45.

(57) Camilleri A, Gatt A, Formosa C. Inter-rater reliability of four validated diabetic foot ulcer classification systems. Journal of Tissue Viability. 2020;29(4):284-90.

(58) Forsythe RO, Ozdemir BA, Chemla ES, Jones KG, Hinchliffe RJ. Interobserver reliability of three validated scoring systems in the assessment of diabetic foot ulcers. The International Journal of Lower Extremity Wounds. 2016;15(3):213-9.

(59) Jørgensen TS, Hellsten Y, Gottlieb H, Brorson S. Assessment of diabetic foot ulcers based on pictorial material: an interobserver study. Journal of Wound Care. 2020;29(11):658-63.

(60) Santema TB, Lenselink EA, Balm R, Ubbink DT. Comparing the Meggitt-Wagner and the University of Texas wound classification systems for diabetic foot ulcers: inter-observer analyses. International wound journal. 2016;13(6):1137-41.

(61) Bates-Jensen B. New pressure ulcer status tool. Decubitus. 1990;3(3):14-5.

(62) Arisandi D, Oe M, Roselyne Yotsu R, Matsumoto M, Ogai K, Nakagami G, et al. Evaluation of validity of the new diabetic foot ulcer assessment scale in Indonesia. Wound repair and regeneration. 2016;24(5):876-84.

(63) Oe M, Yotsu RR, Arisandi D, Sakai Y, Takehara K, Nakagami G, et al. Validity of DMIST for monitoring healing of diabetic foot ulcers. Wound Repair and Regeneration. 2020;28(4):539-46.

(64) Thomas DR, Rodeheaver GT, Bartolucci AA, Franz RA, Sussman C, Ferrell BA, et al. Pressure ulcer scale for healing: derivation and validation of the PUSH tool. The PUSH Task Force. Advances in wound care: the journal for prevention and healing. 1997;10(5):96-101.

(65) Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes care. 2002;25(10):1835-9.

(66) Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. The American journal of medicine. 2003;115(8):627-31.

(67) Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. Wound Repair and Regeneration. 2005;13(3):230-6.

(68) Van Battum P, Schaper N, Prompers L, Apelqvist J, Jude E, Piaggesi A, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabetic medicine. 2011;28(2):199-205.

(69) Gardner SE, Frantz RA, Troia C, Eastman S, MacDonald M, Buresh K, et al. A tool to assess clinical signs and symptoms of localized infection in chronic wounds: development and reliability. Ostomy/Wound Management. 2001;47(1):40-7.

(70) Younes NA, Albsoul AM. The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers. The Journal of foot and ankle surgery. 2004;43(4):209-13.

(71) Lee DW, Kwak SH, Kim JH, Choi HJ. Prediction of diabetic foot amputation using newly revised DIRECT coding system: Comparison of accuracy with that of five existing classification systems. International Wound Journal. 2022.

(72) Kumar S, Arava S, Pavan B, Kiran G, Chandan G, Kumar N. Diabetic ulcer severity score: clinical validation and outcome. International Surgery Journal. 2016;3(3):1606-10.

(73) Shashikala C, Nandini VK, Kagwad S. Validation of Diabetic Ulcer Severity Score (DUSS). 2017.

(74) Yang S, Gu Z, Lu C, Zhang T, Guo X, Xue G, et al. Neutrophil extracellular traps are markers of wound healing impairment in patients with diabetic foot ulcers treated in a multidisciplinary setting. Advances in wound care. 2020;9(1):16-27.

(75) Spanos K, Saleptsis V, Athanasoulas A, Karathanos C, Bargiota A, Chan P, et al. Factors associated with ulcer healing and quality of life in patients with diabetic foot ulcer. Angiology. 2017;68(3):242-50.

(76) Jun YJ, Shin D, Choi WJ, Hwang JH, Kim H, Kim TG, et al. A Mobile application for wound assessment and treatment: findings of a user trial. The International Journal of Lower Extremity Wounds. 2016;15(4):344-53.

(77) Jun D, Kwon Y, Bae J, Lee M, Kim J, Choi H, et al. Using DIRECT wound assessment to predict limb salvage and provide prognosis of diabetic foot ulcers. Journal of Wound Management and Research. 2021;17(1):9-18.

(78) Wong C-H, Khin L-W, Heng K-S, Tan K-C, Low C-O. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Critical care medicine. 2004;32(7):1535-41.

(79) Sen P, Demirdal T. Predictive ability of LRINEC score in the prediction of limb loss and mortality in diabetic foot infection. Diagnostic Microbiology and Infectious Disease. 2021;100(1):115323.

(80) Chaudhary N, Huda F, Roshan R, Basu S, Rajput D, Singh SK. Lower Limb Amputation Rates in Patients With Diabetes and an Infected Foot Ulcer: A Prospective Observational Study. Wound Management & Prevention. 2021;67(7):22-30.

(81) Amadou C, Carlier A, Amouyal C, Bourron O, Aubert C, Couture T, et al. Five-year mortality in patients with diabetic foot ulcer during 2009–2010 was lower than expected. Diabetes & Metabolism. 2020;46(3):230-5.

(82) Treece K, Macfarlane R, Pound N, Game F, Jeffcoate W. Validation of a system of foot ulcer classification in diabetes mellitus. Diabetic medicine. 2004;21(9):987-91.

(83) Chipchase S, Treece K, Pound N, Game F, Jeffcoate W. Heel ulcers don't heal in diabetes. Or do they? Diabetic medicine. 2005;22(9):1258-62.

(84) Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. Diabetic Medicine. 2007;24(9):977-81.

(85) Martínez-De Jesús FR. A checklist system to score healing progress of diabetic foot ulcers. The international journal of lower extremity wounds. 2010;9(2):74-83.

(86) Huang Y, Xie T, Cao Y, Wu M, Yu L, Lu S, et al. Comparison of two classification systems in predicting the outcome of diabetic foot ulcers: the W agner grade and the S aint E lian W ound score systems. Wound Repair and Regeneration. 2015;23(3):379-85.

(87) Carro GV, Saurral R, Carlucci E, Gette F, Llanos MdlÁ, Amato PS. A comparison between diabetic foot classifications WIfI, Saint Elian, and Texas: description of wounds and clinical outcomes. The International Journal of Lower Extremity Wounds. 2022;21(2):120-30.

(88) NIȚĂ G, GHERASIM A, NIȚĂ O, POPA AD, ARHIRE LI, MIHALACHE L, et al. Factors influencing length of hospital stay in patients with diabetic foot ulcers. Romanian JouRnal of medical PRactice. 2021;16(2):77.

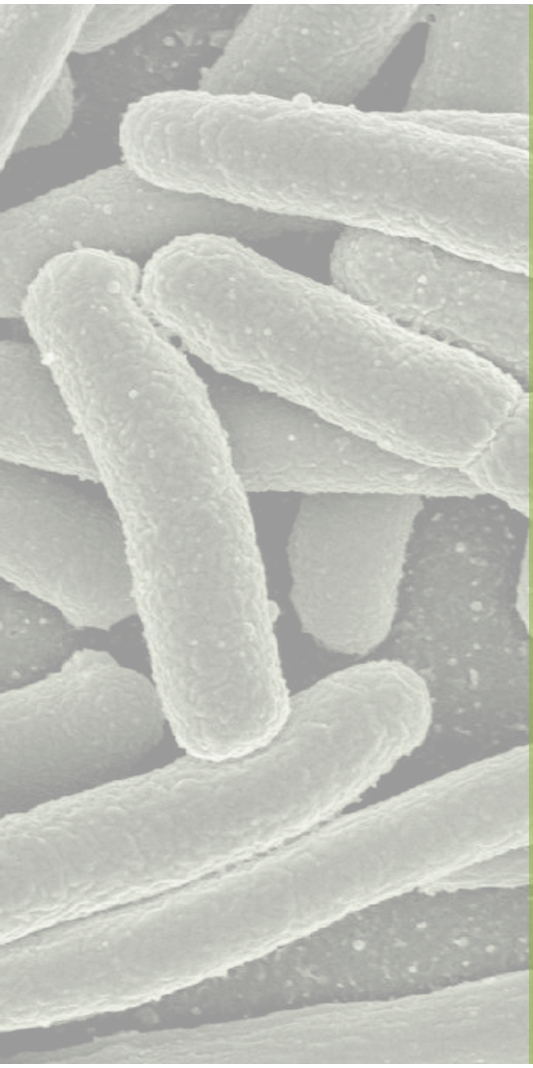
(89) Leese G, Schofield C, McMurray B, Libby G, Golden J, MacAlpine R, et al. Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diabetes care. 2007;30(8):2064-9.

(90) Tardivo JP, Baptista MS, Correa JA, Adami F, Pinhal MAS. Development of the tardivo algorithm to predict amputation risk of diabetic foot. PLoS One. 2015;10(8):e0135707.

(91) Pertama D, Suryadhi N, Yeasa I. Validitas skor tardivo untuk memprediksi terjadinya amputasi pada kaki diabetes di Rsup Sanglash. Medicina. 2018;49(1):33-7.

(92) Van Acker K, De Block C, Abrams P, Bouten A, De Leeuw I, Droste J, et al. The choice of diabetic foot ulcer classification in relation to the final outcome. Wounds. 2002;14:16-25.

(93) Fife CE, Horn SD, Smout RJ, Barrett RS, Thomson B. A predictive model for diabetic foot ulcer outcome: the wound healing index. Advances in Wound Care. 2016;5(7):279-87.



Guidelines on the diagnosis and treatment of foot infection in persons with diabetes

IWGDF/IDSA 2023

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the management and prevention of diabetes-related foot diseases since 1999. The present guideline is an update of the 2019 IWGDF guideline on the diagnosis and management of infections of the foot in persons with diabetes mellitus.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used for the development of this guideline. This was structured around identifying clinically relevant questions in the P(A)ICO format, determining patient-important outcomes, systematically reviewing the evidence, assessing certainty of the evidence, and finally moving from evidence to recommendation. This guideline was developed for healthcare professionals involved in diabetes- related foot care to inform clinical care around patient-important outcomes. Two systematic reviews from 2019 were updated to inform this guideline, and a total of 149 studies (62 new) meeting inclusion criteria were identified from the updated search and incorporated in this guideline. Updated recommendations are derived from these systematic reviews, and best practice statements made where evidence was not available.

Evidence was weighed in light of benefits and harms to arrive at a recommendation. The certainty of the evidence for some recommendations was modified in this update with a more refined application of the GRADE framework centred around patient important outcomes. This is highlighted in the rationale section of this update. A note is also made where the newly identified evidence did not alter the strength or certainty of evidence for previous recommendations.

The recommendations presented here continue to cover various aspects of diagnosing soft tissue and bone infection, including the classification scheme for diagnosing infection and its severity. Guidance on how to collect microbiological samples, and how to process them to identify causative pathogens, is also outlined. Finally, we present: the approach to treating foot infections in persons with diabetes, including selecting appropriate empiric and definitive antimicrobial therapy for soft tissue and for bone infections; when and how to approach surgical treatment; and, which adjunctive treatments may or may not affect the infectious outcomes of diabetes-related foot problems.

We think that following these recommendations will help healthcare professionals provide better care for persons with diabetes and foot infections, prevent the number of foot and limb amputations, and reduce the patient and healthcare burden of diabetes-related foot disease.

ABBREVIATIONS

IWGDF: international working group on the diabetic foot

IDSA: infectious diseases society of America

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

PCT: procalcitonin

PCR: polymerase chain reaction

MRI: magnetic resonance imaging

TDM: tomodensitometry

SPECT: single photon emission computed tomography

PET: positron emission tomography

HMPAO: hexa methyl propylene amine oxime

HBOT: hyperbaric oxygen therapy

SR: systematic review

DFU: diabetes-related foot ulcer

IDFU: infected diabetes-related foot ulcer

DFI: diabetes-related foot infection

DFO: diabetes-related osteomyelitis of the foot

PICO: population intervention control outcome

PACO: population assessment control outcome diabetes-related

LIST OF RECOMMENDATIONS

1a. Diagnose a soft tissue diabetes-related infection clinically, based on the presence of local or systemic signs and symptoms of inflammation. (GRADE recommendation: Strong; Certainty of evidence: Low)

1b. Asses the severity of any diabetes-related foot infection using the IWGDF/IDSA classification scheme. (Strong; Low)

2. Consider hospitalising all persons with diabetes and a foot infection who have either a severe foot infection as classified by the IWGDF/IDSA classification, or a moderate infection which is associated with key relevant morbidities. (Conditional; Low)

3. Assess inflammatory serum biomarkers such as C-reactive protein, erythrocyte sedimentation rate, or procalcitonin in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable. (Best Practice Statement)

4. For diagnosing diabetes-related foot soft-tissue infection, we suggest not using foot temperature (however measured) or quantitative microbial analysis. (Conditional; Low)

5. In a person with suspected soft tissue diabetes-related foot infection, consider a sample for culture to determine the causative microorganisms, preferably by aseptically collecting a tissue specimen (by curettage or biopsy) from the wound. (Conditional; Moderate)

6. Use conventional, rather than molecular, microbiology techniques for the first-line identification of pathogens from soft tissue or bone samples in a patient with a diabetes-related foot infection. (Strong; Moderate)

7. In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and erythrocyte sedimentation rate, or C-reactive protein, or procalcitonin as the initial studies to diagnose osteomyelitis of the foot. (Conditional; Low)

8. Perform magnetic resonance imaging when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings. (Strong; Moderate)

9. Consider using positron emission tomography, leukocyte scintigraphy or single photon emission computed tomography as an alternative to magnetic resonance imaging for the diagnosis of diabetes-related osteomyelitis of the foot. (Conditional; Low)

10. In a person with diabetes for whom there is suspicion of osteomyelitis of the foot (before or after treatment), consider obtaining bone (rather than soft tissue) samples for culture, either intraoperatively or percutaneously. (Conditional; Moderate)

11. Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy when the goal is to reduce the risk of new infection, or to promote ulcer healing. Best Practice Statement

12a. Use any of the systemic antibiotic regimens that have shown to be effective in published randomised controlled trials at standard (usual) dosing to treat a person with diabetes and a soft tissue infection of the foot. (Strong; High)

12b. Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1 to 2 weeks. (Strong; High)

12c. Consider continuing treatment, perhaps for up to 3 to 4 weeks, if the infection is improving but is extensive and is resolving slower than expected or if the patient has severe peripheral artery disease. (Conditional, Low)

12d. If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient, and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low)

13. Select an antibiotic agent for treating a diabetes-related foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of the efficacy of the agent for infections of the diabetes-related foot; risk of adverse events including collateral damage to the commensal flora; the likelihood of drug interactions; agent availability and, costs. Best Practice Statement

14. Target aerobic gram-positive pathogens only (beta-haemolytic streptococci and *Staphylococcus aureus* including methicillin-resistant strains if indicated) for people with a mild diabetes-related foot infection, who have not recently received antibiotic therapy, and who reside in a temperate climate area. Best Practice Statement

15. Select an antibiotic agent for treating a diabetes-related foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of the efficacy of the agent for infections of the diabetes-related foot; risk of adverse events including collateral damage to the commensal flora; the likelihood of drug interactions; agent availability and, costs. Best Practice StatementTarget aerobic gram-positive pathogens only (beta-haemolytic streptococci and Staphylococcus aureus including methicillin-resistant strains if indicated) for people with a mild diabetes-related foot infection, who have not recently received antibiotic therapy, and who reside in a temperate climate area. Best Practice Statement

16. Do not empirically target antibiotic therapy against Pseudomonas aeruginosa in cases of diabetes-related foot infection in temperate climates, but use empirical treatment of P. aeruginosa if it has been isolated from cultures of the affected site within the previous few weeks, in a person with moderate or severe infection who resides in tropical/subtropical climates. Best Practice Statement

17. Consider a duration of up to 3 weeks of antibiotic therapy after minor amputation for diabetes-related osteomyelitis of the foot and positive bone margin culture and 6 weeks for diabetes-related foot osteomyelitis without bone resection or amputation. (Conditional; Low)

18. Use the outcome at a minimum follow-up duration of 6 months after the end of the antibiotic therapy to diagnose remission of diabetes-related osteomyelitis of the foot. Best Practice Statement

19. Urgent surgical consultation should be obtained in cases of severe infection or moderate diabetes-related foot infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia. Best Practice Recommendation

20. Consider performing early (within 24-48 hours) surgery combined with antibiotics for moderate and severe diabetes-related foot infections to remove infected and necrotic tissue. (Conditional; Low)

21. In people with diabetes, peripheral artery disease and a foot ulcer or gangrene with infection involving any portion of the foot, obtain an urgent consultation by a surgical specialist as well as a vascular specialist in order to determine the indications and timings of a drainage procedure and/or revascularisation procedure. Best Practice Statement

22. Consider performing surgical resection of infected bone combined with systemic antibiotics in a person with diabetes-related osteomyelitis of the foot. (Conditional; Low)
23. Consider antibiotic treatment without surgery in case of (i) forefoot osteomyelitis without an immediate need for incision and drainage to control infection, and (ii) without peripheral artery disease, and (iii) without exposed bone. (Conditional; Low)
24. We suggest not using the following treatments to address diabetes-related foot infections: (a) adjunctive granulocyte colony-stimulating factor treatment or (b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative pressure wound therapy (with or without instillation). (Conditional; Low)
25. We suggest not using topical (sponge, cream, and cement) antibiotics in combination with systemic antibiotics for treating either soft-tissue infections or osteomyelitis of the foot in patients with diabetes. (Conditional; Low)
26. We suggest not using hyperbaric oxygen therapy or topical oxygen therapy as an adjunctive treatment for the sole indication of treating a diabetes-related foot infection. (Conditional; Low)

Note: the available data did not allow making a recommendation on the use of rifampicin for the treatment of diabetes-related osteomyelitis of the foot.

INTRODUCTION

The prevalence of diabetes continues to increase globally and the International Diabetes Foundation has estimated that 537 million adults aged between 20 and 79 years worldwide were living with diabetes in 2021.[1] This situation leads to a rising incidence of foot complications, including infections.[1] Diabetes-related foot infections (DFIs) are associated with substantial morbidities, requiring frequent healthcare provider visits, daily wound care, antimicrobial therapy, surgical procedures, and high healthcare costs.[2] Of particular importance, DFIs remain the most frequent diabetes-related complications requiring hospitalisation and the most common precipitating events leading to lower extremity amputation.[3,4] Outcomes in patients presenting with an infected diabetes-related foot ulcer (DFU) are suboptimal in one large prospective study, at the end of 1 year, the ulcer had healed in only 46% (and it later recurred in 10% of these), while 15% had died and 17% required a lower extremity amputation.[5]

Managing DFIs requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting antimicrobial therapy, quickly determining when surgical interventions are required, and providing any needed additional wound and overall patient care. A systematic, evidence-based approach to managing DFIs likely improves outcomes, specifically the resolution of difficult cases of infection, and helps avoid complications, such as life-threatening infections and limb loss. This is best delivered by interdisciplinary teams, which should include among the membership, whenever possible, an infectious diseases or clinical/medical microbiology specialist.[6] This team should also attempt to ensure optimal local wound care (e.g., cleansing and debridement), pressure off-loading, peripheral vascular assessment (with revascularization if needed), and metabolic (particularly glycaemic) control. For these aspects, the reader is referred to the other chapters of the IWGDF guideline on the management of diabetes-related foot ulcers in this special issue.[7-9] If these aspects are not adequately addressed, and the focus is only on infection, the chance of treatment failure is greatly increased.

Several guidelines are available to assist clinicians in managing DFIs. The Infectious Diseases Society of America (IDSA) produced a guideline in 2004, which was updated in 2012.[10,11] A panel of experts convened by the International Working Group on the Diabetic Foot (IWGDF) has published widely used guideline documents quadrennially since 2004.[12] The present 2023 edition of the IWGDF guidelines on the management of diabetes-related foot infection updates the content of the 2019 edition on the diagnosis and treatment of diabetes-related foot infections and is part of the aforementioned guidelines.[13] The IWGDF and IDSA have now agreed to provide a combined intersociety guideline on the diagnosis and treatment of DFIs; as a result, the expert panel involved in the creation of the new guideline document included for the first time members from both IWGDF and IDSA working on a single document.

BACKGROUND

Infections of the skin and soft tissues of the foot in a person with diabetes most often follow a break in the protective skin envelope. The most common such break is a DFU, which usually involves at least the epidermis and part of the dermis. This complication most often occurs in those with peripheral neuropathy, and frequently those with peripheral artery disease (PAD).[14] Infection follows colonisation of the wound by a complex microbiological flora. Wound colonisation by bacteria is a constant phenomenon, defined by the presence of bacteria on a wound surface, but without evidence of invasion of the host tissues. Wound infection is a pathological state caused by the invasion and multiplication of microorganisms in host tissues that induce an inflammatory response, usually followed by tissue damage. Since all wounds are colonised (often with potentially pathogenic microorganisms), wound infection cannot be defined using only the results of wound cultures. Instead, DFIs are defined clinically, based on the presence of manifestations of an inflammatory process involving a foot wound located below the malleoli. In persons with diabetes-related foot complications, signs and symptoms of inflammation may, however, be masked by the presence of peripheral neuropathy, peripheral artery disease (PAD), or immune dysfunction. A patient with diabetes-related complications may need to undergo a lower extremity amputation to control infection, or develop multiorgan failure, without local clinical signs that define a DFI, but this is highly uncommon. While rarely the primary cause of foot ulcers, the presence of PAD increases the risk of an ulcer becoming infected[15-18] and adversely affects the outcome of infection.[15,19,20] Because the combination of infection with PAD is associated with a markedly increased risk of poor healing and amputation, clinicians should evaluate the state of wound perfusion and the potential need for a revascularisation procedure as soon as possible in all patients with a DFI.[7]

Factors that predispose to foot infection include: having a wound that is deep, long-standing, recurrent, or of traumatic aetiology; the presence of diabetes-related immunological perturbations, particularly neutrophil dysfunction; or, having concomitant chronic renal failure.[17,19-24] Although examined in only a few studies, a history of chronic hyperglycaemia may predispose to DFIs, and the presence of hyperglycaemia at presentation may suggest a rapidly progressive or destructive (necrotising) infection.[25,26]

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscles, joints, and bones. The anatomy of the foot, which is divided into several separate but intercommunicating compartments, fosters the proximal spread of infection.[27] The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischaemic tissue necrosis in the affected compartment and thereby progressive infection.[28,29] The tendons within the compartments facilitate the proximal spread of infection, which usually moves from higher to lower pressure areas. Bacterial virulence factors may also play a role in these complex infections.[30,31] Systemic symptoms (e.g., feverishness or chills), marked leukocytosis, or major metabolic disturbances, are uncommon in patients with a DFI, but their presence denotes a more severe, potentially limb-threatening (or even life-threatening) infection.[4,32,33] If not quickly diagnosed and properly treated, DFIs tend to progress, sometimes rapidly.[34] Thus, an experienced medical specialist (or team) with experience in infectious diseases should evaluate a patient with a severe DFI within 24 hours.[35] Accumulations of purulent secretions, especially if under pressure or associated with necrosis, require prompt (usually within 24 hours) surgical decompression and

drainage. Although bone and/or joint resection (preferably using a conservative approach, with limited resection and avoiding amputation, if possible) may be required for successfully treating osteomyelitis, it is usually an infection of the soft tissues that requires urgent antimicrobial therapy and surgical intervention.

This document aims to provide a comprehensive, evidence-based overview of guidelines for the diagnosis and treatment of foot infections in people with diabetes. These are intended to be of practical use for treating clinicians, based on all available scientific evidence.

METHODOLOGY

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used for developing this guideline.[36] This is structured around identifying key clinical questions in the PACO (Population, Assessment, Comparison, Outcome) and PICO (patient/population, intervention, comparison, outcomes) format, determining patient-important outcomes, presenting the evidence, assessing the certainty of the evidence, and finally moving from evidence to recommendation.

The IWGDF editorial board appointed a multidisciplinary working group of independent experts (the authors of this guideline) to update the previously published 2019 guidelines. In addition, three members were delegated by the IDSA to join the committee.

The key clinical questions were developed by revising the 2019 guideline PICOs and refining each component to reflect clinical relevance. Guidance is aimed at clinicians and other healthcare professionals involved in the diagnosis and management of DFIs. Patient important outcomes were generated and then classified based on their importance for decision-making. Outcomes defined by Jeffcoate et al were also used as a reference guide.[37] All members voted on the outcomes, and those identified by consensus as "critically important" were included. The editorial board reviewed and approved the final set of P(A)ICOs through a consultation process with external experts from various geographical regions and the IDSA.

The committee members then systematically reviewed the literature to address the set of pre-specified P(A)ICOs. The two updated IWGDF systematic reviews supporting this guideline have been completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which will be published separately.[38] The updated protocols are available from PROSPERO (CRD42022324795, CRD42022324812).[39,40]

After careful weighing of the summary of judgements, the same teams of two members of the working group determined the direction, strength, and wording of the recommendation(s) for the specific clinical question. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Recommendations were rated as 'for' or 'against' the particular intervention or 'either the intervention or the comparison', and the strength of each recommendation was rated as 'strong' or 'conditional'. The certainty of evidence, rated as 'high',

'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE, as explained above, was added to the strength of the recommendation.

Summary of judgements tables and recommendations for each question were extensively discussed in online meetings of the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention (or 'either the intervention or the comparison'), and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the summary of judgement tables in the supplemental information of the guideline documents.

Based on the summary of judgement tables, the rationales for the recommendations were written by the same team of two assessors of the working groups. These rationales are narrative (systematic) descriptions of how the working group came to the direction and strength of the recommendation and summarizes the research evidence for the items in the summary of judgement tables.[36,41] In addition, expert opinion and aspects relevant to communicate to the reader regarding the intervention or recommendation can be added to these rationales.

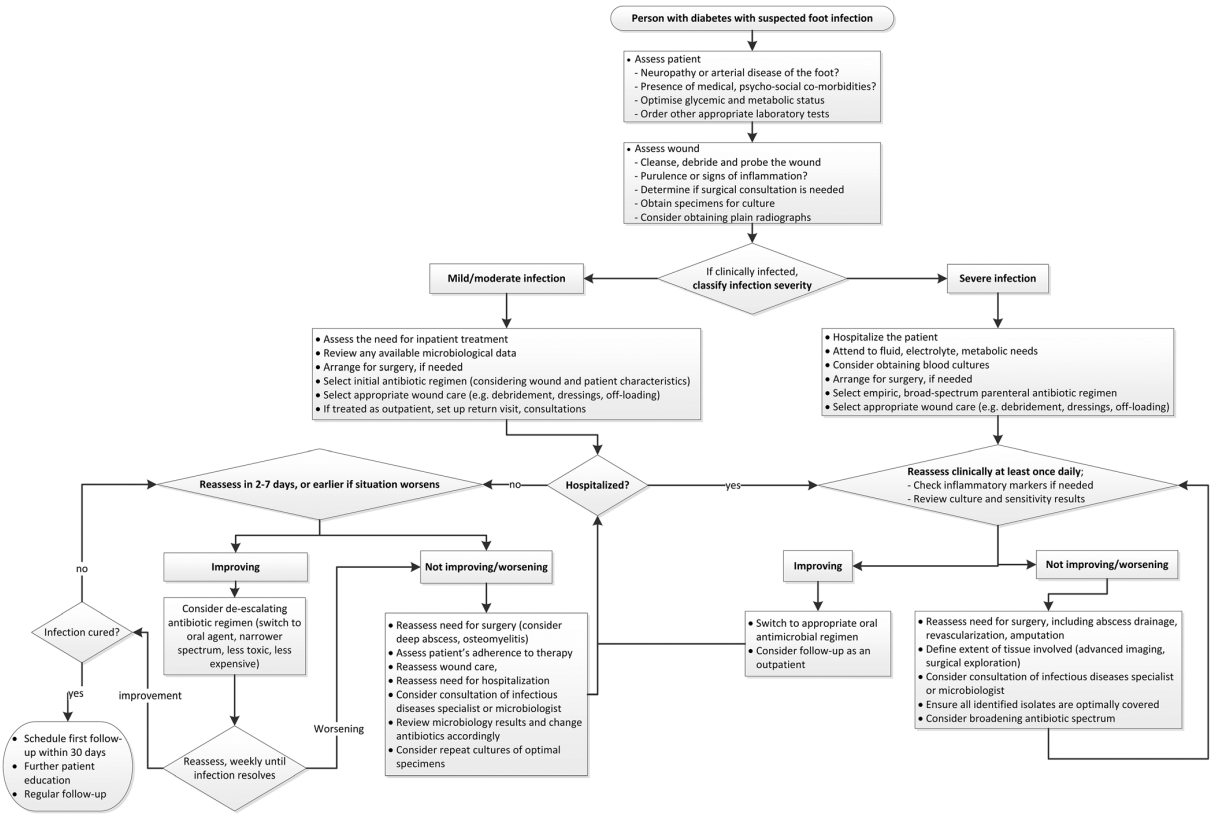
Finally, all recommendations, with their rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same international external experts and persons with lived experience who reviewed the clinical questions and outcomes, as well as by the IWGDF Editorial Board. The working group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline.

In the publication "Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guideline" the details of the methodology for the development of this guideline are described.[42]

RECOMMENDATIONS

See Figure 1 for a synthesising overview of the overall diagnosis and management of patients with diabetes-related foot infections including diabetes-related osteomyelitis of the foot.

Figure 1: an overview of the diagnosis and management of patients with diabetes-related foot infections (from Lipsky et al.[13])



Remark: perform non-invasive bedside test for PAD

DIAGNOSIS

Clinical question: Can the International Working Group of the Diabetic Foot/Infectious Diseases Society of America (IWGDF/IDSA) classification system for foot infections in persons with diabetes predict the outcome of such an infection?

Recommendation 1:

a. Diagnose a soft tissue diabetes-related infection clinically, based on the presence of local or systemic signs and symptoms of inflammation. (Strong; Low)
b. Assess the severity of any diabetes-related foot infection using the IWGDF/IDSA classification scheme. (Strong; Low)

Rationale: The clinician seeing a patient with diabetes and a foot ulcer should always assess for the presence of an infection and, if present, classify the infection's severity.[43,44] Experts have proposed many classification schemes for DFU, many of which only include the presence or absence of "infection".[9] Previous prospective and retrospective studies have validated all or part of the IWGDF/IDSA DFI classification as part of a larger diabetes-related foot classification system (PEDIS) (see Table 1).[15,16] Other classifications for severe infection, eg, National Early Warning Score (NEWS)[45,46] or quick sequential organ failure assessment (qSOFA)[47], were developed for the identification or prediction of outcomes in patients with sepsis. There are, however, no data to support changing from using the systemic inflammatory response syndrome (SIRS) that is part of the IWGDF/IDSA classification to any other classification for DFIs. Two commonly used classifications for DFUs, Wound, Ischemia, and foot Infection (WIfI), and Site, Ischaemia, Neuropathy, Bacterial Infection, and Depth (SINBAD), which use the IWGDF/IDSA classification for the infection component, have been validated with patient data.48,49

Importantly, in the current guideline, we define a DFI based on the presence of evidence of (a) inflammation of any part of the foot, not just of an ulcer, or (b) findings of SIRS. Because of the important diagnostic, therapeutic, and prognostic implications of osteomyelitis, we separate it out by indicating the presence of bone infection with "(O)" after the grade number (3 or 4) (see Table 1). We did not use the term osteitis, which would be an infection of the cortical bone only, without involvement of the medulla. Although the pathogens enter the bone through contiguous spread from an ulcer to the cortex and not by haematological spread to the medulla, it is hard to distinguish cortical bone infection from medullary bone infection clinically, by imaging or by histology. Also, we think the two entities do not require separate therapeutic interventions. We therefore decide to use the term osteomyelitis for both disease entities.

In our systematic review on diagnosis of infection of the foot in persons with diabetes[50], new studies with a high risk of bias were identified that examined the outcomes of interest.[51-55] The main questions addressed concerned whether there should be modifications of the current IDSA/IWGDF classification by combining the moderate and severe categories and considering risk categories according to soft tissue infections or osteomyelitis. Insufficient quality of evidence led us to not consider either laboratory risk indicators for necrotizing fasciitis or systemic inflammatory response syndrome as reliable tools for predicting lower extremity amputation, mortality, or other health outcomes.[53,54] In the absence of

additional validation studies, and moderate certainty attributed to the risk of bias, we elected not to alter the IDSA/IWGDF classification, as shown in Table 1.

Defining infection of the foot in persons with diabetes is of utmost importance, given the possible negative consequences of missing this diagnosis. Additionally, distinguishing infected from non-infected wounds may help avoid the unnecessary use of antibiotics in the absence of an infection. Although based on low quality of evidence, but given the major impact the use of the IWGDF/IDSA classification may have on outcome and antibiotic use in persons with DFIs, we made a strong recommendation.

Table 1: The classification system for defining the presence and severity of an infection of the foot in a person with diabetes[a]

Clinical classification of infection, definitions	IWGDF/IDSA classification
No systemic or local symptoms or signs of infection	1 / Uninfected
Infected: At least two of these items are present: • Local swelling or induration • Erythema > 0.5 but < 2 cm[b] around the wound • Local tenderness or pain • Local increased warmth • Purulent discharge And, no other cause of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-arthropathy, fracture, thrombosis, or venous stasis)	2 / Mild
Infection with no systemic manifestations and involving: • erythema extending ≥ 2 cmb from the wound margin, and/or • tissue deeper than skin and subcutaneous tissues (e.g., tendon, muscle, joint, and bone)	3 / Moderate
Infection involving bone (osteomyelitis)	Add "(O)"
Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome [SIRS]), as manifested by ≥ 2 of the following: • temperature, > 38°C or < 36°C • heart rate, > 90 beats/min • respiratory rate, >20 breaths/min, or PaCO2 < 4.3 kPa (32 mmHg) • white blood cell count >12,000/mm^3, or < 4G/L, or > 10% immature (band) forms	4 / Severe
Infection involving bone (osteomyelitis)	Add "(O)"

Note: The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

[a] infection refers to any part of the foot, not just of a wound or an ulcer.

[b] in any direction, from the rim of the wound.

[c] if osteomyelitis is demonstrated in the absence of ≥ 2 signs/symptoms of local or systemic inflammation, classify the foot as either grade 3(O) (if <2 SIRS criteria) or grade 4(O) if ≥ 2 SIRS criteria) (see text).

Recommendation 2: Consider hospitalising all persons with diabetes and a foot infection who have either a severe foot infection as classified by the IWGDF/IDSA classification, or a moderate infection which is associated with key relevant morbidities. (Conditional; Low)

Rationale: Regarding the decision to hospitalise a patient with a DFI, the IWGDF/IDSA infection classification system facilitates risk stratification to inform this decision.[4] Hospitalisation is an expensive and finite resource and may subject the patient to major inconvenience and potential nosocomial risks. But while many patients with a DFI do not need to be hospitalised, some certainly should be. Consideration should be given to hospitalise all persons with a severe foot infection to ensure timely and effective management, as well as those with a moderate infection associated with key relevant co-morbidities, in particular, PAD (see details in Table 2). This is due to a higher risk of poor outcomes in these cases, especially amputation or death.[4, 17-19]Of note, the presence of osteomyelitis does not necessarily require hospitalisation, since many of these patients are clinically stable and can be treated with oral antibiotic agents. Hospitalisation may be preferable (at least initially) in those patients who require intravenous antibiotic therapy, have substantial associated soft tissue infection, require special diagnostic testing, or need urgent surgical treatment. Fortunately, almost all patients with a mild infection, and many with a moderate infection but without any key relevant morbidities, can be treated in an ambulatory setting. The availability of home parenteral antibiotic programs in some countries is another site-dependent factor that influences the need for hospitalisation.

Most published studies of DFIs have enrolled hospitalised patients, but over the past two decades, several have reported good results with outpatient treatment.[52-54] It is therefore of utmost importance to correctly assess the infection severity as the patient management significantly differs from oral antibiotic treatments to complex combinations of surgery and parenteral broad-spectrum antibiotic regimens. Given the low certainty of the evidence, with inconsistency between studies, and that differences in patient characteristics as well as health care policies between countries will influence the decision to hospitalise, we made a conditional recommendation.

Table 2: Characteristics suggesting a more serious diabetes-related foot infection and potential indications for hospitalisation.[4, 17-19]

A. Findings suggesting a more serious diabetes-related foot infection	
Wound specific	
Wound	Penetrates to subcutaneous tissues (e.g., fascia, tendon, muscle, joint, or bone)
Cellulitis	Extensive (>2 cm), distant from ulceration, or rapidly progressive (including lymphangitis)
Local signs / symptoms	Severe inflammation or induration, crepitus, bullae, discoloration, necrosis or gangrene, ecchymoses or petechiae, and new anesthesia or localised pain
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic	Fever, chills, hypotension, confusion, and volume depletion
Laboratory tests	Leukocytosis highly elevated C-reactive protein, or erythrocyte sedimentation rate, severe or worsening hyperglycemia, acidosis, new/worsening azotaemia and electrolyte abnormalities tests
Complicating features	Presence of a foreign body (accidentally or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphedema, immunosuppressive illness or treatment, acute kidney injury
Failing treatment	Progression while on apparently appropriate antibiotic and supportive therapy

B. Factors that should lead to considering hospitalisation
Severe infection (see findings suggesting a more serious diabetes-related foot infection above)
Metabolic or haemodynamic instability
Intravenous therapy needed (and not available/appropriate as an outpatient)
Diagnostic tests needed that are not available as an outpatient
Severe foot ischaemia is present
Surgical procedures (more than minor) required
Failure of outpatient management
Need for more complex dressing changes than patient/caregivers can provide
Need for careful, continuous observation

Recommendation 3: Assess inflammatory serum biomarkers such as C-reactive protein, erythrocyte sedimentation rate, or procalcitonin in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable. (Best Practice Statement)

Rationale: Serum tests for inflammatory biomarkers such as white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) are widely available, easily obtained, and most, except PCT, are relatively inexpensive. A few studies investigated other inflammatory markers for their role in diagnosing or following DFIs, but they were small and of low quality.[11] Most available studies assessed the value of these inflammatory biomarkers by comparing them with the results of IDSA/IWGDF criteria for infection.[4,55] Unfortunately, the severity of infection in patients included in the available studies was not always clearly defined, which may account for

interstudy differences in findings. In addition, many studies do not specify if enrolled patients were recently treated with antibiotic therapy, which could affect results. Of particular note is the white blood cell (WBC) level, as it is used as part of the IDSA/IWGDF criteria for classifying infection as severe/grade 4. The available studies[59-64] found little correlation of WBC with infection severity, with about half of the patients diagnosed with a DFI having a normal WBC.[63,64] In most studies, ESR values have been higher in patients with an infected DFU compared with a noninfected DFU.[59,60] ESR values can be affected by various co-morbidities (eg, anaemia and azotaemia) and may not be elevated in acute infections, due to the relatively slow response of this inflammatory biomarker. A highly elevated ESR (≥ 70 mm/h) has a sensitivity, specificity, and AUC for the diagnosis of DFO of 81%, 80%, and 0.84, respectively.[65]

Compared with ESR, CRP levels tend to rise more quickly with infection and fall more quickly with the resolution of infection. Serum values of CRP have consistently been found to be significantly higher in infected than noninfected DFUs and in patients with noninfected DFU than in those with no foot ulcer, with levels increasing significantly with the severity of infection.[65,66] Compared to WBC and ESR, CRP has shown higher diagnostic accuracy for grade 2 (infected) DFU.[66] Studies of serum PCT levels have also found that levels were significantly higher in infected DFU than noninfected DFU, but there was little correlation between the values and the infection severity.[55-57,60,61] The highly variable cut-off values used make it difficult to interpret the results reported in studies that have investigated these inflammatory markers. Due to their limited specificity and sensitivity, not exceeding 0.85, when used as sole diagnostic tools, inflammatory biomarkers should rather be used when uncertainty persists after clinical assessment. We make a Best Practice Statement about the use of ESR, CRP, or PCT due to the potential harms related to potential over or underdiagnosing DFI, with low certainty of evidence based on studies of low quality, with inconsistency about the results and heterogeneity in cut-off values;.

Recommendation 4: For diagnosing diabetes-related foot soft-tissue infection, we suggest not using foot temperature (however measured) or quantitative microbial analysis. (Conditional; Low)

Rationale: While various imaging tests are widely used for diagnosing bone infection (see below), there are few data on their usefulness for soft-tissue infections. Other diagnostic tests studied for assessing DFI include photographic foot imaging and infrared thermography. Several studies with these instruments have examined their value in predicting the occurrence of foot ulcerations. Overall, employing either infrared or digital thermography does not appear to provide substantial help in diagnosing infection or predicting the clinical outcome in patients with a DFU seen in the hospital setting.[67-70] While infrared imaging likely causes no harm, its use is limited by low availability.

Some advocate using the presence of high numbers of bacteria on culture (usually defined as $\geq 10^5$ colony-forming units per gram of tissue) as a basis for differentiating infected from uninfected DFUs.[71,72] However, there is no convincing data (from studies using either conventional culture or molecular methods) supporting this concept.[73] In published studies that assessed the validity of clinical signs for the diagnosis of DFI using microbial analysis as a referent test, the criteria used to define infection varied among the authors, and even between studies conducted by the same team. In some microbial analysis studies, patients receiving antibiotics at the time of the wound sampling (which may suppress bacterial growth and cause diminished organism counts) were included, while others failed to provide information on this important confounding issue. Of note, these methods of measuring what is sometimes called

"wound bioburden" are time-consuming and relatively expensive. Furthermore, neither quantitative classical culture nor molecular quantitative techniques are currently available to most clinicians in their daily care of patients. Our recommendation against these diagnostic methods is based on the limited data to support the use of these time-and resources consuming techniques, which are frequently unavailable, and may lead to overdiagnosing (and unnecessarily treating) IDFU. The recommendation is conditional based on low certainty of evidence.

Clinical question: In a person with diabetes and infection of the foot, which test(s) can best identify the causative pathogen(s), and result in tailored use of antibiotics?

Recommendation 5: In a person with suspected soft tissue diabetes-related foot infection, consider a sample for culture to determine the causative microorganisms, preferably by aseptically collecting a tissue specimen (by curettage or biopsy) from the wound. (Conditional; Moderate)

Rationale: In the great majority of cases, obtaining a specimen (after cleansing and debridement and trying to avoid contamination) for culture from a DFI provides useful information on the causative pathogen(s) and their antibiotic susceptibility, allowing appropriate selection of antibiotic therapy. In cases of an acute, non-severe DFI in a patient who has not recently received antibiotic therapy and has no other risk factors for unusual or antibiotic-resistant pathogens (e.g., based on specific exposures or previous culture results), selecting empiric therapy without culture may be reasonable. In other situations, despite superficial swabs being easier to perform, we advise collecting a soft tissue specimen by superficial swab on the basis of two systematic reviews[70,71] (with low-quality evidence), one small prospective study[72] and one well-designed prospective study,[73] which reported higher sensitivity and specificity of tissue specimens for culture results than superficial swabs. Collecting a tissue specimen may require slightly more training and poses a slight risk of discomfort or bleeding, but we believe the benefits clearly outweigh these minimal risk of harms. The evidence informing which method of specimen collection to use is limited by the absence of a definitive criterion standard for defining ulcer infection.

Repeating cultures may be useful for a patient who is not responding to apparently appropriate therapy, but this may result in isolating antibiotic-resistant strains likely to be contaminants rather than pathogens. A key caveat is that the accuracy of culture results depends on the quality of the information provided between clinical and microbiology staff throughout the sample pathway, from collecting, to transporting, to processing, and to reporting. Clinicians should provide key clinical details associated with the patient and the sample, and clinical microbiology services should provide adequately comprehensive and clear reporting of the isolated organisms and their susceptibility profiles. For persons presenting in a low-income limited resource setting without ready access to culture or follow-up care, performing a Gram-stained smear of material from a DFI could be a relatively easy and inexpensive way to visualize the class of the likely causative pathogens, thus helping direct empiric therapy.[78] The recommendation is conditional with a moderate certainty of evidence based on clinical studies with varying quality, including one large prospective study.

Recommendation 6: Use conventional, rather than molecular, microbiology techniques for the first-line identification of pathogens from soft tissue or bone samples in a patient with a diabetes-related foot infection (Strong; Moderate)

Rationale: Molecular microbiology techniques have demonstrated that the flora in most DFIs is more diverse and abundant than that revealed by conventional culture methods.[79-83] Our systematic review identified 4 recent single-centre prospective studies that compared the results of different non-culture (molecular microbiological) methods to those of conventional culture.[50,84-87] These studies addressed this question in both skin and soft-tissue infections (SSTI) and osteomyelitis of the foot. They consistently found an agreement of more than 0.70 between molecular microbiology and conventional culture methods regarding the most clinically relevant pathogens identified, except for anaerobes, which are more frequently identified by non-culture techniques.[83] The studies also confirmed that non-culture techniques, especially metagenomic next-generation sequencing (NGS), identify more bacteria from tissue samples, including bone, than conventional cultures.[84-87] Currently, the use of metagenomic next-generation sequencing (mNGS) techniques does not lead to a shorter time until pathogen identification, but this might change with the deployment of newer techniques. These techniques may help choose the empirical antibiotic therapy and reduce the risk of inappropriate treatment (i.e., failing to cover bacteria involved, including multiresistant ones). On the other hand, as molecular microbiology techniques are currently unable to distinguish dead from living bacterial cells, there are concerns that they may lead to the unjustified use of broad-spectrum antibiotics. The studies that addressed molecular microbiology for either STI or DFO have included relatively few subjects, were at high risk of bias, and did not provide information on the value of the findings for guidance on clinical management. Specifically, we do not know which of the many bacterial genera identified by molecular methods contribute to the clinical state of infection or require targeted antibiotic therapy. Overall, we acknowledge the essential role of molecular microbiology techniques in the understanding of the pathophysiology of DFIs, and that these are promising techniques for application in clinical practice in the future. We do not, however, recommend their use in daily practice, given the unclear significance of positive results, absence of demonstrated impact on antibiotic treatment, high costs and limited availability. This a strong recommendation against the use of non-culture techniques, based on a moderate certainty of evidence from prospective studies with high risk of bias, the relative high costs and the lack of information to which extent these techniques will influence clinical management. Thus, for now, clinicians should continue to request conventional cultures of specimens to determine the identity of causative microorganisms and their antibiotic sensitivities.

Clinical question: In a person with diabetes and suspected bone or joint infection of the foot, which tests have the best correlation with bone biopsy results for diagnosing diabetes-related osteomyelitis, including residual/postoperative osteomyelitis)?

Recommendation 7: In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and erythrocyte sedimentation rate, or C-reactive protein, or procalcitonin as the initial studies to diagnose osteomyelitis of the foot. (Conditional; Low)

Rationale: The diagnosis of osteomyelitis in the foot of a person with diabetes may be difficult, partly because of a lack of a universally accepted definition or criterion standard, and partly related to low levels of inter-test agreement among commonly used diagnostic tests.[88] Osteomyelitis may be present underlying any foot wound, especially those that have been present for many weeks or that are wide, deep, located over a bony prominence, showing visible bone, or accompanied by an erythematous, swollen ("sausage") toe[89].

Diagnosing bone infection of the foot is of paramount importance, given that its presence greatly increases the risk of minor and major amputations. The investigation of diabetes-related foot wounds suspected of having bone infection usually includes a physical examination and a conventional radiograph, while some blood biomarkers might be of interest; these issues are discussed below. An accurate diagnosis of DFO is essential to initiate appropriate therapy and to avoid unjustified prolonged antibiotic treatment and surgery in patients who do not have a DFO.

a) Probe-to-bone test

Among clinical examinations of the foot, the PTB test is the most useful, but the performing clinician's technique and experience, the ulcer's location, and its aetiology may affect the test's reliability.[90,91] A systematic review of the PTB test found that for detecting DFO the sensitivity was 0.87 and specificity 0.83.[92] Overall, in diagnosing DFO, the PTB test suggests the diagnosis if it is positive in a high-risk patient, and helps rule it out if it is negative in a low-risk patient. The procedure is easy to learn and perform, requiring only a sterile blunt metal probe (gently inserted into the wound, with a positive test defined by feeling a hard, gritty structure), is inexpensive and essentially harmless, but interobserver agreement is only moderate.[93] Of note, if clinicians are not skilled in this test, they should not rely on its results as it may have been performed incorrectly resulting in incorrect results.

b) Plain X-ray

Any patient with a possible bone infection should initially have plain X-rays of the foot. Interpreted by an experienced reader, characteristic findings of bone infection (see Table 3) are highly suggestive of osteomyelitis, but similar abnormal findings can be caused by Charcot osteoarthropathy and other disorders. As plain X-rays are relatively inexpensive, widely available, and cause minimal harm, we recommend them as part of the routine assessment of patients presenting with a diabetes-related foot infection. This imaging exam provides useful information, especially about the status of the underlying osteoarticular tissues, the presence of gas in deep tissues, and the presence of any radio-opaque foreign body. In addition, the image can be used as a reference against which to compare new images if the patient presents with another foot problem. Because plain X-rays are insensitive to acute osteomyelitis, it is often useful to repeat a normal examination in 2 to 3 weeks when suspicion of osteomyelitis is still high.[94] A retrospective study of patients with histologically proven DFO found that after adjusting for confounders, inflammatory biomarkers, and plain X-rays were actually more useful than magnetic resonance imaging (MRI).[95] Because interpretation of plain X-rays can be difficult (even for an experienced reader) when non-infectious changes (especially those related to neuro-osteoarthropathy) are present, advanced imaging techniques or even bone culture may ultimately be needed to confirm or exclude osteomyelitis in the foot.

c) Serum biomarkers

In a systematic published in 2019, it was found that ESR ≥70mm/hr had a sensitivity, specificity, and AUC of 0.81, 0.8 and 0.84 respectively while the value of PCT could not be assessed due to paucity of the data.[65] A more recent systematic review and meta-analysis published in 2022 found that PCT had the highest diagnostic test accuracy when compared to that of ESR, WBC and ESR with a sensitivity, specificity, and AUC of 0.85, 0.67 and 0.844 at a cut-off value of 0.33ng/mL.[66]

Given the lack of inter-operator variability, the use of either ESR, CRP, and PCT as a sole biomarker for the detection of DFO in a patient with soft tissue DFI is not appropriate but their use in combination with other diagnostic tests may be useful.[50,96] Two recent large-scale retrospective single-centre studies with high risk of bias that used the results of culture and/or histology of bone samples as a reference standard found that ESR > 60 mm/Hr plus CRP ≥ 80 mg/L had a high positive predictive value, but a modest negative predictive value, for the diagnosis of DFO. They also found that the combination of elevated ESR (>43 mm/h) with a positive PTB test showed a high correlation with having positive bone culture and/or histology results.[97,98] Overall, neither plain X-rays, inflammatory biomarkers (ESR, CRP and PCT), nor probe-to-bone test can one their own solely and reliably rule in or rule out the diagnosis of DFO. When diagnostic doubt persists after the clinical assessment and review of plain X-rays of the foot, we recommend testing for ESR, CRP or PCT. This recommendation is, however, conditional because of the risk of over or under-diagnosis of bone infection, based on a low quality of evidence with inconsistency in the data on diagnostic accuracy results.

Table 3: Features characteristic of diabetes-related osteomyelitis of the foot on plain X-rays

- New or evolving radiographic featuresa on serial radiographsb, including:
  - Loss of bone cortex, with bony erosion or demineralisation
  - Focal loss of trabecular pattern or marrow radiolucency (demineralisation)
  - Periosteal reaction or elevation
- Bone sclerosis, with or without erosion
- Abnormal soft tissue density in the subcutaneous fat, or gas density, extending from skin towards underlying bone, suggesting a deep ulcer or sinus tract
- Presence of sequestruma: devitalized bone with radiodense appearance separated from normal bone
- Presence of involucrum: layer of new bone growth outside previously existing bone resulting, and originating, from stripping off the periosteum
- Presence of cloacaea: opening in the involucrum or cortex through which sequestrum or granulation tissue may discharge

[a] some features (e.g., sequestrum, involucrum, and cloacae) are seen less frequently in diabetes-related foot osteomyelitis than in younger patients with osteomyelitis of larger bones

[b] usually spaced several weeks apart

Recommendation 8: Perform magnetic resonance imaging when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings. (Strong; Moderate)

Recommendation 9: Consider using positron emission tomography, leukocyte scintigraphy or single photon emission computed tomography as an alternative to magnetic resonance imaging for the diagnosis of diabetes-related osteomyelitis of the foot. (Conditional; Low)

Rationale: Depending on the patient setting, advanced imaging for diagnosing osteomyelitis is not needed in many patients. When needed, magnetic resonance imaging (MRI) has been the most commonly ordered advanced imaging technique to diagnose DFO, with moderate costs (but about 10 times higher than that of plain X-rays) and wide availability in high-income countries. Besides being used

as a (very sensitive) diagnostic tool, MRI gives a good overview of the anatomy of soft tissues as well as bones and joints, which can be of aid for detecting pre-operatively any purulent collections or the extent of bone involvement. Among advanced imaging techniques, MRI has been the most studied, is associated with lower costs than some other advanced imaging technique and gives an overview of the presence and extent of both soft tissue and bone infections in the foot.[99,100] It is important to note that the presence of reactive bone marrow oedema from non-infectious pathologies, such as trauma, previous foot surgery or Charcot neuroarthropathy, lowers its specificity and positive predictive value.[101,102] In selected patients with possible neuro-osteoarthropathy, newer techniques such as MR angiography, dynamic contrast-enhanced MRI or neurography may better distinguish Charcot arthropathy from osteomyelitis.[103-106] The accuracy of MRI findings can be improved by using the results of a second read by an expert musculoskeletal radiologist.[107]Another finding likely to augment the sensitivity of MRI for the diagnosis of DFO is the detection of an increased ratio of marrow region of interest (ROI) / joint fluid ROI on T2/ Short Tau Inversion Recovery (STIR) sequences.[108] A systematic review and meta-analysis that compared the diagnostic accuracy of imaging tests (plain X-rays, scintigraphy, MRI, single photon emission computed tomography (SPECT) and positron emission tomography (PET)) for the diagnosis of DFO showed that ^{18}F-fluorodeoxyglucose (FDG)–PET and ^{99}mTc- exametazime Hexa Methyl Propylene Amine Oxime (HMPAO) labeled WBC scintigraphy offer the highest specificity (0.92 for both).[109] In patients with a contraindication to MRI, clinicians may choose other imaging techniques (e.g., FDG-PET/CT, HMPAO-labelled leukocyte scintigraphy or 99mTc labeled Ubiquicidin (UBI) SPECT/CT). [109-114]

Compared to nuclear (e.g., leukocyte) imaging, positron emission tomography (PET), especially combined with CT scan, offers high spatial resolution, precise anatomic localization, possibly higher sensitivity for chronic infection, easier performance, faster results, and low radiation exposure. Overall, the available studies that compared the diagnostic accuracy of MRI and nuclear imaging techniques in patients with a suspicion of DFO show conflicting results. [106-109-]MRI and FDG PET/CT have several advantages compared to other anatomical and functional imaging methods, including short acquisition time, high resolution, low radiation dose, and better tolerability.[112] The availability and cost of these advanced imaging techniques may vary in different geographic locations, but they might be useful in situations when the diagnosis remains in doubt, and when there are limited options to obtain a bone biopsy.

For the diagnostic accuracy of advanced imaging in DFO, the overall certainty of the evidence is moderate because of serious inconsistency, imprecision, and indirectness of results in the included studies. Although certainty of evidence was moderate, a strong recommendation is made regarding MRI use in DFO because of the high accuracy in results, especially regarding the information on both soft tissue and bone and joint structures. Despite certainty of evidence being moderate, a conditional rather than a strong recommendation is made regarding SPECT/CT & PET/CT use in DFO because of the lack of accessibility and feasibility of this modality and the great resources and expertise required to implement this technique.

Recommendation 10: In a person for whom there is suspicion of osteomyelitis of the foot (before or after treatment), consider obtaining bone (rather than soft tissue) samples for culture, either intraoperatively or percutaneously. (Conditional; Moderate)

Rationale: Obtaining a specimen of bone to diagnose osteomyelitis is the generally accepted criterion standard for diagnosing the infection, and the only definitive way to determine the causative pathogen(s). Bone biopsy is, however, usually not performed in most cases of suspected DFO due to the absence of a health care professional adequately trained to perform the procedure and/or the fear of possible adverse effects, especially fracture or induced infection of the bone.[115] Published studies consistently report a low correlation between bone and non-bone culture results , most < 50%, with the highest correlation for *Staphylococcus aureus*.[116-118] This is of potential importance, as incorrect identification of the bone pathogens could increase the risk of treatment failure, although this has only been reported in one published study.[119] An ongoing multicentre, prospective, randomised study (BonE BiOPsy (BeBoP) trial) is designed to determine if treatment outcomes of DFO differ depending on the chosen diagnostic strategy, i.e., a culture of bone versus one of wound.[120]

In order to provide the most accurate assessment of true pathogens, and to avoid contamination of the bone samples by the skin flora, it is important to collect a bone specimen in an aseptic manner (i.e., percutaneously via intact and uninfected skin, or intraoperatively).[116] A prospective direct comparison of 46 paired per-wound versus transcutaneous bone biopsies in patients with suspected DFO found that results were identical in only 42%.[121] To avoid a false-negative culture, some experts suggest delaying bone biopsy in a patient who is receiving antibiotics until they have been off therapy for at least a few days, and ideally for at least 2 weeks. This is still a matter of debate, and the optimal duration of any antibiotic-free period before the biopsy is not known. In recent studies a history of prior antibiotic therapy was associated with an increased likelihood of false negative bone culture.[123,124] Available published studies have established that obtaining percutaneous and intraoperative bone biopsies are both safe. A percutaneous biopsy is generally not painful (as the majority of affected patients have sensory neuropathy, and local anaesthetics can be offered), and complications are rare.[117,118] Obtaining a bone sample generally requires the services of a surgeon or radiologist, but recent studies suggest it can be performed safely at the bedside by any trained medical caregiver.[124,125] Bedside percutaneous biopsy may make it easier to obtain a bone culture when operating/imaging facilities are not feasible or available. Of note, bone biopsy may not be needed if an aseptically collected specimen from a deep soft tissue infection grows only a single virulent pathogen, especially *S. aureus*.[11] Culture of bone has the advantage of determining the causative pathogen, but histology may be more sensitive if the patient is on antibiotic therapy, and more specific if specimen contamination is a concern.

Several studies have shown one- to two-thirds of patients who undergo bone resection and from whom the surgeon obtains a sample of retained bone (variously called "marginal," "distal," or "proximal" bone) that appears clinically uninfected will have culture or pathological evidence of residual infection.[126-130] The possibility that many of the theses positive residual bone cultures are false positives is supported by the finding of a substantially lower rate of positive histology on the same specimen in two studies.[129-130] Of note, cultures may also be falsely negative, especially in patients treated with antibiotics or when samples are not appropriately transported to and processed by the microbiology laboratory. The low inter-rater agreement among pathologists on the diagnosis of osteomyelitis by histopathology[131], and the weak concordance between histopathology and culture of foot bone specimens[128], are subjects of debate.[132] This question was addressed in two more recent studies, but these also provide conflicting results. [133,134]

Since there are no available data demonstrating a clear benefit of using bone biopsy results on the outcome of patients treated for a DFO, and facilities for obtaining bone biopsy are not always available, our recommendation for undertaking a bone biopsy in patients with a suspicion of DFO was graded "conditional". The certainty of the evidence is moderate, based on several retrospective studies with consistency in the results regarding the diagnostic accuracy of bone cultures compared to no-bone cultures and the safety of the procedure established in these studies.

TREATMENT

Clinical question: In a person with diabetes and a soft-tissue infection of the foot which specific antibiotic regimen (specific agent[s], route of administration, duration of therapy) should be chosen when taking into account the resolution and recurrence of infection, and the acquisition of antimicrobial resistance?

Recommendation 11: Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy when the goal is to reduce the risk of new infection, or to promote ulcer healing. Best Practice Statement

Recommendation 12a: Use any of the systemic antibiotic regimens that have shown to be effective in published randomised controlled trials at standard (usual) dosing to treat a person with diabetes and a soft tissue infection of the foot. (Strong; High)

Recommendation 12b: Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1 to 2 weeks. (Strong; High)

Recommendation 12c: Consider continuing treatment, perhaps for up to 3 to 4 weeks, if the infection is improving but is extensive and is resolving slower than expected or if the patient has severe peripheral artery disease. (Conditional, Low)

Recommendation 12d: If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient, and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low)

Recommendation 13: Select an antibiotic agent for treating a diabetes-related foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of the efficacy of the agent for infections of the diabetes-related foot; risk of adverse events including collateral damage to the commensal flora; the likelihood of drug interactions; agent availability and, costs. Best Practice Statement

Recommendation 14: Target aerobic gram-positive pathogens only (beta-haemolytic streptococci and *Staphylococcus aureus* including methicillin-resistant strains if indicated) for people with a mild diabetes-related foot infection, who have not recently received antibiotic therapy, and who reside in a temperate climate area. Best Practice Statement

Recommendation 15: Do not empirically target antibiotic therapy against Pseudomonas aeruginosa in cases of diabetes-related foot infection in temperate climates, but use empirical treatment of *P. aeruginosa* if it has been isolated from cultures of the affected site within the previous few weeks in a person with moderate or severe infection who resides in tropical/subtropical climates. Best Practice Statement

Rationale: In our systematic review we could not identify data supporting the concept that prescribing antibiotic therapy for clinically uninfected ulcers either accelerates healing or reduces the risk of developing clinically apparent infection.[135] Since cultures of such open wounds will usually reveal microorganisms, including some that are commonly considered pathogens, this does not mean it is infected. As about half of all DFUs are clinically uninfected at presentation, prescribing antibiotic therapy for these could result in a substantial exposure of patients to potentially unnecessary and often harmful treatment.[136] We strongly believe that for patients with a clinically uninfected ulcer, the potential harms (to the patient, the health care system, and society as a whole) of antibiotic therapy (adverse effects of antibiotic therapy, inconvenience to the patient, cost for the drug, and likelihood of driving antibiotic resistance) outweigh any theoretical (but unproven) benefits.

Based on many studies (most limited by methodological flaws) that compared various oral or parenteral antibiotic agents in patients with DFI, treatment with any appropriately selected agent of most classes of antibiotics by either route is effective in the great majority of cases.[137-143] The choice of an antibiotic regimen should be based on the:

- likely or proven causative pathogen(s) and their antibiotic susceptibilities,
- availability of the antibiotic,
- published evidence of efficacy of the agent for DFIs,
- clinical severity of the infection
- experience of the treating team and presence of local protocols,
- presence of patient related factors, including a history of drug allergies, recent hospitalisation, and comorbidities such as impaired kidney function or renal dialysis,
- likelihood of adverse events or potential drug interactions,
- risk of collateral damage to the commensal flora,
- costs (see our propositions for the antibiotic therapy in Table 4).

Table 4: Proposals for the empirical antibiotic therapy according to clinical presentation and microbiological data (from Lipsky et al. [11])

Infection severity	Additional factors	Usual pathogen(s)[b]	Potential empirical regimens[c]
Mild	No complicating features	GPC	Semisynthetic penicillinase-resistant penicillin (cloxacillin) 1st generation cephalosporin (cephalexin)
	ß-lactam allergy or intolerance	GPC	Clindamycin; Fluoroquinolone (levo/moxi-floxacin);trimethoprim-sulfamethoxazole; doxycycline
	Recent antibiotic exposure	GPC + GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin /clavulanate, ampicillin/sulbactam)

			Fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole
	High risk for MRSA	MRSA	Linezolid; trimethoprim-sulfamethoxazole; clindamycin; doxycycline, Fluoroquinolone (levofloxacin, moxifloxacin)
Moderate or severe[d]	No complicating features	GPC ± GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin /clavulanate, ampicillin/sulbactam) 2nd , 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone)
	Recent antibiotics	GPC ± GNR	ß-lactam- ß lactamase inhibitor2 (ticarcillin /clavulanate, piperacillin/tazobactam) 2nd , 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone) group 1 carbapenem (ertapenem) ; (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including Pseudomonas sp.	ß-lactam- ß lactamase inhibitor2 (ticarcillin /clavulanate, piperacillin/tazobactam) semisynthetic penicillinase-resistant penicillin (cloxacillin) + ceftazidime or ciprofloxacin group 2 carbapenem (mero/imi-penem)
	Ischaemic limb/necrosis/gas forming	GPC ± GNR ± strict Anaerobes	ß-lactam- ß lactamase inhibitor1 (amoxicillin /clavulanate, ampicillin/sulbactam) or ß-lactam- ß lactamase inhibitor2 (ticarcillin /clavulanate, piperacillin/tazobactam) Group 1 (ertapenem) or 2 (mero/imi-penem) carbapenem 2nd (cefuroxime) /3rd (cefotaxime, ceftriaxone) generation cephalosporin + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides (vancomycin, teicoplanin); llLinezolid; daptomycin; fusidic acid, trimethoprim-sulfamethoxazole; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenem (erta/mero/imi-penem); Fluoroquinolone (ciprofloxacin); Aminoglycoside (amikacin); colistin

Abbreviations: GNR, gram-negative rod; GPC, gram-positive cocci (staphylococci and streptococci); MRSA, methicillin-resistant *Staphylococcus aureus* ; ESBL: extended-spectrum ß-lactamase

[a] Recommendations are based upon theoretical considerations and results of available clinical trials.

[b] Refers to isolates from an infected foot ulcer, not just colonization at another site.

[c] Given at usual recommended doses for serious infections. Where more than one agent is listed, only one of them should be prescribed, unless otherwise indicated. Consider modifying doses or agents selected for patients with comorbidities such as azotaemia, liver dysfunction, obesity.

[d] Oral antibiotic agents should generally not be used for severe infections, except as follow-on (switch) after initial parenteral therapy.

High risk for MRSA: previous MRSA infection or colonisation

MRSA risk factors: prolonged hospitalization, intensive care admission, recent hospitalization, recent antibiotic use, invasive procedures, HIV infection, admission to nursing homes, open wounds, hemodialysis, discharge with long-term central venous access

Note: antibiotics enclosed in brackets are cited as examples

With appropriately selected antibiotic therapy (combined with any necessary surgery and proper metabolic control and wound care), most DFIs can be treated successfully, with limited treatment-related harms.[142-144] In case of mild infections, the most likely causative organisms are gram-positive pathogens (beta-haemolytic streptococci and *S. aureus*).[11] For these mild infections, there is also time to adjust the antibiotic therapy if cultures reveal resistant organisms or those that are not gram-positive cocci. If the infection does not resolve, therapy should be adjusted to target the bacteria cultured from the submitted specimens. Proposals for the empirical antibiotic therapy of moderate or severe DFIs are presented in Table 4. *Pseudomonas* species are less commonly isolated in studies from North America and Europe, but are more prevalent in studies from (sub)tropical climates.[138] In light of the complexity and often polymicrobial nature of DFI, definitive treatment should especially be based on principles of antibiotic stewardship: infection source control with surgery if possible; preferably starting with empiric antibiotic treatment, when appropriate, with the narrowest spectrum, shortest duration, fewest adverse effects, safest and least expensive route; and, switching to targeted (preferably oral) antibiotic therapy with agents based on the cultured pathogens.[139]

As the pathogenic versus colonising role of some bacteria identified in a wound sample, such as *Corynebacterium* sp. or coagulase-negative staphylococci, is debateable, the quality of the sample sent to the laboratory is of utmost importance. The goal is to avoid the presence of colonisers in the sample, thereby limiting the risk of unjustifiably prescribing broad-spectrum antibiotic agents. Clinicians should consider consulting an infectious diseases/ microbiology expert about antibiotic therapy for difficult cases, such as those caused by unusual or highly resistant pathogens.

No antibiotic class or agent has been found to be superior to others for treating DFIs except in two studies, one of which found tigecycline to be significantly worse than ertapenem [140], and another that found ertapenem to have a slightly lower clinical cure rate than piperacillin-tazobactam [141] Two recent retrospective studies[142,143], and one systematic review of RCTs[144], all confirmed our previous recommendations regarding the absence of evidence to recommend any specific antibiotic choice regarding its efficacy and the final cure of infection. In a country with a high prevalence of multi-resistant pathogens, the use of carbapenems was identified as an independent predictor of need for a major amputation, and use of vancomycin was an independent predictor of reinfection or death in one study. [145] But, as these antibiotics are often used in more severe or non-responsive cases, it is difficult to draw clear conclusions.[145]

Given the paucity of data on the resolution of infection, recurrence of infection, and the acquisition of antimicrobial resistance, our recommendation is to choose any of the systemic antibiotics regimens that have shown to be effective in published randomised controlled trials to treat a patient with diabetes and a soft tissue infection of the foot. Antibiotic dosing for skin and soft tissue infection is usually standard, but therapy for DFO may require higher than standard doses. We refer treating clinicians to their national guidelines for dosing advice. We suggest considering beta-lactam antibiotics (penicillins- with or without beta-lactamase inhibitors, cephalosporins, carbapenems), metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, tetracyclines, trimethoprim-sulfamethoxazole, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. Data about new combinations of beta-lactams plus beta-lactamase inhibitors, new lipoglycopeptides such as dalbavancin or oritavancin are insufficient to

make any recommendation on their use in DFIs. The recommendation on how to treat patients with diabetes-related foot infections with these new antibiotics is conditional, based on moderate evidence.

Our systematic review did not find any new studies that justify modifying our previous recommendations about the duration of the antibiotic therapy for soft-tissue DFIs, except for post-surgical debridement of moderate or severe DFIs, for which a 10-day duration was found sufficient in a recent pilot prospective study.[146] Clinicians frequently monitor serum CRP levels during therapy for DFIs, but evidence supporting this is of low quality and based on only one study[147] Compared to our 2019 guideline, in which we advised a duration of 1-2 weeks for any soft-tissue DFIs, we make a conditional recommendation for a 10-day duration of the antibiotic therapy following a surgical debridement for moderate or severe soft tissue DFIs, with low certainty of evidence based on only one study with high risk of bias. For the other situations, we only made a best practice recommendation because of the lack of data from clinical studies on these questions. The specific aspects of the microbiology of DFIs and the potential severity of these infections are key elements that guided our recommendations. Our recommendations are in line with the general rules of the use of antimicrobial agents regarding the choice of the molecules, their way of administration and duration.[139]

Clinical question: In a person with diabetes and a bone or joint infection of the foot, is any particular antibiotic regimen (specific agent[s], route of administration, total and parenteral duration) better than any other regarding the resolution and recurrence of infection?

Recommendation 16: Consider a duration of up to 3 weeks of antibiotic therapy after minor amputation for diabetes-related osteomyelitis of the foot and positive bone margin culture and 6 weeks for diabetes-related foot osteomyelitis without bone resection or amputation. (Conditional; Low)

Rationale: When prescribing antibiotic therapy for DFO, the clinician must consider several issues, in particular achieving a high enough serum level to ensure penetration to bone. It is particularly important to consider the bioavailability for oral agents (i.e., absorption from the gastrointestinal tract into the bloodstream) if that route of therapy is selected. Penetration of antibiotic agents from the blood into bone is variable, but most classes can attain adequate levels in infected bone.[148] We suggest administering antibiotic agents at their upper recommended dosage range, and usually for a total duration of treatment (see Table 5) substantially longer than for soft-tissue infection. Prescribing long-term suppressive antibiotic therapy is generally warranted only for individuals with retained orthopaedic hardware or extensive necrotic bone that is not amenable to complete debridement.

Two randomised controlled studies suggest that the total duration of antibiotic therapy for DFO treated non-surgically does not need to be more than 6 weeks.[149,150] There are only preliminary data available that address the possibility to reduce this duration to less than 6 weeks, but this is currently under study. The duration of antibiotic therapy required for patients with DFO who undergo surgical debridement is likely to be shorter than for patients treated non-surgically. In addition, it is unclear if the level of amputation should play a role in deciding on antibiotic duration. For instance, a patient who undergoes a toe amputation without successful clinical cure can undergo another minor amputation, while a patient who undergoes a total transmetatarsal amputation that fails to responds may need a below-knee amputation. In a prospective, randomized, non-inferiority, pilot trial, patients with DFO who underwent surgical debridement and received either a 3- or 6-week course of antibiotic therapy had similar

outcomes and antibiotic-related adverse events.[151] As treatment with oral antibiotic regimens for residual osteomyelitis are associated with similar failure rates to those with intravenous regimens, this may help reduce the length of hospital stay in those patients.[152] The recommendation about the duration and administration of post-surgical antibiotic therapy is conditional with a low certainty of evidence, based on a few studies with high risk of bias.

Table 5: Duration of antibiotic therapy according to the clinical situation

Infection severity (skin and soft tissues)	Route	Duration
Class 2: mild	oral	1-2 weeks*
Class 3 / 4: moderate / severe	oral/initially iv	2-4 weeks
Bone/joint	Route	Duration
Resected	oral/initially iv	2-5 days
Debrided (soft tissue infection)	oral/initially iv	1-2 weeks
Positive culture or histology of bone margins after bone resection	oral/initially iv	3 weeks
	oral/initially iv	6 weeks
No surgery or dead bone		

*: 10 days following surgical debridement
iv: intravenous

Recommendation 17: Use the outcome at a minimum follow-up duration of 6 months after the end of the antibiotic therapy to diagnose remission of diabetes-related osteomyelitis of the foot. Best Practice Statement

Rationale: It may be difficult to know when DFO has been successfully treated. For a chronic infection that resolves slowly, and frequently recurs if not adequately treated, we prefer initially using the term remission to cure. This is defined as the absence of any persistent or new episode of DFO at the initial or contiguous site but the delay for which a remission should be assessed is uncertain.

In patients with DFO, there are often few clinical signs and symptoms to follow, although resolution of any overlying soft tissue infection is reassuring. A decrease in previously elevated serum inflammatory markers suggests improving infection. Plain X-rays showing no further bone destruction, and better yet signs of bone healing, also suggest improvement. Some of the newer advanced imaging studies, eg, WBC-labelled SPECT/CT, FDG PET/CT, may be more sensitive in assessing resolution of infection. Long-term (typically at least a year) follow-up is classically recommended before declaring the infection cured. Of note, if the underlying conditions that predisposed the patient to the index episode of DFO are not adequately addressed (e.g., pressure off-loading, surgery to correct foot deformity), another infection at the same site may be a new recurrence, rather than a relapse. We think that using an overly long post-treatment period to define remission may result in calling a new episode of DFO associated with a new DFU, thus overestimating the risk of relapse in these cases. We therefore suggest using a minimum follow-up duration of 6 months after the end of the antibiotic therapy to define remission of a DFO. In addition, life-long frequent foot examinations in this population are warranted since most patients with a history of DFI are at high risk for future foot complications.[21]

Clinical question: In a person with diabetes and moderate or severe infection of the foot, including osteomyelitis, are there circumstances in which non-surgical (antibiotic only) treatment is as safe and effective in achieving remission as surgical treatment (combined with antibiotic therapy)?

Recommendation 18: Urgent surgical consultation should be obtained in cases of severe infection or moderate diabetes-related foot infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia. Best Practice Recommendation

Recommendation 19: Consider performing early (within 24-48 hours) surgery combined with antibiotics for moderate and severe diabetes-related foot infections to remove infected and necrotic tissue. (Conditional; Low)

Recommendation 20: In people with diabetes, peripheral artery disease and a foot ulcer or gangrene with infection involving any portion of the foot, obtain an urgent consultation by a surgical specialist as well as a vascular specialist in order to determine the indications and timings of a drainage procedure and/or revascularisation procedure. Best Practice Statement

Rationale: Retrospective studies comparing early surgery (variously defined, but usually within 72 hours of presentation) versus delayed surgery (3-6 days after admission) in hospitalised patients with a severe, deep DFI, with or without osteomyelitis have reported lower rates of major lower extremity amputation and higher rates of wound healing.[153-155] Similarly, patients with moderate or severe DFIs who had a delayed admission at specialised foot centres were more likely to require a major amputation.[156] We think that surgical therapy should always be at least considered in cases of severe DFI, and in other cases for which non-surgical treatment is likely to fail. For such an evaluation, consultation by a surgical specialist is essential, which we therefore formulated a Best Practice Statement. Severe DFIs include those described in the background section of the present paper. Current guidelines on PAD associated with diabetes-related foot highlight that the combination of infection plus PAD portents a poor clinical outcome if both are not treated adequately.[7] Therefore, in case of infection, the patient should be assessed for the presence and severity of PAD. As clinical assessment are often unreliable, it is important to also perform non-invasive tests, e.g., Doppler waveform analysis combined with ankle pressure measurement, as well as toe pressure measurements.[7] Based on the assessment of the wound and the amount of tissue loss, the results of non-invasive tests, and the IWGDF/IDSA infection severity score, all patients should be classified according to the WIfI classification scheme,[9] which helps to further determine the need for a vascular intervention as described in the IWGDF PAD guidelines.[7]

Recommendation 21: Consider performing surgical resection of infected bone combined with systemic antibiotics in a person with diabetes-related osteomyelitis of the foot. (Conditional; Low)

Recommendation 22: Consider antibiotic treatment without surgery in case of (i) forefoot osteomyelitis without an immediate need for incision and drainage to control infection, and (ii) without peripheral artery disease, and (iii) without exposed bone. (Conditional; Low)

Rationale: Surgical resection of infected bone has long been the standard treatment of osteomyelitis, but over the past two decades, evidence from several retrospective case series,[157-159] retrospective cohort studies,[160-162] and one prospective controlled study [163] have demonstrated that in properly selected patients mostly with forefoot DFO, antibiotic therapy alone is as effective as surgery regarding remission of DFO and need for amputation. This suggestion is largely based on studies that have generally not stratified patients with DFO based on the presence or severity of any concomitant soft tissue infection.[164] The studies that have addressed this issue have generally found that patients with DFO who had concomitant soft tissue infection (and perhaps those with peripheral artery disease) required more urgent and extensive surgery, had longer lengths of stay, and had worse outcomes.[165]

The subjects in most studies, specifically in the RCT, were excluded if they obviously needed surgery (e.g., exposed bone, compartment syndrome, undrained abscess) and did not have peripheral artery disease. If perfusion is severely compromised, revascularisation should always be performed (either before or after any soft-tissue/bone resection). In a subsequently well-perfused foot, the treatment of the DFI should not be different. The dilemma will be how to treat a patient with DFO with limited soft tissue infection, seemingly mild ischaemia, and no indication for drainage. Given the unreliability of any vascular assessment, there is a clear risk that the perfusion deficit may be underestimated and any operation could result in a non-healing wound. One small study suggests that patients with a concomitant acute soft-tissue infection and osteomyelitis of the foot not requiring urgent surgical debridement can be treated using a two-step approach consisting firstly of antibiotic therapy for the soft-tissue infection, and secondly, after a free-antibiotic period, bone culture-guided antibiotics for treatment of DFO.[166] Overall, there is inconsistency in results of studies that compared surgical versus medical approaches for DFO between the RCT and the cohort studies, and a high risk of bias (in the cohort studies). The results seem, however, to have no serious imprecision. Compared to the previous guideline, in which strong recommendations were made regarding the indications for predominantly medical versus surgical approaches for DFO, we classified the strength of the recommendation as conditional, due to the low certainty of the evidence of the available data.

Clinical question: In a person with diabetes and a foot infection, does the addition of any specific adjunctive or topical antibiotic treatment to systemic antibiotic therapy and surgery improve the outcome of infection?

Recommendation 23: We suggest not using the following treatments to address diabetes-related foot infections: (a) adjunctive granulocyte colony-stimulating factor treatment or (b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative pressure wound therapy (with or without instillation). Conditional; Low

Rationale: According to systematic reviews[50,115] adding granulocyte colony-stimulating factor (G-CSF) to a diabetes-related foot treatment does not significantly affect the likelihood of resolution of infection, healing of the wound, or the duration of systemic antibiotic therapy. It does seem to be associated with a reduced likelihood of lower extremity surgical interventions (including amputation) and a reduced duration of hospital stay, although the profile of patients who might benefit is unclear, especially in relation to the costs and potential adverse effects.

Various types of topical antiseptics have been used to treat DFUs, but the available evidence does not support any beneficial effect for most of these.[167] Silver has been shown to have an antibacterial effect, and topical silver-containing treatments (creams, dressings, etc..) are widely used for IDFUs. Silver compounds do not offer benefits in ulcer healing (as described in the IWGDF wound healing guidelines[8]) and there is no evidence to support their effectiveness in the treatment of the infectious aspects of a DFU. Topical administration of other agents only seems to have a marginal effect on outcomes of these infections in low-quality studies.[50]

Recommendation 24: We suggest not using topical (sponge, cream, and cement) antibiotics in combination with systemic antibiotics for treating either soft-tissue infections or osteomyelitis of the foot in patients with diabetes. (Conditional; Low)

Rationale: Treatment with topical antimicrobial therapy has many theoretical advantages, particularly requiring only a small dose directly at the site of infection, thus potentially limiting issues of cost, adverse events, and antibiotic resistance. The potential advantage of topical versus systemic antibiotic therapy is to deliver at the site of infection very high concentrations of antibiotics that could not be achieved by using the systemic route of administration. Another potential advantage is to limit potential collateral damage on the gut microflora, including the emergence of multiresistant bacteria and *Clostridioides difficile*-associated diarrhoea.

Studies that have addressed the potential benefit of topical administration of antibiotics as adjunctive treatment to systemic antibiotic therapy for soft-tissue DFIs have provided conflicting results.[167-173] Limited data from studies with high-risk of bias suggest a potential benefit of antibiotic-loaded cement and intraoperative site vancomycin powder application in patients with DFO treated by surgical debridement.[174,177] Overall, these studies, characterised by a potentially high risk of bias, inconsistency, imprecision and low certainty, do not demonstrate a significant clinical benefit of topical antibiotics in the treatment of either diabetes-related foot soft tissue or bone infections. There is also insufficient evidence on whether adjunctive agents meaningfully affect clinical outcome and the safety of routinely using local antibiotics has not yet been clearly established. Therefore, we elected to suggest against the use of topical antibiotics. Future studies should apply learnings from prior studies to ensure statistically robust and clinically useful RCTs.

Recommendation 25: We suggest not using hyperbaric oxygen therapy or topical oxygen therapy as an adjunctive treatment for the sole indication of treating a diabetes-related foot infection. (Conditional; Low)

Rationale: Hyperbaric oxygen (HBO) therapy is often used in an attempt to improve diabetes-related foot ulcer healing, but there are few data on its potential role in controlling infection. The results of one RCT suggested that use of hyperbaric oxygen treatment led to fewer positive wound cultures after treatment, but the study's high risk of bias (small study size, poor quality, non-standardised methods, and non-standardized definitions used) and indirectness of the evidence do not offer support for the use of systemic hyperbaric oxygen in DFI .[50] We found no studies on using topical hyperbaric oxygen for infection upon which to base a recommendation. Equity and feasibility are limited due to high costs and low availability of HBO therapy. In the absence of any substantial data to support its effect in treating either soft tissue or bone infection, or in accelerating ulcer healing via an antimicrobial effect, we think

the costs and inconvenience outweigh any theoretical benefits. The recommendation against the use of HBO therapy for DFIs is conditional given the absence of compelling data on its efficacy, based on low certainty of evidence.

AREAS WITH ABSENT OR INCONSISTENT EVIDENCE

Bioactive glass compounds have been used topically as an adjunctive treatment in surgical cases of DFO, but the insufficient data available prevent us from providing a recommendation on this therapeutic approach.[178,179] Current treatment guidelines do not endorse any specific antibiotic agent for diabetes-related osteomyelitis of the foot, but our systematic review identified two retrospective studies that suggest the addition of rifampicin to combination antimicrobial regimens results in improved cure rates for osteomyelitis.[119,180] The certainty of the evidence is low, based on the inconsistency of outcomes. The potential of drug-related adverse events and the risk of drug-drug interactions, especially in aged patients usually treated with other medications, justify obtaining valid data on its potential benefit before considering its routine use.

KEY CONTROVERSIES

Some areas concerning the management of DFIs still need further development. The following questions are those we found of most interest:

- How and when to determine whether an infection, including soft-tissue and osteomyelitis, has resolved?
- What are the most useful serum biomarkers to help determine if a diabetes-related foot ulcer is infected and if underlying osteomyelitis is present, especially when clinical and imaging assessments are inconclusive?
- To what extent can the currently recommended durations of antibiotic therapy be reduced for soft-tissue and for osteomyelitis?
- When, and which, available advanced imaging studies should clinicians order in a patient with a DFI?
- Does using information from a bone biopsy, including at the amputation site, improve outcomes of DFO?
- What is the place of various new antibiotics in the management of DFIs?
- Is there a definition for, and practical clinical use of, the concept of chronic biofilm infection of a diabetes-related foot ulcer?
- Does molecular (genotypic) microbiological testing for DFI help guide antimicrobial therapy and improve outcomes?
- What is the potential of the topical administration of antimicrobials to limit the use of systemic antibiotics in DFIs?

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CONFLICT OF INTERESTS

The guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and these can be found at *www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies*. No company was involved in the development or review of the guideline. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting on-site.

Working group members were additionally requested to declare COI and refrain from the risk of bias scoring process or voting process for particular interventions if they had a professional working relationship with any of the co-authors on a particular paper.

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AUTHOR CONTRIBUTIONS

ES, EJP, SAV, and ZA participated in the writing of the document, and all the working group members participated in the literature search, the evaluation of the content and quality of the papers selected for the analysis, and the review of the final document.

REFERENCES

(1) International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: *www.diabetesatlas.org*

(2) Raspovic KM, Wukich DK. Self-reported quality of life and diabetic foot infections. J Foot Ankle Surg. 2014;53:716-719.

(3) Peters EJ, Childs MR, Wunderlich RP, Harkless LB, Armstrong DG, Lavery LA. Functional status of persons with diabetes-related lower extremity amputations. Diabetes Care. 2001;24:1799-1804.

(4) Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis. 2007;44:562-565.

(5) Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabet Med. 2018;35:78-88.

(6) Tan TW, Shih CD, Concha-Moore KC, et al. Disparities in outcomes of patients admitted with diabetic foot infections. PLoS One. 2019; 14:e0211481.

(7) Fitridge R, Chuter V, Mills J, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023; in press.

(8) Chen P, Campillo Vilorio N, Dhatariya K, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3644.

(9) Monteiro-Soares M, Hamilton EJ, Russell DA, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3648.

(10) Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004;1;39(7):885-910.

(11) Lipsky BA, Berendt AR, Cornia PB, et al. Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132-173.

(12) Peters EJ, Lipsky BA, Aragon-Sanchez J, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes Metab Res Rev. 2016;32(Suppl 1):145-153.

(13) Lipsky BA, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, Kono S, Lavery LA, Malone M, van Asten SA, Urbančič-Rovan V, Peters EJG; International Working Group on the Diabetic Foot (IWGDF). Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020 Mar;36 Suppl 1:e3280. doi: 10.1002/dmrr.3280.

(14) Peters EJ, Lipsky BA. Diagnosis and management of infection in the diabetic foot. Med Clin North Am. 2013;97:911-946.

(15) Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis. 2007;44:562-565.

(16) Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes Care. 2006;29:1288-1293.

(17) Hao D, Hu C, Zhang T, Feng G, Chai J, Li T. Contribution of infection and peripheral artery disease to severity of diabetic foot ulcers in Chinese patients. Int J Clin Pract. 2014;68:1161-1164.

(18) Peters EJ, Lavery LA, Armstrong DG. Diabetic lower extremity infection: influence of physical, psychological, and social factors. J Diabetes Complications. 2005; Mar-Apr;19:107-112.

(19) Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. Diabetologia. 2008;51:747-755.

(20) Chu Y, Wang C, Zhang J, et al. Can we stop antibiotic therapy when signs and symptoms have resolved in diabetic foot infection patients? Int J Low Extrem Wounds. 2015;14:277-283

(21) Lavery LA, Peters EJ, Armstrong DG, Wendel CS, Murdoch DP, Lipsky BA. Risk factors for developing osteomyelitis in patients with diabetic foot wounds. Diabetes Res Clin Pract. 2009;83:347-352.

(22) McMahon MM, Bistrian BR. Host defenses and susceptibility to infection in patients with diabetes mellitus. Infect Dis Clin North Am. 1995;9:1-9.

(23) Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med. 2003;29:642-645

(24) Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997;14:29-34.

(25) Callahan D, Keeley J, Alipour H, et al. Predictors of severity in diabetic foot infections. Ann Vasc Surg. 2016;33:103-108.

(26) Uckay I, Jornayvaz FR, Lebowitz D, Gastaldi G, Gariani K, Lipsky BA. An overview on diabetic foot infections, including issues related to associated pain, hyperglycemia and limb ischaemia. Curr Pharm Des. 2018;24:1243-1254.

(27) Aragon-Sanchez J, Lazaro-Martinez JL, Pulido-Duque J, Maynar M. From the diabetic foot ulcer and beyond: how do foot infections spread in patients with diabetes? Diabet Foot Ankle. 2012;3.

(28) Bridges RM Jr, Deitch EA. Diabetic foot infections. Pathophysiology and treatment. Surg Clin North Am. 1994;74:537-555.

(29) Maharaj D, Bahadursingh S, Shah D, Chang BB, Darling RC. Sepsis and the scalpel: anatomic compartments and the diabetic foot. Vasc Endovascular Surg. 2005;39:421-423.

(30) Richard JL, Lavigne JP, Sotto A. Diabetes and foot infection: more than double trouble. Diabetes Metab Res Rev. 2012;28(Suppl 1): 46-53.

(31) Sotto A, Richard JL, Jourdan N, Combescure C, Bouziges N, Lavigne JP. Miniaturized oligonucleotide arrays: a new tool for discriminating colonization from infection due to Staphylococcus aureus in diabetic foot ulcers. Diabetes Care. 2007;30:2051-2056.

(32) Lavery LA, Peters EJ, Williams JR, Murdoch DP, Hudson A, Lavery DC. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diabetes Care. 2008;31: 154-156.

(33) Wukich DK, Hobizal KB, Brooks MM. Severity of diabetic foot infection and rate of limb salvage. Foot Ankle Int. 2013;34:351-358.

(34) Tobalem M, Uckay I. Images in clinical medicine. Evolution of a diabetic foot infection. N Engl J Med. 2013;369:2252.

(35) National Institute for Health and Clinical Excellence. Diabetic foot–inpatient management of people with diabetic foot ulcers and infection. *http://guidanceniceorguk/CG119* 2011.

(36) Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.

(37) Jeffcoate WJ, Bus SA, Game FL, et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 2016;4:781-788.

(38) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. PRISMA group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006-1012.

(39) Malone M, Senneville E, Peters E et al. A Systematic review of diagnosis of infection of the diabetic foot (soft tissue and bone): Update. PROSPERO 2022 CRD42022324795

(40) Malone M, Senneville E, Peters E et al. A Systematic review of Interventions for diabetic foot infections (soft tissue and bone): Update. PROSPERO 2022 CRD42022324812

(41) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ (Clinical research ed). 2016;353:i2089.

(42) Bus SA, Game F, Monteiro-Soares M, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;e3656.

(43) Pickwell K, Siersma V, Kars M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. Diabetes Care. 2015;38:852-857.

(44) Seth A, Attri AK, Kataria H, Kochhar S, Seth SA, Gautam N. Clinical profile and outcome in patients of diabetic foot infection. Int J Appl Basic Med Res. 2019;9:14-19.

(45) Royal College of Physicians. National Early Warning Score (NEWS). Standardising the assessment of acute-illness severity in the NHS. Report of a working party. London, RCP 2012.

(46) Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013;84:465-470.

(47) Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-810.

(48) Zhan LX, Branco BC, Armstrong DG, Mills JL Sr. The Society for Vascular Surgery lower extremity threatened limb classification system based on wound, ischaemia, and foot infection (WIfI) correlates with risk of major amputation and time to wound healing. J Vasc Surg. 2015;61:939-944.

(49) Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care. 2008;31:964-967.

(50) Senneville E, Albalawi Z, van Asten SA, et al. Diagnosis of infection in the foot of patients with diabetes: update 2023 systematic review. Diab Metab Res Rev. 2023;in press.

(51) Lavery LA, Ryan EC, Ahn J, et al. The Infected Diabetic Foot: Re-evaluating the Infectious Diseases Society of America Diabetic Foot Infection Classification. Clin Infect Dis. 2020;70(8):1573-1579.

(52) Ryan EC, Crisologo PA, Oz OK, et al. Do SIRS Criteria Predict Clinical Outcomes in Diabetic Skin and Soft Tissue Infections? J Foot Ankle Surg. 2019; 58: 1055-57.

(53) Johnson LJ, Crisologo PA, Sivaganesan S, Caldwell CC, Henning J. Evaluation of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score for detecting necrotizing soft tissue infections in patients with diabetes and lower extremity infection. Diabetes Res Clin Pract. 2021;171:108520.

(54) Sen P, Demirdal T. Predicitive Ability of LRINEC Score in the Prediction of Limb Loss and Mortality in Diabetic Foot Infection. Diagn Microbiol Infect Dis. 2021 100: 115323.

(55) Ozer Balin S, Sagmak Tartar A, Ugur K et al. Pentraxin-3: A New Parameter in Predicting the Severity of Diabetic Foot Infection? Int Wound J. 2019; 16(3): 659-664.

(56) Lipsky BA, Pecoraro RE, Larson SA, Hanley ME, Ahroni JH. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Arch Intern Med. 1990;150:790-797.

(57) Commons RJ, Raby E, Athan E, et al. Managing diabetic foot infections: a survey of Australasian infectious diseases clinicians. J Foot Ankle Res. 2018;11:13.

(58) Barwell ND, Devers MC, Kennon B, et al. Diabetic foot infection: antibiotic therapy and good practice recommendations. Int J Clin Pract. 2017;71:e13006.

(59) Park JH, Suh DH, Kim HJ, Lee YI, Kwak IH, Choi GW. Role of pro- calcitonin in infected diabetic foot ulcer. Diabetes Res Clin Pract. 2017;128:51-57.

(60) Al-Shammaree SAW, Abu ABA, Salman IN. Procalcitonin levels and other biochemical parameters in patients with or without diabetic foot complications. J Res Med Sci. 2017;22:95.

(61) Korkmaz P, Kocak H, Onbasi K, et al. The role of serum pro- calcitonin, interleukin-6, and fibrinogen levels in differential diagnosis of diabetic foot ulcer infection. J Diabetes Res. 2018;2018: 7104352.

(62) Armstrong DG, Perales TA, Murff RT, Edelson GW, Welchon JG. Value of white blood cell count with differential in the acute diabetic foot infection. J Am Podiatr Med Assoc. 1996;86:224-227.

(63) Jeandrot A, Richard JL, Combescure C, et al. Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected from non-infected diabetic foot ulcers: a pilot study. Diabetologia. 2008;51:347-352

(64) Umapathy D, Dornadula S, Rajagopalan A, et al. Potential of circulatory procalcitonin as a biomarker reflecting inflammation among South Indian diabetic foot ulcers. J Vasc Surg. 2018;67:1283- 1291e2

(65) Majeed A, Mushtaq A, Iftikhar A, Zahid U, Malik MN, Faryal R, et al. Role of inflammatory markers in diagnosing diabetic foot infection: a meta-analysis. Infect Dis Clin Pract. 2019; 27(5):251–259.

(66) Sharma H, Sharma S, Krishnan A, et al. The efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis: Systematic review and meta-analysis. PloS one. 2022;17(4), e0267412.

(67) van Netten JJ, Prijs M, van Baal JG, Liu C, van der Heijden F, Bus SA. Diagnostic values for skin temperature assessment to detect diabetes-related foot complications. Diabetes Technol Ther. 2014;16: 714-721.

(68) Hazenberg CE, van Netten JJ, van Baal SG, Bus SA. Assessment of signs of foot infection in diabetes patients using photographic foot imaging and infrared thermography. Diabetes Technol Ther. 2014;16: 370-377.

(69) Liu C, van Netten JJ, van Baal JG, Bus SA, van der Heijden F. Auto matic detection of diabetic foot complications with infrared ther-mography by asymmetric analysis. J Biomed Opt. 2015;20:26003.

(70) Armstrong DG, Lipsky BA, Polis AB, Abramson MA. Does dermal thermometry predict clinical outcome in diabetic foot infection? Analysis of data from the SIDESTEP* trial. Int Wound J. 2006;3: 302-307.

(71) Gardner SE, Frantz RA. Wound bioburden and infection-related complications in diabetic foot ulcers. Biol Res Nurs. 2008;10:44-53.

(72) Gardner SE, Hillis SL, Frantz RA. Clinical signs of infection in diabetic foot ulcers with high microbial load. Biol Res Nurs. 2009;11:119-128.

(73) Kallstrom G. Are quantitative bacterial wound cultures useful? J Clin Microbiol. 2014;52:2753-2756.

(74) O'Meara S, Nelson EA, Golder S, et al. Systematic review of methods to diagnose infection in foot ulcers in diabetes. Diabet Med. 2006; 23:341-347.

(75) Nelson EA, O'Meara S, Craig D, et al. A series of systematic reviews to inform a decision analysis for sampling and treating infected dia- betic foot ulcers. Health Technol Assess 2006;10:iii-iv, ix-x, 1–221.

(76) Huang Y, Cao Y, Zou M, et al. A comparison of tissue versus swab culturing of infected diabetic foot wounds. Int J Endocrinol. 2016; 2016:8198714.

(77) Nelson A, Wright-Hughes A, Backhouse MR, et al. CODIFI (concordance in diabetic foot ulcer infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. BMJ Open. 2018;8:e019437.

(78) Abbas ZG, Lutale JK, Ilondo MM, Archibald LK. The utility of Gram stains and culture in the management of limb ulcers in persons with diabetes. Int Wound J. 2012;9:677-682.

(79) Noor S, Raghav A, Parwez I, Ozair M, Ahmad J. Molecular and cul ture based assessment of bacterial pathogens in subjects with diabetic foot ulcer. Diabetes Metab Syndr. 2018;12:417-421.

(80) Percival SL, Malone M, Mayer D, Salisbury AM, Schultz G. Role of anaerobes in polymicrobial communities and biofilms complicating diabetic foot ulcers. Int Wound J. 2018;15:776-782.

(81) Malone M, Johani K, Jensen SO, et al. Next generation DNA sequencing of tissues from infected diabetic foot ulcers. EBioMedicine. 2017;21:142-149.

(82) Johani K, Fritz BG, Bjarnsholt T, et al. Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches. Clin Microbiol Infect. 2019;25:332–339.

(83) Malone M, Gosbell IB, Dickson HG, Vickery K, Espedido BA, Jensen SO. Can molecular DNA-based techniques unravel the truth about diabetic foot infections? Diabetes Metab Res Rev. 2017;33: e2834.

(84) Chen Y, Shi Y, Zhu W, You J, Yang J, Xie Y, Zhao H, Li H, Fan S, Li L, Liu C. Combining CRISPR-Cas12a-Based Technology and Metagenomics Next Generation Sequencing: A New Paradigm for Rapid and Full-Scale Detection of Microbes in Infectious Diabetic Foot Samples. Front Microbiol. 2021 Oct 7;12:742040. doi: 10.3389/fmicb.2021.742040.

(85) Lipof JS, Jones CMC, Daiss J, Oh I. Comparative study of culture, next-generation sequencing, and immunoassay for identification of pathogen in diabetic foot ulcer. J Orthop Res. 2021 Dec;39(12):2638-2645.

(86) Choi Y, Oda E, Waldman O, Sajda T, Beck C, Oh I. Next-Generation Sequencing for Pathogen Identification in Infected Foot Ulcers. Foot Ankle Orthop. 2021 Jul 12;6(3):24730114211026933.

(87) Malone M, Fritz BG, Vickery K, Schwarzer S, Sharma V, Biggs N, Radzieta M, Jeffries TT, Dickson HG, Jensen SO, Bjarnsholt T. Analysis of proximal bone margins in diabetic foot osteomyelitis by conventional culture, DNA sequencing and microscopy. APMIS. 2019 Oct;127(10):660-670.

(88) Meyr AJ, Seo K, Khurana JS, Choksi R, Chakraborty B. Level of agreement with a multi-test approach to the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg. 2018;57:1137-1139.

(89) Lázaro-Martínez JL, Tardáguila-García A, García-Klepzig JL. Diagnostic and therapeutic update on diabetic foot osteomyelitis. Endocrinología, Diabetes y Nutrición (English Ed). 2017;64:100-108.

(90) Senneville E. Editorial commentary: probe-to-bone test for detecting diabetic foot osteomyelitis: rapid, safe, and accurate-but for which patients? Clin Infect Dis. 2016;63:949-950.

(91) Alvaro-Afonso FJ, Lazaro-Martinez JL, Aragon-Sanchez J, Garcia- Morales E, Garcia-Alvarez Y, Molines-Barroso RJ. Inter-observer reproducibility of diagnosis of diabetic foot osteomyelitis based on a combination of probe-to-bone test and simple radiography. Diabetes Res Clin Pract. 2014;105:e3-e5.

(92) Lam K, van Asten SA, Nguyen T, La Fontaine J, Lavery LA. Diagnostic accuracy of probe to bone to detect osteomyelitis in the diabetic foot: a systematic review. Clin Infect Dis. 2016;63:944-948.

(93) Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 1995:721–3.

(94) Leone A, Bianco NC, D'Ambra G, et al. The Role of Serial Radiographs in Diagnosing Diabetic Foot Bone Osteomyelitis. Mediterr J Hematol Infect Dis. 2022;14(1):e2022055

(95) Ramanujam CL, Han D, Zgonis T. Medical imaging and laboratory analysis of diagnostic accuracy in 107 consecutive hospitalized patients with diabetic foot osteomyelitis and partial foot amputations. Foot Ankle Spec. 2018;11:433-443.

(96) Van Asten SA, Nichols A, La Fontaine J, Bhavan K, Peters EJ, Lavery LA. The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis. Int Wound J.2017;14(1),40–45.

(97) Lavery LA, Ahn J, Ryan EC, et al. What are the Optimal Cutoff Values for ESR and CRP to Diagnose Osteomyelitis in Patients with Diabetes-related Foot Infections? Clin Orthop Relat Res. 2019;477(7):1594-1602.

(98) Xu J, Cheng F, Li Y, Zhang J, Feng S, Wang P. Erythrocyte Sedimentation Rate Combined With the Probe-to-Bone Test for Fast and Early Diagnosis of Diabetic Foot Osteomyelitis. Int J Low Extrem Wounds. 2021;20(3):227-231.

(99) Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. Clin Infect Dis. 2008;47:519-527.

(100) Cohen M, Cerniglia B, Gorbachova T, Horrow J. Added value of MRI to X-ray in guiding the extent of surgical resection in diabetic forefoot osteomyelitis: a review of pathologically proven, surgically treated cases. Skeletal Radiol. 2019;48:405-411.

(101) Baker JC, Demertzis JL, Rhodes NG, Wessell DE, Rubin DA. Diabetic musculoskeletal complications and their imaging mimics. Radiographics. 2012;32:1959-1974.

(102) Chatha DS, Cunningham PM, Schweitzer ME. MR imaging of the diabetic foot: diagnostic challenges. Radiol Clin North Am. 2005;43: 747-759. ix.

(103) Cildag MB, Ertugrul BM, Koseoglu OF, Cildag S, Armstrong DG. Angiographic assessment of atherosclerotic load at the lower extremity in patients with diabetic foot and Charcot neuroarthropathy. J Chin Med Assoc. 2018;81:565-570.

(104) Cildag MB, Ertugrul MB, Koseoglu OF, Armstrong DG. A factor increasing venous contamination on bolus chase three-dimensional magnetic resonance imaging: Charcot neuroarthropathy. J Clin Imaging Sci. 2018;8:13.

(105) Ertugrul BM, Lipsky BA, Savk O. Osteomyelitis or Charcot neuro- osteoarthropathy? Differentiating these disorders in diabetic patients with a foot problem. Diabet Foot Ankle. 2013;4: 10.3402/dfa.v4i0.21855.

(106) La Fontaine J, Bhavan K, Lam K, Van Asten S, Erdman W, Lavery LA, Öz OK. Comparison Between Tc-99m WBC SPECT/CT and MRI for the Diagnosis of Biopsy-proven Diabetic Foot Osteomyelitis. Wounds. 2016;28(8):271-27

(107) La Fontaine J, Bhavan K, Jupiter D, Lavery LA, Chhabra A. Magnetic Resonance Imaging of Diabetic Foot Osteomyelitis: Imaging Accuracy in Biopsy-Proven Disease. J Foot Ankle Surg. 2021;60(1):17-20

(108) Sax AJ, Halpern EJ, Zoga AC, Roedl JB, Belair JA, Morrison WB. Predicting osteomyelitis in patients whose initial MRI demonstrated bone marrow edema without corresponding T1 signal marrow replacement. Skeletal Radiol. 2020;49(8):1239-1247

(109) Lauri C, Tamminga M, Glaudemans AWJM, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigra phy, and FDG-PET. Diabetes Care. 2017;40:1111-1120.

(110) Rastogi A, Bhattacharya A, Prakash M, et al. Utility of PET/CT with fluorine-18-fluorodeoxyglucose-labeled autologous leukocytes for diagnosing diabetic foot osteomyelitis in patients with Charcot's neuroarthropathy. Nucl Med Commun. 2016;37:1253-1259.

(111) Arnon-Sheleg E, Keidar Z. Diabetic foot infection: the role of PET-CT imaging. Curr Pharm des. 2018;24:1277-1286.

(112) Llewellyn A, Kraft J, Holton C, Harden M, Simmonds M. Imaging for detection of osteomyelitis in people with diabetic foot ulcers: A systematic review and meta-analysis. Eur J Radiol. 2020;131:109215

(113) Diez AIG, Fuster D, Morata L, et al. Comparison of the diagnostic accuracy of diffusion-weighted and dynamic contrast-enhanced MRI with 18F-FDG PET/CT to differentiate osteomyelitis from Charcot neuro-osteoarthropathy in diabetic foot. Eur J Radiol. 2020;132:109299

(114) Atif M, Hussain F, Dar ZS, Khatoon J, Ajmal S, Adil M. Diagnostic accuracy of 99mtc labeled (29-41) Ubiquicidin SPECT/CT for diagnosis of osteomyelitis in diabetic foot. Pak Armed Forces Med J. 2021; 71 (3): 1015-19

(115) Senneville E, Lipsky BA, Abbas ZG, et al. Diagnosis of infection in the foot in diabetes: a systematic review. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3281

(116) Senneville EM, Lipsky BA, van Asten SAV, Peters EJ. Diagnosing diabetic foot osteomyelitis. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3250.

(117) Senneville E, Melliez H, Beltrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis. 2006;42: 57-62.

(118) Senneville E, Morant H, Descamps D, et al. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. Clin Infect Dis. 2009;48:888-893.

(119) Senneville E, Lombart A, Beltrand E, et al. Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care. 2008;31:637-642.

(120) Gramberg MCTT, Lagrand RS, Sabelis LWE, et al. Using a BonE BiOPsy (BeBoP) to determine the causative agent in persons with diabetes and foot osteomyelitis: study protocol for a multicentre, randomised controlled trial. Trials. 2021;22(1):517.

(121) Couturier A, Chabaud A, Desbiez F, et al. Comparison of microbiological results obtained from per-wound bone biopsies versus trans- cutaneous bone biopsies in diabetic foot osteomyelitis: a prospective cohort study. Eur J Clin Microbiol Infect Dis. 2019;38: 1287-1;188:1529- 1534.

(122) Manas AB, Taori S, Ahluwalia R, Slim H, Manu C, Rashid H, Kavarthapu V, Edmonds M, Vas PRJ. Admission Time Deep Swab Specimens Compared With Surgical Bone Sampling in Hospitalized Individuals With Diabetic Foot Osteomyelitis and Soft Tissue Infection. Int J Low Extrem Wounds. 2021 Dec;20(4):300-308.

(123) Macauley M, Adams G, Mackenny P, et al. Microbiological evaluation of resection margins of the infected diabetic foot ulcer. Diabet Med. 2021;38(4):e14440.

(124) Féron F, de Ponfilly GP, Potier L, et al. Reliability and Safety of Bedside Blind Bone Biopsy Performed by a Diabetologist for the Diagnosis and Treatment of Diabetic Foot Osteomyelitis. Diabetes Care. 2021 Nov;44(11):2480-2486.

(125) Kosmopoulou OA, Dumont IJ. Feasibility of Percutaneous Bone Biopsy as Part of the Management of Diabetic Foot Osteomyelitis in a 100% Neuropathic, Grade 3 IDSA/IWGDF Population on an Outpatient Basis. Int J Low Extrem Wounds. 2020;19(4):382-387.

(126) Kowalski TJ, Matsuda M, Sorenson MD, Gundrum JD, Agger WA. The effect of residual osteomyelitis at the resection margin in patients with surgically treated diabetic foot infection. J Foot Ankle Surg. 2011;50:171-175.

(127) Atway S, Nerone VS, Springer KD, Woodruff DM. Rate of residual osteomyelitis after partial foot amputation in diabetic patients: a standardized method for evaluating bone margins with intraoperative culture. J Foot Ankle Surg. 2012;51:749-752.

(128) Hachmoller A. Outcome of minor amputations at the diabetic foot in relation to bone histopathology: a clinical audit. Zentralbl Chir. 2007; 132:491-496.

(129) Mijuskovic B, Kuehl R, Widmer AF, et al. Culture of bone biopsy specimens overestimates rate of residual osteomyelitis after toe or forefoot amputation. J Bone Joint Surg Am. 2018;100:1448-1454.

(130) Schmidt BM, McHugh JB, Patel RM, Wrobel JS. Prospective analysis of surgical bone margins after partial foot amputation in diabetic patients admitted with moderate to severe foot infections. Foot Ankle Spec. 2018:12:131–137.

(131) Meyr AJ, Singh S, Zhang X, et al. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg. 2011;50:663-667.

(132) Elmarsafi T, Kumar A, Cooper PS, et al. Concordance between bone pathology and bone culture for the diagnosis of osteomyelitis in the presence of Charcot neuro-osteoarthropathy. J Foot Ankle Surg. 2018;57:919-923.

(133) Tardáguila-García A, Sanz-Corbalán I, García-Morales E, García-Álvarez Y, Molines-Barroso RJ, Lázaro-Martínez JL. Diagnostic Accuracy of Bone Culture Versus Biopsy in Diabetic Foot Osteomyelitis. Adv Skin Wound Care. 2021;34(4):204-208.

(134) Lavery LA, Crisologo PA, La Fontaine J, Bhavan K, Oz OK, Davis KE. Are We Misdiagnosing Diabetic Foot Osteomyelitis? Is the Gold Standard Gold? [published correction appears in J Foot Ankle Surg. 2020 May - Jun;59(3):646]. J Foot Ankle Surg. 2019;58(4):713-716.

(135) Peters EJG, Albalawi Z, van Asten SA, et al. Diagnosis of infection in the foot of patients with diabetes: update 2023 systematic review. Diab Metab Res Rev. 2023;in press.

(136) Gardner SE, Haleem A, Jao YL, et al. Cultures of diabetic foot ulcers without clinical signs of infection do not predict outcomes. Diabetes Care. 2014;37:2693-2701

(137) Selva Olid A, Sola I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections. Cochrane Database Syst Rev. 2015;CD009061.

(138) Hatipoglu M, Mutluoglu M, Turhan V, Uzun G, Lipsky BA; Turk-Day Study Group; Causative pathogens and antibiotic resistance in diabetic foot infections: A prospective multi-center study. J Diabetes Complications. 2016 Jul;30(5):910-6.

(139) Uçkay I, Berli M, Sendi P, Lipsky BA. Principles and practice of antibiotic stewardship in the management of diabetic foot infections. Curr Opin Infect Dis. 2019 Apr;32(2):95-101.

(140) Lauf L, Ozsvar Z, Mitha I, et al. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagn Microbiol Infect Dis. 2014;78:469-480.

(141) Xu ZR, Ran XW, Xian Y, et al. Ertapenem versus piperacillin/tazobactam for diabetic foot infections in China: a Phase 3, multicentre, randomized, double-blind, active-controlled, non-inferiority trial. J Antimicrob Chemother. 2016;71(6):1688-1696. doi:10.1093/jac/dkw004.

(142) Gariani K, Lebowitz D, von Dach E, Kressmann B, Lipsky BA, Uçkay I. Remission in diabetic foot infections: Duration of antibiotic therapy and other possible associated factors. Diabetes Obes Metab. 2019;21(2):244-251.

(143) Haug F, Waibel FWA, Lisy M, Winkler E, Uçkay I, Schöni M. The impact of the length of total and intravenous systemic antibiotic therapy for the remission of diabetic foot infections. Int J Infect Dis. 2022;120:179-186.

(144) Pratama V, Risni HW, Yunir E, Sauriasari R. A Systematic Review of Randomized Controlled Trials of Antibiotic Use in Diabetic Foot Ulcer Infections: Focus on Clinical Cure. Infect Chemother. 2022;54(1):125-139.

(145) Saltoglu N, Surme S, Ezirmik E, et al. The Effects of Antimicrobial Resistance and the Compatibility of Initial Antibiotic Treatment on Clinical Outcomes in Patients With Diabetic Foot Infection. Int J Low Extrem Wounds. 2021 Apr 15:1534734621004141.

(146) Pham TT, Gariani K, Richard JC, et al. Moderate to Severe Soft Tissue Diabetic Foot Infections: A Randomized, Controlled, Pilot Trial of Post-debridement Antibiotic Treatment for 10 versus 20 days. Ann Surg. 2022;276(2):233-238.

(147) Pham TT, Wetzel O, Gariani K, et al. Is routine measurement of the serum C-reactive protein level helpful during antibiotic therapy for diabetic foot infection? Diabetes Obes Metab. 2021;23(2):637-641.

(148) Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012;54:393-407.

(149) Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care. 2015;38:302-307.

(150) Iranparvar M, Arzanlou O, Afrouzeh E. Comparison of the efficacy of six-week versus twelve-week antibiotic therapy for the treatment of nonsurgical diabetic foot osteomyelitis. Int Med 2019; 1(5): 274-279.

(151) Gariani K, Pham T, Benjamin K; et al. (2021). Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: A prospective, randomized, non-inferiority pilot trial. Clin Inf Dis. 2021;73(7):e1539-e1545.

(152) Gill AS, Gorski M, Strage KE, et al. Oral Versus Intravenous Antibiotics for Residual Osteomyelitis After Amputation in the Diabetic Foot. J Foot Ankle Surg. 2022,61: 735−738.

(153) Tan JS, Friedman NM, Hazelton-Miller C, Flanagan JP, File TM, Jr. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? Clin Infect Dis. 1996;23:286-91.

(154) Faglia E, Clerici G, Caminiti M, Quarantiello A, Gino M, Morabito A. The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. J Foot Ankle Surg. 2006;45:220-6.

(155) Zhou S, Schmidt BM, Henig O, Kaye KS. Deferring Amputation in Diabetic Foot Osteomyelitis: Doing More Harm Than Good? Open Forum Infect Dis. 2021;4;8(7): ofab184. doi: 10.1093/ofid/ofab184.

(156) Lin CW, Yang HM, Hung SY, Chen IW, Huang YY. The analysis for time of referral to a medical center among patients with diabetic foot infection. BMC Fam Pract. 2021;9;22(1):16. doi: 10.1186/s12875-020-01363-y.

(157) Ulcay A, Karakas A, Mutluoglu M, Uzun G, Turhan V, Ay H. Antibiotherapy with and without bone debridement in diabetic foot osteomyelitis: a retrospective cohort study. Pak J Med Sci. 2014;30:28-31.

(158) Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. Diabetologia. 2008;51:962-967.

(159) Acharya S, Soliman M, Egun A, Rajbhandari SM. Conservative management of diabetic foot osteomyelitis. Diabetes Res Clin Pract. 2013;101:e18-e20.

(160) Kim JJ, Littman AJ, Sorkin JD, Roghmann MC. Association Between Foot Surgery Type and Subsequent Healing in Veterans With Moderate-to-Severe Diabetic Foot Infections. Open Forum Infect Dis. 2021;9(2):ofab650.

(161) Feldman V, Segal D, Atzmon R, et al. Amputation versus Primary Nonoperative Management of Chronic Osteomyelitis Involving a Pedal Digit in Diabetic Patients. J Am Podiatr Med Assoc. 2021;111(4):Article_2. doi:10.7547/19-155.

(162) Lesens O, Desbiez F, Theis C, et al. Staphylococcus aureus-related diabetic osteomyelitis: medical or surgical management? A French and Spanish retrospective cohort. Int J Low Extrem Wounds. 2015; 14:284-290.

(163) Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes Care. 2014;37: 789-795.

(164) Aragon-Sanchez J, Lipsky BA. Modern management of diabetic foot osteomyelitis. The when, how and why of conservative approaches. Expert Rev Anti Infect Ther. 2018;16:35-50.

(165) Tardáguila-García A, García-Álvarez Y, García-Morales E, López-Moral M, Sanz-Corbalán I, Lázaro-Martínez JL. Long-Term Complications after Surgical or Medical Treatment of Predominantly Forefoot Diabetic Foot Osteomyelitis: 1 Year Follow Up. J Clin Med. 2021;1;10(9):1943. doi: 10.3390/jcm10091943.

(166) Berthol N, Robineau O, Boucher A, et al. Two-step sequential approach for concomitant skin and soft tissue infection and osteomyelitis complicating the diabetic foot. Diabetes Care. 2017;40:e170-e171.

(167) Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev. 2017;6:CD011038

(168) Pexiganan versus placebo control for the treatment of mild infections of diabetic foot ulcers (OneStep-2). Clinicaltrialsgov. 2017; NCT01594762.

(169) Pexiganan versus placebo control for the treatment of mild infections of diabetic foot ulcers (OneStep-1). Clinicaltrialsgov. 2017; NCT01590758.

(170) Lipsky BA, Kuss M, Edmonds M, Reyzelman A, Sigal F. Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial. J Am Podiatr Med Assoc. 2012;102(3):223-232.

(171) Uckay I, Kressmann B, Di Tommaso S, et al. A randomized controlled trial of the safety and efficacy of a topical gentamicin-collagen sponge in diabetic patients with a mild foot ulcer infection. SAGE Open Med. 2018;6:205031211877395.

(172) Uckay I, Kressmann B, Malacarne S, et al. A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. BMC Infect Dis. 2018;18:361.

(173) Memon ML, Ikram M, Azhar M, Balouch V. Comparison of efficacy of systemic antibiotics alone and combination of systemic antibiotics with gentamicin cream in diabetic foot infections. Pak J Med Sci. 2022;38(3Part-I):663-667.

(174) Mendame Ehya RE, Zhang H, Qi B, Yu A. Application and Clinical Effectiveness of Antibiotic-Loaded Bone Cement to Promote Soft Tissue Granulation in the Treatment of Neuropathic Diabetic Foot Ulcers Complicated by Osteomyelitis: A Randomized Controlled Trial. J Diabetes Res. 2021; 2021:9911072.

(175) Qin CH, Zhou CH, Song HJ, et al. Infected bone resection plus adjuvant antibiotic-impregnated calcium sulfate versus infected bone resection alone in the treatment of diabetic forefoot osteomyelitis. BMC Musculoskelet Disord. 2019;20(1):246.

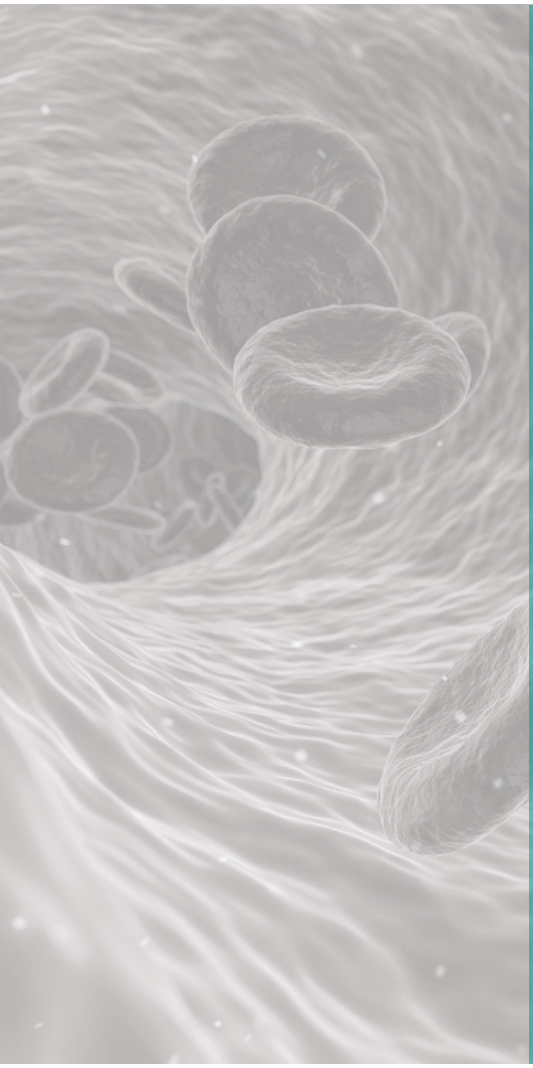
(176) Brodell JD Jr, Kozakiewicz LN, Hoffman SL, Oh I. Intraoperative Site Vancomycin Powder Application in Infected Diabetic Heel Ulcers With Calcaneal Osteomyelitis. Foot Ankle Int. 2021;42(3):356-362.

(177) Marson BA, Deshmukh SR, Grindlay DJC, Ollivere BJ, Scammell BE. A systematic review of local antibiotic devices used to improve wound healing following the surgical management of foot infections in diabetics. Bone Joint J. 2018;100-B (11):1409-1415.

(178) De Giglio, R., Di Vieste, G., Mondello, T., Balduzzi, G., Masserini, B., Formenti, I., Lodigiani, S., Pallavicini, D., Pintaudi, B., & Mazzone, A. . Efficacy and Safety of Bioactive Glass S53P4 as a Treatment for Diabetic Foot Osteomyelitis. J Foot Ankle Sur. 2021; 60(2), 292–296.

(179) Kastrin M, Urbančič Rovan V, Frangež I. Possible Advantages of S53P4 Bioactive Glass in the Treatment of Septic Osteoarthritis of the First Metatarsophalangeal Joint in the Diabetic Foot. J Clin Med. 2021;10(6), 1208. *www.doi.org/10.3390/jcm10061208*

(180) Wilson BM, Bessesen MT, Doros G, et al. Adjunctive Rifampin Therapy for Diabetic Foot Osteomyelitis in the Veterans Health Administration. JAMA Netw Open. 2019;2(11): e1916003.



The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

Diabetes-related foot complications have become a major cause of morbidity and are implicated in most major and minor amputations globally. Approximately 50% of people with diabetes and a foot ulcer have peripheral artery disease (PAD) and the presence of PAD significantly increases the risk of adverse limb and cardiovascular events.

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the management and prevention of diabetes-related foot complications since 1999. This guideline is an update of the 2019 IWGDF guideline on the diagnosis, prognosis and management of peripheral artery disease in people with diabetes mellitus and a foot ulcer. For this updated guideline the IWGDF, the European Society for Vascular Surgery and the Society for Vascular Surgery decided to collaborate to develop a consistent suite of recommendations relevant to clinicians in all countries.

This guideline is based on three new systematic reviews. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework clinically relevant questions were formulated, and the literature was systematically reviewed. After assessing the certainty of the evidence, recommendations were formulated which were weighed against the balance of benefits and harms, patient values, feasibility, acceptability, equity, resources required, and when available, costs.

Through this process five recommendations were developed for diagnosing PAD in a person with diabetes, with and without a foot ulcer or gangrene. Five recommendations were developed for prognosis relating to estimating likelihood of healing and amputation outcomes in a person with diabetes and a foot ulcer or gangrene. Fifteen recommendations were developed related to PAD treatment encompassing prioritisation of people for revascularisation, the choice of a procedure and post-surgical care. In addition, the Writing Committee has highlighted key research questions where current evidence is lacking.

The Writing Committee believes that following these recommendations will help healthcare professionals to provide better care and will reduce the burden of diabetes-related foot complications.

ABBREVIATIONS

ABI: Ankle Brachial index

ADA: American Diabetes Association

AP: Ankle pressure

CDUS: Colour Duplex ultrasound

CI: Confidence interval

CLTI: Chronic limb-threatening ischaemia

COI: Conflict of interest

CTA: Computed tomography angiography

CWD: Continuous-wave Doppler

DFU: Diabetes-related foot ulcer:

DSA: Digital subtraction angiography

EAS: European Atherosclerosis Society

EASD: European Association for the Study of Diabetes

eGRF: Estimated glomerular filtration rate

ESC: European Society of Cardiology

ESVM: European Society of Vascular Medicine

ESVS: European Society for Vascular Surgery

GLASS: Global Anatomic Staging System

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

GVG: Global Vascular Guidelines

HbA1c: Haemoglobin A1c

IDSA: Infectious Diseases Society of America

IWGDF: International Working Group on the Diabetic Foot

LDL: Low Density Lipoproteins

MAC: Medial arterial calcification

MACE: Major adverse cardiovascular events

MALE: Major adverse limb events

MRA: Magnetic resonance angiography

NLR: Negative likelihood ratio

PAD: Peripheral artery disease

PICO: Population, Intervention, Comparison, Outcome

PLR: Positive likelihood ratio

SGLT-2: sodium–glucose cotransporter 2

SPP: Skin perfusion pressure

SVS: Society for Vascular Surgery

TBI: Toe Brachial index

$TcPO_2$: Transcutaneous oxygen pressure

TP: Toe pressure

WIfI: Wound/Ischaemia/foot Infection

WFVS: World Federation of Vascular Societies

LIST OF RECOMMENDATIONS

DIAGNOSIS

1. In a person with diabetes without a foot ulcer, take a relevant history for peripheral artery disease, examine the foot for signs of ischaemia and palpate the foot pulses at least annually, or with any change in clinical status of the feet. (Strong, Low)
2. In a person with diabetes without a foot ulcer, if peripheral artery disease (PAD) is suspected, consider performing pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI). No single modality has been shown to be optimal for diagnosis of PAD and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥ 0.70; and triphasic or biphasic pedal Doppler waveforms. (Conditional, Low)
3. In a person with diabetes and a foot ulcer or gangrene, take a relevant history for peripheral artery disease, examine the person for signs of ischaemia and palpate the foot pulses. (Strong, Low)
4. In a person with diabetes and a foot ulcer or gangrene, evaluate pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI) measurements to identify the presence of peripheral artery disease (PAD).
   No single modality has been shown to be optimal for diagnosis of PAD, and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥ 0.70; and triphasic or biphasic pedal Doppler waveforms. (Strong, Low)
5. In a person with diabetes without a foot ulcer in whom a non-emergency invasive foot procedure is being considered, peripheral artery disease should be excluded by performing assessment of pedal Doppler waveforms in combination with ankle-brachial index and toe-brachial index. Best Practice Statement

PROGNOSIS

6. In a person with diabetes and a foot ulcer, or gangrene, consider performing ankle pressures and ankle-brachial index (ABI) measurements to assist in the assessment of likelihood of healing and amputation.
   Ankle pressure and ABI are weak predictors of healing. A low ankle pressure (e.g. < 50 mmHg) or ABI (e.g. < 0.5) may be associated with greater likelihood of impaired healing and greater likelihood of major amputation. (Conditional, Low)
7. In a person with diabetes and a foot ulcer or gangrene consider performing a toe pressure measurement to assess likelihood of healing and amputation.
   A toe pressure ≥ 30 mmHg increases the pre-test probability of healing by up to 30% and a value < 30mmHg increases the pre-test probability of major amputation by approximately 20%. (Conditional, Low)

8. In a person with diabetes and a foot ulcer or gangrene, if toe pressure cannot be performed, consider performing a transcutaneous oxygen pressure (TcPO2) measurement or a skin perfusion pressure (SPP) to assess likelihood of healing.
   A TcPO2 ≥ 25 mmHg increases the pre-test probability of healing by up to 45% and value < 25 mmHg increases the pre-test probability of major amputation by approximately 20%. A SPP ≥ 40mmHg, increases the pre-test probability of healing by up to 30%. (Conditional, Low)
9. In a person with diabetes and a foot ulcer or gangrene it is suggested that the presence of peripheral artery disease and other causes of poor healing should always be assessed. Diabetes-related microangiopathy should not be considered the primary cause of foot ulceration, gangrene or poor wound healing without excluding other causes. (Conditional, Low)
10. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, consider using the Wound/Ischaemia/foot Infection (WIfI) classification system to estimate healing likelihood and amputation risk. (Conditional, Low)

TREATMENT

11. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who is being considered for revascularisation, evaluate the entire lower extremity arterial circulation (from aorta to foot) with detailed visualization of the below knee and pedal arteries. Best Practice Statement
12. In a person with diabetes, peripheral artery disease, a foot ulcer and clinical findings of ischaemia, a revascularisation procedure should be considered. Findings of ischaemia include absent pulses, monophasic or absent pedal Doppler waveforms, ankle pressure <100 mmHg or toe pressure <60 mmHg. Consult a vascular specialist unless major amputation is considered medically urgent. Best Practice Statement
13. In a person with diabetes, peripheral artery disease, a foot ulcer, and severe ischaemia i.e., an ankle-brachial index <0.4, ankle pressure <50mmHg, toe pressure <30mmHg or transcutaneous oxygen pressure <30mmHg or monophasic or absent pedal Doppler waveforms, urgently consult a vascular specialist regarding possible revascularisation. Best Practice Statement
14. In a person with diabetes, peripheral artery disease and a foot ulcer with infection or gangrene involving any portion of the foot, urgently consult a vascular specialist in order to determine the timing of a drainage procedure and a revascularisation procedure. Best Practice Statement
15. In a person with diabetes and a foot ulcer, when the wound deteriorates or fails to significantly improve (e.g. a less than 50% reduction in wound area within 4 weeks) despite appropriate infection and glucose control, wound care, and offloading, reassess the vascular status and consult with a vascular specialist regarding possible revascularisation. Best Practice Statement
16. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, avoid revascularisation when the risk–benefit ratio for the probability of success of the intervention is clearly unfavourable. Best Practice Statement

17. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who has an adequate single segment saphenous vein in whom infrainguinal revascularisation is indicated and who are suitable for either approach, consider bypass in preference to endovascular therapy (Conditional, Moderate)
18. A person with diabetes, peripheral artery disease (PAD) and a foot ulcer or gangrene, should be treated in centres with expertise in, or rapid access to, endovascular and surgical bypass revascularisation. In this setting, consider making treatment decisions based on the risk to and preference of the individual, limb threat severity, anatomic distribution of PAD, and the availability of autogenous vein. Best Practice Statement
19. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, revascularisation procedures should aim to restore in-line blood flow to at least one of the foot arteries. Best Practice Statement
20. In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene undergoing an endovascular procedure, consider targeting the artery on angiography that supplies the anatomical region of the ulcer, when possible or practical. (Conditional, Very low)
21. In a person with diabetes and either a foot ulcer or gangrene who has undergone revascularisation, objectively assess the adequacy of perfusion e.g., using non-invasive bedside testing. Best Practice Statement
22. A person with diabetes, peripheral artery disease and either a foot ulcer or gangrene should be treated by a multidisciplinary team as part of a comprehensive care plan. Best Practice Statement
23. In a person with diabetes and peripheral artery disease the following target levels should be:
    - HbA1c < 8% (< 64 mmol/mol), but higher target HbA1c value can be necessary depending on the risk of severe hypoglycaemia.
    - Blood pressure < 140/ 90 mmHg but higher target levels can be necessary depending on the risk of orthostatic hypotension and other side-effects.
    - Low density lipoprotein target of < 1.8 mmol/L (<70 mg/dLdL) and reduced by at least 50% of baseline. If high intensity statin therapy (with or without ezetimibe) is tolerated, target levels < 1.4 mmol/L (55 mg/dL) are recommended.

    Best Practice Statement
24. A person with diabetes and symptomatic peripheral artery disease:
    - should be treated with single antiplatelet therapy,
    - treatment with clopidogrel may be considered as first choice in preference to aspirin
    - combination therapy with aspirin (75 mg to 100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for people without a high bleeding risk.

    Best Practice Statement

25. In a person with type 2 diabetes and peripheral artery disease:
    with an eGFR > 30 ml/min/1.73m2, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit should be considered, irrespective of the blood glucose level.
    SGLT-2 inhibitors should not be started in drug-naïve people with a diabetes-related foot ulcer or gangrene and temporary discontinuation should be considered in people already using these drugs, until the affected foot is healed. Best Practice Statement

EXTERNAL EXPERTS, PATIENT REPRESENTATIVES AND REVIEW PROCESS

The review process had several steps, in which six external experts, four patient representatives and guideline reviewers of the International Working Group for the Diabetic Foot (IWGDF) , European Society for Vascular Surgery (ESVS) and Society of Vascular Surgery (SVS) were involved. The external experts and patient representatives were from various countries and continents (Singapore, Japan, South Africa, China, Hong Kong, Colombia, Bulgaria, Australia, England, the United States of America) . The process started with review of the clinical questions that the Writing Committee proposed to address, which were subsequently adjusted and which formed the basis of the guideline development. The first preliminary version of the guideline was reviewed by the IWGDF, ESVS and members of SVS Document Oversight Committee. The revised text was then reviewed by the external experts and patient representatives, and subsequently a new version was submitted for review to the three organisations. The Writing Committee met for the first time in late 2020 and the first draft of the guideline was sent out for review in December 2022.

METHODOLOGY

This guideline is also part of a set of guidelines (and their supporting systematic reviews) of the IWGDF on the management of diabetes-related foot ulcers, which all used the same GRADE methodology. These guidelines address the other aspects of management and are published separately. The IWGDF editorial board had the task of ensuring that there would not be too much overlap between these documents and that they were consistent with each other. The ESVS and SVS Executive Board agreed with this approach. The methodology used is described in detail in a separate IWGDF document; here a summary is provided (1).

In brief, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was followed (2, 3). GRADE is structured by the development of clinical questions and selection of critical outcomes which are subsequently translated in the PICO (Population, Intervention, Comparison, Outcome) format. The Writing Committee developed the clinical questions to be investigated after consultation with the external experts and patient representatives. Critically important outcomes for clinical questions were voted upon by the Writing Committee members. Subsequently, the PICOs were created and voted on for inclusion by Writing Committee members. The PICOs to be included were

then reviewed by the external experts, patient representatives and the guideline committee of the societies involved. The systematic reviews of the literature to address the clinical questions were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (4). The process of identifying and evaluating the available evidence, with its main conclusions, resulted in three systematic reviews on Diagnosis, on Prognosis and on Management, of Peripheral Artery Disease in Diabetes Mellitus. These systematic reviews are published separately (insert link here). The population of interest was people with diabetes mellitus (with or without a foot ulcer or gangrene, depending on the clinical question). For diagnosis the intervention was any non-invasive bedside test and the comparator an objective imaging study; for prognosis the intervention was any non-invasive bedside test and for treatment the interventions were bypass (open) and direct revascularisation and the comparators endovascular and indirect revascularisation respectively. The primary outcomes were wound healing, minor and major amputation and adverse events, limb salvage and wound healing. After the literature search all abstracts and subsequently selected articles were reviewed by two authors, as described in our systematic reviews. We included studies in which at least 80% of participants had diabetes or in which the results of the participants with diabetes were reported separately. All included studies were assessed for quality and risk of bias with the following instruments, depending on the type of study: Quality in Prognosis Studies (QUIPS), the revised quality appraisal tool for studies of diagnostic reliability (QUADAS-2), ROBINS-I (for assessing risk of bias in non-randomised studies of interventions),the Newcastle-Ottawa Scale (for non-randomised studies, including observational and cohort studies where details regarding allocation to intervention groups were not provided, and the Cochrane risk of bias 2 tool for randomised-controlled trials (5-10). For each PICO the quality of evidence was graded for risk of bias, inconsistency, imprecision, publication bias and overall quality. The certainty of the evidence was then rated as "high," "moderate," "low" or "very low".

The GRADE evidence to decision approach was subsequently used for the development of the recommendations during online discussions of the Writing Committee (which were all recorded and available for later review from the Secretary). In developing each recommendation and its strength the following aspects were taken into account: benefits, harms, effect size and certainty; balance of benefits and harms; resource use; acceptability; feasibility; equity. The strength of each recommendation was graded as "Strong" or "Conditional". All Writing Committee members voted on each recommendation, for a 'Strong" recommendation at least 75% and for a "Conditional" recommendation at least 60% had to agree. After each recommendation, a rationale is provided for how we determined each recommendation (1, 11).

There were situations where we could not identify sufficient direct evidence supporting the formulation of a recommendation, but performing the actions recommended would very likely result in clear benefit or not performing the test or intervention in marked harm. In these situations, we formulated an ungraded Best Practice Statement with a rationale explaining how we came to this statement and we considered GRADE criteria for developing such a statement, as advised in a recent publication of the GRADE group on this topic (12). According to GRADE such recommendations should be formulated as actionable statements when they are deemed necessary for practice and when the desirable effects of an intervention clearly outweigh its undesirable effects. Although in these cases direct evidence is lacking, they should be supported by indirect evidence.For the clinical question on the use of current medical therapies to reduce cardiovascular risk or lower limb events in people with diabetes and

symptomatic peripheral artery disease (PAD) we did not perform a systematic review or develop graded recommendations, as recent high-quality guidelines on these topics already exist (13-20). However, in order to give the reader a complete overview we created a summary of these existing guidelines, where relevant for our clinical question and adapted these to the person with diabetes mellitus and symptomatic PAD. These recommendations were also formulated as Best Practice Statements. We do acknowledge that for certain recommendations high quality evidence exists, as summarised in other guidelines of organisations such as ESVS, SVS and American Diabetes Association, but for others there is only lesser quality evidence. In order not to repeat all these evidence-based guidelines already developed by other relevant organisations we chose to make in this area ungraded Best Practice Statements, with references provided to the relevant guidelines. Finally, the Writing Committee considered topics for future research and voted to focus on 5 key topics which are discussed at the end of the guideline.

The recommendations and corresponding rationales were reviewed by the same international external experts and committees responsible for guideline development of the three aforementioned societies. Further details are provided in the IWGDF guidelines methodology document (1). The background materials we developed, i.e. the three systematic reviews, the relevant evidence tables for each of the systematic reviews as well as the summary of judgements tables that were the basis for formulating each recommendation and Best Practice Statement, can be found in the Supplementary Materials of this article. These systematic reviews provide the evidence for the graded recommendations made in this Guideline.

TARGET POPULATION AND TARGET AUDIENCE

Poorly healing foot ulcers or gangrene in people with diabetes mellitus are frequently caused by several factors acting in concert. The primary target population of this guideline is people with diabetes mellitus with a foot ulcer or gangrene on any portion of the foot (with or without neuropathy) in whom the presence of PAD could have contributed to the development of the ulcer and/or its poor healing potential. The secondary target group was people with diabetes mellitus in whom the presence of PAD was considered or needed to be excluded. People with pure venous ulcers, ulcers above the ankle , acute limb ischaemia, embolic disease, and non-atherosclerotic chronic vascular conditions of the lower extremity were excluded.

The primary target audience of this guideline are vascular specialists and all other health care professionals who are involved in the diagnosis, management and prevention of diabetes-related foot ulcers and gangrene, who work in primary, secondary and tertiary care.

Once the guidelines are approved, the patient representatives will be approached to discuss which elements of the guideline should be included in the "Information for Patients". This will result in a list of items that should be addressed in this information. Given cultural and language differences , the final text should be produced on a national or local level.

GUIDELINE WRITING GROUP CONFLICT OF INTEREST POLICY

The three organizations participating in these guidelines are committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the Writing Committee were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the Writing Committee, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit an updated COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks or options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the three organisations and these can be found at *www.iwgdfguidelines.org*. No company was involved in the development or review of the guidelines. Nobody else involved in the guideline received any payment or remuneration of any costs.

DEFINITIONS AND TERMINOLOGY AS USED IN THIS DOCUMENT

The definitions and criteria for diabetes-related foot disease were standardised by the IWGDF and in parallel to this guideline an update is published (21). In addition, in this guideline we used the following terminology:

Bedside testing: any non-invasive test assessing for PAD in the lower limb using a measure of blood flow that could be conducted at the bedside.

Chronic Limb Threatening Ischaemia: a clinical syndrome defined by the presence of peripheral artery disease in combination with rest pain, gangrene or foot ulcer of at least 2 weeks duration. Venous, embolic, non-atherosclerotic and traumatic aetiologies are excluded.

Diabetes-related microangiopathy: pathological structural and functional changes in the microcirculation of people with diabetes mellitus, that can occur in any part of the body as a consequence of the disease.

Diabetes-related foot ulcer: A break of the skin of the foot that involves as a minimum the epidermis and part of the dermis in a person with diabetes and usually accompanied by neuropathy and/or PAD in the lower extremity.

Diabetes-related foot gangrene: A condition that occurs when body tissue dies because of insufficient blood supply, infection or injury.

Foot perfusion: Tissue perfusion strictly means the volume of blood that flows through a unit of tissue and is often expressed in ml blood/100 gm of tissue. With respect to clinical assessment of the foot,

perfusion is traditionally measured by the surrogate markers of systolic arterial pressure at the level of the ankle and toe arteries. Pressure measurements may be misleading in people with diabetes due to the frequent presence of medial calcinosis. This has led to the development of a number of alternative, clinically used means of assessing tissue perfusion, including $TcPO_2$ (transcutaneous pressure of Oxygen), SPP (skin perfusion pressure), PAT (pedal acceleration time) and near-infrared spectrophotometry (NIRS).

Multidisciplinary team: A grouping of people from relevant clinical disciplines, whose interactions are guided by specific team functions and processes to achieve team- and person-defined favourable outcome.

Peripheral artery disease (PAD): Obstructive atherosclerotic vascular disease of the arteries from aorta to foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities.

INTRODUCTION

The incidence of diabetes continues to increase in all countries. Recent estimates are that 537 million people are affected by diabetes (1 in 11 adults worldwide) and that 783 million individuals will be affected by 2045 (22). Diabetes is associated with significant risk of foot complications including ulceration, gangrene and amputation. Development of diabetes-related foot ulceration (DFU) precedes up to 85% of non-traumatic amputations with an annual incidence of ulceration of approximately 2% and lifetime incidence of DFU up to 34% (23). Diabetes-related complications in the lower limb including peripheral neuropathy and peripheral artery disease (PAD) typically precede the development of DFU (24). Collectively these complications are a leading global cause of disability, hospitalisation and amputation, with high mortality following amputation (25).

Diabetes is a significant risk factor for the development of PAD. In a recent systematic review, Stoberock et al. (26) found that the prevalence of PAD was 10-26% in the general adult population and 20-28% in those with diabetes . In those with DFU, the prevalence of PAD was 50% which is consistent with the findings of the multicentre Eurodiale study (26, 27). PAD in people with diabetes is characterised by a disease pattern that is frequently multi-segmental and bilateral with impaired collateral formation, often long segment tibial artery occlusions, and is more distally distributed in the lower limb including frequent presentation of infragenicular arterial occlusive disease (28-30), with an increased risk of amputation. The diagnosis of PAD and chronic limb-threatening ischaemia (CLTI) is frequently complicated by the absence of classical symptoms of PAD such as intermittent claudication and rest pain, probably due to factors such as sedentary lifestyle and loss of pain sensation due to, diabetes-related peripheral neuropathy, which is present in the majority of people with an (ischaemic) DFU (27, 29). Co-existent medial artery calcification (MAC), which is also associated with peripheral neuropathy, is common and can affect the accuracy of non-invasive tests such as the ankle-brachial index (ABI) by causing elevation of ankle and, to a lesser extent, digital pressures (31).

In people with diabetes early diagnosis of PAD is essential (26). The disease process is associated with greater likelihood of delayed or non-healing of DFU, gangrene and amputation in addition to elevated rates of cardiovascular morbidity and mortality (32). The prognosis of a person with diabetes, PAD, and foot ulceration requiring amputation is worse than many common cancers—up to 50% of people will not survive 5 years (23, 33). PAD places the person at very high risk of adverse cardiovascular events and thus optimal medical management of cardiovascular risk factors should be ensured (29). Early and adequate assessment of foot perfusion is necessary to ensure that the elevated risk of delayed or poor wound healing and amputation are identified early so that they can be addressed without treatment delay.

Despite the severity of the outcomes of PAD in people with diabetes, and particularly for those with DFU, there are few practice guidelines that specifically address the diagnosis and management of PAD in this population. Formulating recommendations for this specific population should take into account the multi-system nature of diabetes and the impact of other diabetes complications on the utility of diagnostic tests, wound healing, amputation and survival outcomes. One of the guidelines that specifically addressed these topics has been that of the IWGDF, with the last version produced in 2019 (34). Instead of making a new updated version, the IWGDF together with the ESVS and the SVS decided to

collaborate in writing this new, intersociety, practice guideline on PAD in diabetes mellitus, with emphasis on people with diabetes-related foot ulcers or gangrene. We aim to provide evidence-based recommendations on the diagnosis, prognosis (i.e., the prognostic value of different non-invasive tests), and treatment of PAD in people with a foot ulcer and diabetes. Each of these topics is discussed in the different sections below. It is not our intention to detail the specific roles, tasks and responsibilities of each medical specialty involved as these vary markedLy between and within countries and this guideline is a multinational initiative. However, we do emphasize which expertise should be present, in terms of knowledge, skills and competence, in order to manage the people according to the expected standards of care.

RELATED GUIDELINES

This guideline is also part of the IWGDF Guidelines on the prevention and management of diabetes-related foot disease. Management of PAD in these people without addressing the other aspects of DFU treatment will frequently result in suboptimal outcomes. The reader is therefore referred to the other IWGDF Guidelines for these aspects. This IWGDF, ESVS, SVS Intersocietal guideline on PAD in people with diabetes mellitus is also part of the IWGDF guidelines on the management of diabetes-related foot complications with additional chapters on Prevention, Classification, Infection, Offloading, Wound healing, and Charcot, all available on *www.iwgdfguidelines.org* and published in a special issue in DMRR. These guidelines are summarised for daily clinical use in the Practical Guidelines on the prevention and management of diabetes-related foot disease, all available on *www.iwgdfguidelines.org* and published in a special issue in DMRR. This guideline builds upon a previous version of the IWGDF guideline on peripheral artery disease in patients with foot ulcers and diabetes, and integrates with the Global Vascular Guidelines on the management of Chronic Limb-threatening Ischaemia (17, 34).

RECOMMENDATIONS

DIAGNOSIS

Clinical question: In a person with diabetes with or without a foot ulcer does medical history and clinical examination (including pulse palpation) compared with a reference test (imaging- digital subtraction angiography [DSA], magnetic resonance angiography [MRA], computed tomography angiography [CTA], colour Duplex ultrasound [CDUS]) accurately identify PAD and reliably diagnose PAD?

Clinical question: In a person with diabetes with or without a foot ulcer, which non-invasive bedside testing alone or in combination compared with reference tests (imaging- digital subtraction angiography [DSA], magnetic resonance angiography [MRA], computed tomography angiography [CTA], colour Duplex ultrasound [CDUS]) should be performed to accurately and reliably diagnose PAD?

Recommendation 1: In a person with diabetes without a foot ulcer, take a relevant history for peripheral artery disease, examine the foot for signs of ischaemia and palpate the foot pulses at least annually, or with any change in clinical status of the feet. (Strong, Low)

Recommendation 2: In a person with diabetes without a foot ulcer, if peripheral artery disease (PAD) is suspected, consider performing pedal Doppler waveforms in combination with ankle brachial index (ABI) and toe-brachial index (TBI).

No single modality has been shown to be optimal for the diagnosis of PAD, and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥ 0.70; and triphasic or biphasic pedal Doppler waveforms. (Conditional, Low)

Rationale: Diagnosis and treatment of PAD is critical due to the increased risk of developing DFU as well as the increased rate of complications from co-existent cardiovascular disease including myocardial infarction and stroke (32). Evidence for the diagnostic accuracy of pulse palpation for PAD in people with diabetes without DFU is limited with two studies of low quality demonstrating that although presence of pulses does not exclude disease , there is a small increase in ability to rule disease in where a foot pulse is absent or weak (positive likelihood ratio [PLR]1.84 to 2.46) (35, 36);(The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the negative likelihood ratio [NLR] expresses a change in odds of experiencing an outcome if the test is negative. A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful diagnostic test). However, it is important to recognise that pulse palpation should therefore be performed, and results considered in the context of other clinical examinations that may be associated with PAD including hair loss, muscle atrophy and reduced peripheral skin temperature. It should be noted that these clinical examinations are highly subjective and such findings may also be associated with neuropathy. PAD may also be asymptomatic or have an atypical presentation in people with diabetes as in other elderly or at-risk populations (24, 37, 38). For example, peripheral neuropathy can mask pain symptoms and autonomic neuropathy can result in a warm foot, meaning that the widely recognised signs and symptoms of PAD may not be present (39).

These recommendations are applicable to all people with diabetes. When DFU is absent, but there are clinical signs and symptoms of PAD or PAD is suspected, for example due to long-standing diabetes,

chronic hyperglycaemia, other diabetes complications such as peripheral neuropathy or presence of atherosclerotic disease in other vascular beds, more frequent screening vascular assessment including additional bedside testing is necessary. These recommendations are consistent with other (inter)national guidelines on the management of diabetes, endorsing annual clinical assessment for PAD (and for other foot complications) in people with diabetes (40-43).

Although based on low quality evidence, data demonstrating increased likelihood of PAD in those with weak or absent pulses and elevated risk of cardiovascular morbidity and mortality support the preference of a person with diabetes for clinical examination including pulse palpation to be performed (32, 44). The non-invasive nature of clinical examination and pulse palpation suggest these assessments would be valued by people with diabetes as initial diagnostic tests. As equipment is not required, the Writing Committee considered pulse palpation and other forms of clinical examination having low resource requirements, can be applied on a broad scale by a range of practitioners, and offer a method to increase equity of health care access that is both feasible for health care providers and acceptable for people with diabetes. We therefore made this a strong recommendation based on low certainty of evidence and expert opinion.

Bedside testing techniques that provide objective measurement of peripheral blood flow in the lower extremity (e.g., ankle-brachial index [ABI], toe-brachial index [TBI] and pedal Doppler waveforms) have been shown to be useful as a means to diagnose and exclude PAD in people with diabetes. Our systematic review demonstrates that multiple bedside testing techniques that offer objective measurement of the peripheral circulation in the lower limb are useful as a means to rule disease in or out for people with diabetes without a DFU but who are suspected of having PAD (44).

We identified forty studies investigating the diagnostic accuracy of non-invasive bedside tests in populations with diabetes (44). Twenty-five of the studies were prospective, two cross sectional and the remainder retrospective. Overall, the studies were of low quality and evidence was judged as being of low certainty. . Although we could not identify the absolute threshold or 'normal' values of bedside tests, we suggest that PAD is a more likely to be present in this population with an ABI <0.9 or >1.3, a TBI <0.70, and presence of one or more monophasic Doppler waveforms from assessment of pedal arteries with continuous wave Doppler (CWD) (44). In people without DFU, an ABI of <0.90 is associated with a moderate to large increase in likelihood of PAD with PLRs ranging from 2.1 to 19.9, however the ability to rule disease out is limited (NLR 0.29 to 0.84). A TBI <0.70 has a moderate ability to diagnose and exclude PAD (PLRs 2.0 to 3.55, NLRs 0.25 to 0.44) and the presence of a visual monophasic pedal Doppler waveform has a moderate ability to diagnose and exclude PAD (PLR 7.09, NLR 0.19). Non-invasive tests are therefore likely to be beneficial for people without a DFU, however high quality studies of diagnostic accuracy are required. A summary of results is provided in Supplementary Table 1.

When calculating the ABI in the leg of a person with and without DFU for the purposes of diagnosing PAD we advise to use the lower systolic blood pressure of either the dorsal pedis or posterior tibial artery as this improves the diagnostic accuracy of the test (44). For PAD affecting arteries below the knee this calculation method identifies the most severe disease while using the higher pressure identifies the least affected artery. We also recommend using the three tests (ABI, TBI and pedal Doppler

waveforms). This is due to the fact that the accuracy of the tests may be affected by the presence of other diabetes-related complications.

Due to the use of bedside measures to monitor PAD status over time, reliability (or reproducibility) of the tests is important in determining their clinical effectiveness. Our systematic review showed the reliability of both the ABI and TBI was good to excellent, however these tests are limited by wide margins of error which affect the amount of change required for this to be considered a true change rather than related to error in the measurement. For example, an ABI measured by the same rater requires a change of 0.15 to be considered a true change (45). Therefore, care should be taken in performing the measurement to control for factors that may introduce error including incorrect positioning of the person being tested (this should be horizontal supine) and incorrect testing procedures (e.g. pre-test exercise, caffeine consumption etc).

Our recommendation identifies the need to perform bedside testing in people with diabetes in whom PAD is suspected. In people with diabetes without a DFU, the presence of PAD will increase the risk of a future DFU and amputation, its presence will therefore influence the frequency of screening and the measures that can be safely taken to reduce the risk of amputation, as described in the Prevention Guidelines of the IWGDF. It is therefore critical that apart from the history and foot examination, risk factors for PAD are also considered such as long standing or poorly controlled diabetes or diagnosis of atherosclerosis in other vascular beds Considering the benefits and harms of this recommendation we judge it essential to diagnose or exclude PAD in this population given the large impact of untreated disease, the low burden of the tests to the person undergoing testing and the high likelihood that diagnosis will be valued by them. All aforementioned bedside tests (ABI, TBI, CWD) should be performed by trained health care professionals in a standardized manner and these tests can be applied by a wide range of practitioners, after having received adequate training. From the perspective of middle- or high-income countries the resources required to undertake bedside testing are relatively low in comparison to other methods of diagnosing PAD such as CDUS, CTA, MRA and angiography. It is likely that many people will value the knowledge that their feet need more intensive care to prevent amputation, but this has not been studied in a sufficiently large cohort. Based on the uncertainty of the evidence we made a conditional recommendation for additional non-invasive testing in this group of people with asymptomatic disease. The role of additional testing in those with intermittent claudication is outside the scope of these guidelines.

Recommendation 3: In a person with diabetes with a foot ulcer or gangrene, take a relevant history for peripheral artery disease, examine the person for signs of ischaemia and palpate the foot pulses. (Strong, Low)

Recommendation 4: In a person with diabetes with a foot ulcer or gangrene, evaluate pedal Doppler waveforms in combination with ankle brachial index (ABI) and toe-brachial index (TBI) measurements to identify the presence of peripheral artery disease (PAD).

No single modality has been shown to be optimal for the diagnosis of PAD, and there is no value above which PAD can be excluded. However PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥ 0.70; and triphasic or biphasic pedal Doppler waveforms. (Strong, Low)

Rationale: PAD is present in approximately half of the people with a DFU (26, 27). Therefore, in any person with diabetes and a foot ulcer or gangrene, PAD should be considered and should be excluded with the appropriate diagnostic strategies. Subsequently, once diagnosed the second question is whether the PAD is of sufficient severity to contribute to delayed wound healing and increased risk of amputation. This will inform whether further investigation or intervention is required. In addition, although cardiovascular risk factor modification is always indicated in people with diabetes, those with symptomatic PAD (i.e., also those with a DFU) belong to the very high cardiovascular risk category and need more intensive risk treatment, as described in the Treatment Section.

Apart from taking a clinical history, all people with a DFU or gangrene should undergo a complete physical examination, including palpation of the lower limb pulses which can help to determine the presence of arterial disease (46). In our systematic review on diagnosis, we identified one study of low quality, that assessed the diagnostic accuracy of pedal pulse assessment in people with a DFU (47). Pulse palpation had a PLR of 1.38 and a NLR 0.75 for PAD in people presenting with a foot ulcer (47). These likelihood ratios represent a very small ability of the test to identify or exclude disease. Pulse palpation should be seen as the first step in a systematic evaluation of the affected limb and foot, but when DFU is present further diagnostic procedures should be performed with non-invasive bedside testing techniques as clinical examination is not sufficient to exclude PAD. Although of limited value it should not be discarded as in the early phase of management other tests are sometimes unavailable, or findings may be difficult to interpret. The evidence base is small with low certainty but as previously discussed this form of testing has low resource requirements, can be applied on a broad scale by a range of practitioners, is feasible and may increase equity of health care access. We therefore made this a strong recommendation based on low certainty of evidence and expert opinion. However, a systematic foot examination for signs of ischaemia should be the starting point of a systematic evaluation, as failure to diagnose and treat this condition may have dire consequences in many people. When DFU is present further diagnostic testing using bedside testing techniques in the first instance should performed as palpation of foot pulses and clinical examination alone are not sufficient to exclude PAD.

Our systematic review identified eight studies (47-54) of diagnostic accuracy of bedside testing that included participants with active DFU, with the proportion of the study population affected ranging from 6.6% to 100% (47, 48). One study demonstrated a visual pedal Doppler waveform evaluation to be diagnostic (PLR ≥ 10), with a moderate ability of the test to exclude PAD. In a second study ~40% of the participants having a foot ulcer, the PLR was lower (3.04) and the NLR similar (0.35) (52). In studies in which the majority of the study population had DFU an ABI <0.90 increased the pre-test probability of disease by a small amount (PLR: 1.69 to 2.40) with limited ability of the test to exclude disease (NLR: 0.53 to 0.75) (47, 50, 53, 54). Similarly, data for the TBI were limited and variable with the PLR in -both mixed populations (with and without DFU) and DFU only, ranging from 1.62 (indicating limited ability to diagnose disease) to being diagnostic (PLR ≥ 10) and indicating the test has small to moderate ability to exclude disease (NLR 0.30 to 0.47) (47, 50, 52, 53).

All aforementioned non-invasive tests (ABI, TBI, CWD) can be applied by a wide range of practitioners, in particular in settings where people are treated in secondary care or specialised outpatient foot clinics. These tests have low resource requirements relative to other methods of diagnosing PAD such as CDUS and angiography. These factors are likely to increase equity in health care access and make the

tests feasible and acceptable for both the person having the tests and health care providers. Given the large potential beneficial effect and its impact on subsequent treatment we made a Strong recommendation for this population, although we acknowledge the limitations of the evidence base.

Recommendation 5: In a person with diabetes without a foot ulcer in whom a non-emergency invasive foot procedure is being considered, peripheral artery disease should be excluded by performing pedal Doppler waveforms in combination with ankle-brachial index and toe-brachial index. Best Practice Statement

Rationale: Except when required as an emergency to control severe infection, all people with diabetes who require foot surgery should have vascular testing consisting of pedal Doppler waveforms in combination with ABI and TP or TBI. Non-emergency invasive procedures, such as elective surgery, may be indicated in people with diabetes without a DFU with the intent to address painful foot conditions. Particularly in those with peripheral neuropathy (55), prophylactic procedures could be considered to address risk factors for foot ulceration, such as foot deformity and elevated localised plantar pressures. Prior to any surgical procedure on the foot in a person with diabetes, PAD status should be established and this finding should contribute to determination of suitability of an individual for the procedure. The decision to perform the elective surgery should be made in a shared decision-making process that will be influenced by balancing the benefit of the operation versus the potential harm, such as the risk of poor wound healing based on the non-invasive assessments.

As discussed above bedside testing generally has moderate ability to diagnose PAD or to exclude this disease in people with diabetes mellitus. Any abnormal test result should be considered indicative of PAD. Therefore, we suggest this recommendation will reduce the risk of undiagnosed severe PAD which would potentially negatively affecting post-surgical outcomes and it is likely that people will value this approach. Feasibility and the impact of these tests on resource use are discussed in recommendation 4. No randomised controlled trials (for ethical reasons) or observational studies of sufficient quality have been performed on the added value of performing bedside tests prior to any surgical procedure in the foot. Given the indirect evidence discussed above, the major clinical implications of missing the diagnosis of PAD and the limited harm and additional costs, a "Best Practice Statement" was made.

PROGNOSIS

Clinical question: In a person with diabetes, suspected PAD and a foot ulcer or gangrene, which non-invasive bedside tests, alone or in combination, at any time point (including after revascularisation procedures), predict DFU healing, healing after minor amputation, and major amputation?

Recommendation 6: In a person with diabetes and a foot ulcer, or gangrene, consider performing ankle pressures and ankle-brachial index (ABI) measurements to assist in the assessment of likelihood of healing and amputation.

Ankle pressure and ABI are weak predictors of healing. A low ankle pressure (e.g. <50 mmHg) or ABI (e.g. <0.5) may be associated with greater likelihood of impaired healing and greater likelihood of major amputation. (Conditional, Low)

Recommendation 7: In a person with diabetes and a foot ulcer or gangrene, consider performing a toe pressure measurement in order to assess likelihood of healing and amputation.

A toe pressure ≥ 30 mmHg increases the pre-test probability of healing by up to 30% and a value <30mmHg increases the pretest probability of major amputation by approximately 20%. (Conditional, Low)

Recommendation 8: In a person with diabetes and a foot ulcer or gangrene, if toe pressure cannot be performed, consider performing a transcutaneous oxygen pressure ($TcPO_2$) measurement or a skin perfusion pressure (SPP) to assess likelihood of healing.

A $TcPO_2$ ≥ 25 mmHg increases the pre-test probability of healing by up to 45% and value <25 mmHg has been shown to increase the pre-test probability of major amputation by approximately 20%. An SPP ≥ 40mmHg increases the pre-test probability of healing by up to 30%. (Conditional, Low)

Rationale: The presence of PAD constitutes a significantly increased risk of failure to heal and major lower limb amputation for people with a diabetes-related foot ulcer or gangrene. Bedside testing results are an integral component of determining the severity of ischaemia and, to that end, to determine the need for, and urgency of, further investigations. Non-invasive bedside tests including AP, ABI and TP should be performed in a person with a DFU or gangrene to guide further management as they can help to predict the chance of healing and/or major amputation. $TcPO_2$ and skin perfusion pressure (SPP) give additional information on healing potential and are useful for measuring perfusion following forefoot amputations when TP are no longer possible. However, in our opinion these are secondary tests due to greater expense and less availability of the equipment and the time and expertise required to apply them.

Assessment of the pedal arterial Doppler waveforms combined with measurement of the AP and subsequent calculation of the ABI, are usually the first steps in the assessment of PAD. Although relevant for its diagnosis, as discussed in the Rationales of Recommendations 1 and 2, we could not identify sufficient data on the capacity for Doppler arterial waveform analysis to predict wound healing in populations with DFU (44). We did identify two studies of low quality that concluded that abnormal or absent Doppler waveforms were associated with a small (15%) increase in the likelihood of major amputation (56, 57), further limiting its use. Similarly there are currently insufficient data to support the use of TBI to predict healing or amputation outcomes, however TP (as a component of TBI) has been more widely investigated and is therefore included in our recommendation.

The predictive capacity of APs and ABI for wound healing was inconsistent in the 15 studies included in our systematic review (44). We could not identify thresholds for AP and ABI which were associated with increased probability of healing, however a very low ankle pressure (e.g. <50 mmHg) or ABI (e.g. <

0.5) was associated with a greater likelihood of delayed healing and according to current guidelines revascularisation should be considered when such values are measured in people with PAD and an ulcer or gangrene (17). AP and ABI values > 50 mmHg or > 0.5, should not be used in isolation to predict likelihood of ulcer healing given their uncertainty, but detailed clinical examination and further vascular testing is needed, as stated in recommendation 6. Regarding amputation risk, the probability of major amputation was increased by approximately 45% with an ABI <0.4 based on one study in people who had undergone transmetatarsal amputation however an ABI threshold <0.9 was not associated with any increase (44, 60).Thresholds used for AP were highly variable in the literature and we were unable to determine which threshold was optimal (44). Other research has demonstrated an elevated ABI (>1.3) is associated with both greater likelihood of amputation and worse amputation free survival outcomes and therefore should be recognised as a risk factor for poor DFU outcomes. The same observations were made in people without diabetes and an elevated ABI is therefore seen as a marker for more severe cardiovascular disease with an elevated risk of amputation (61, 62).

TP and TBI can assess blood flow distal to the forefoot and toes, where most DFUs occur (63).Based on ten studies of low quality we found that with TP of ≥ 30 mmHg the pretest probability of healing was increased by up to 30% (64). Regarding major amputation, a value <30 mmHg increases the probability of major amputation by approximately 20%, which suggests a (somewhat) lower predictive capacity compared with the ABI. In the three studies identified, there was inconsistent and insufficient evidence for the use of the TBI to predict either healing or major amputation.

$TcPO_2$ and SPP are additional tests that have the advantage of measuring perfusion at tissue level and therefore reflect both macrovascular and microvascular function. In our systematic review the majority of available studies (n=7) which were of low quality, reported that $TcPO_2$ can be used to predict the likelihood of DFU healing, (58, 59, 64-71) although there is variability in the thresholds used. With a $TcPO_2$ ≥ 25 mmHg the pretest probability of healing is increased by up to 45%, which was higher than reported for the other tests in the studies we included. Regarding amputation, a value < 25 mmHg increases the probability of major amputation by approximately 20%, a predictive value that seems lower than that of the ABI when we compared the different studies. A SPP (≥ 40mmHg) was shown to increase the pre-test probability of healing by up to 30% in one study of low quality (72). There are insufficient data investigating the relationship between SPP and amputation outcomes to formulate a recommendation.

In summary, when comparing different studies, the ABI seemed to have the best predictive capacity for major amputation, while the TP and $TcPO_2$ seemed to have a better predictive capacity for wound healing. It was noteworthy that there was insufficient evidence for the use of the TBI to predict either healing or amputation outcomes. The number of prospective studies and the number of participants included in the aforementioned studies were relatively low, the populations studied differed and results of the tests performed were frequently not blinded. Moreover, comparison of studies was hampered by the fact that different studies used different thresholds for disease and thus combining data for analysis was not possible.

When bedside testing is not performed the risks of a poor clinical outcome or unnecessary, more costly, investigations are large. As discussed earlier the majority of bedside tests are of low burden to both the

person and the health care system although training and expertise are necessary. If these tests are not performed, the clinician has to rely only on clinical judgement and on imaging investigations. Although imaging will provide details of the arterial anatomy, the non-invasive tests will inform the clinician about the perfusion in the foot. However, absolute perfusion thresholds applicable for all people cannot be provided as the outcome of the DFU is determined not only by the degree of ischaemia. Other factors such as infection, extent of tissue loss and ulcer depth, can have a major effect on healing potential and amputation risk, as discussed below. For this reason and the uncertainty of the evidence, we made Conditional recommendations for use of AP, ABI and TP to predict the likelihood of healing and amputation.

$TcPO_2$ and SPP tests require more expensive equipment and greater expertise for application than other bedside testing which may be a barrier for centres in low- or middLe-income countries. Although health care expenditures may increase with each of these measurements, incorrect assessment of the severity of PAD can result in inadequate treatment and poorer outcomes with ultimately an increase in costs. Importantly all the aforementioned bedside tests have varying capacity to predict likelihood of healing and of amputation, as summarised in our systematic review(73). Based on current evidence no test has convincingly been shown to perform better than other tests as a prognostic indicator of both healing and amputation. In the opinion of the Writing Committee multiple tests should be used. Given the limited available evidence on $TcPO_2$ and SPP and their higher costs we made a conditional recommendation on these two tests.

Recommendation 9: In a person with diabetes and a foot ulcer or gangrene, it is suggested the presence of peripheral artery disease and other causes of poor healing should always be assessed. Diabetes-related microangiopathy should not be considered the primary cause of foot ulceration, gangrene or poor wound healing without excluding other causes. (Conditional, Low)

Rationale: The definition of microvascular disease in DFU and its role in wound healing are not well understood. Many clinicians have assumed that microvascular disease is present in a high proportion of people with DFU and that it is a major cause of delayed wound healing- often despite a lack of thorough investigation of large vessel arterial disease. As discussed elsewhere in this guideline, people with diabetes and a DFU frequently have distal, lower leg obstructive atherosclerotic disease often with involvement of the pedal arteries, which due to their smaller size can be difficult to image. However, advances in imaging and technology have shown that tibial and pedal arteries are potentially treatable by endovascular and open surgical techniques.

The term "microvascular" disease describes abnormalities affecting the arteriolar, capillary and venular vessels. Several studies have reported microvascular abnormalities in the skin and subcutaneous tissues in people with diabetes. These abnormalities can be structural, i.e. occlusive disease and alterations in the blood vessel wall, and functional, such as impaired vasodilatory responses to endogenous or noxious stimuli (74). However, in our systematic review on this topic we could not identify studies of sufficient quality showing that such abnormalities contribute to impaired wound healing (75). One prospective study did report that microvascular changes observed in skin-biopsies in the feet in people with diabetes and neuro-ischaemia were associated with poorer wound healing after revascularisation (76). However, both these microvascular changes and poorer wound healing could be due to tissue damage caused by

ischaemia and not by pre-existing diabetes-related microangiopathy. If perfusion of the foot ulcer is adequate but the ulcer fails to heal, other causes of poor wound healing should be sought and treated, such as infection, insufficient protection from biomechanical stress, oedema, poor glycaemic control, poor nutritional state and underlying co-morbidities (77). Based on the lack of studies showing that diabetes-related micro-angiopathy contributes to poor wound healing in DFU and the potential harm if this is assumed, we made a conditional recommendation based on low certainty of evidence.

Recommendation 10: In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, consider using the Wound/Ischaemia/foot Infection (WIfI) classification system to estimate healing likelihood and amputation risk. (Conditional, Low)

Rationale: The Wound, Ischaemia and Foot infection (WIfI) classification system was developed to guide the clinician in estimating the risk of amputation and potential benefit of revascularisation in people with a foot ulcer or gangrene and is recommended by the Global Vascular Guideline for limb staging (relating to severity of limb threat) in people with chronic limb threatening ischaemia (CLTI) (17). This system was developed by an interdisciplinary panel of experts and stages the limb based on the presence of, and severity of, the foot wound, ischaemia and infection. A Delphi consensus process was used to allocate these combinations into 4 clinical stages based on very low (stage 1), low (stage 2), moderate (stage 3) and high (stage 4) predicted one-year risk of major amputation. Consistent with all other commonly used limb staging systems, co-morbidities of individuals which are likely to influence wound healing and amputation risk are not incorporated into WIfI. A second distinct aspect of the WIfI system is the predicted likelihood of benefit from revascularisation (78).

A recent systematic review concluded that in people undergoing a revascularisation procedure, the likelihood of an amputation after one-year increases with higher WIfI stages. The estimated one-year major amputation rates from four studies comprising 569 participants were 0%, 8% (95% CI 3-21%), 11% (95% CI 6-18%) and 38% (95% CI 21-58%), for WIfI clinical stages 1-4, respectively (79). For the population of people with a DFU, the WIfI system was evaluated in the IWGDF systematic review on classification systems, that is published in parallel to this guideline. In summary, in people with diabetes, PAD and a foot ulcer this systematic review identified seven studies, with low certainty evidence, demonstrating that a high WIfI limb clinical stage is associated with longer time to healing and increased likelihood of non-healing at 6 and 12 months (80-86). Higher WIfI clinical stages are also associated with increased likelihood of major amputations with one study reporting amputation rate of 64% for stage 4 (87). Similarly, higher WIfI clinical stages have been linked to high rates of minor amputation and lower rates of amputation free survival at 12 months (82, 83, 86, 88-93). For prediction of revascularisation benefit there are few data available and inadequate evidence to determine whether WIfI revascularisation benefit staging predicts healing or amputation outcomes in people undergoing revascularisation.

The WIfI tool (Table 1) has demonstrated predictive capacity for the key outcomes of wound healing and amputation in people with DFU (82, 83, 86, 88-93). It uses clinical grading of infection and wound characteristics in combination with non-invasive bedside testing to determine severity of ischaemia and it has wide availability, also as an online tool (*apps.apple.com/us/app/svs-ipg/id1014644425*). Moreover, it can be used by a wide range of practitioners making application in clinical practice feasible, its costs are

relatively limited, and it is expected to be acceptable to practitioners as well as being of value to people receiving the care. It is likely to stimulate a standardised access to a form of vascular assessment, which is also relevant for low-income countries where invasive testing may not be a widely available. Due to the observational and often retrospective nature of most of the current evidence, this recommendation was made conditional.

Table 1A: Wound Infection foot Ischaemia Classification System: Wound clinical category

Grade	Clinical Description
0	Ischaemic rest pain; without frank ulcer or gangrene
1	Minor tissue loss: small shallow ulceration < 5 cm^2 on foot or distal leg No gangrene. Salvageable with simple skin coverage or ≤ 2 toe amputations
2	Major tissue loss: deeper ulceration(s) with exposed bone, joint or tendon, ulcer 5-10 cm^2 not involving calcaneus; gangrenous changes limited to digits. Salvageable with extensive forefoot surgery
3	Extensive ulcer/gangrene > 10 cm^2 involving forefoot or midfoot; full thickness heel ulcer > 5 cm^2 + calcaneal involvement. Salvageable only with complex foot reconstruction

Table 1B: Wound Infection foot Ischaemia Classification System: Ischaemia category

Grade	ABI	Ankle SP (mmHg)	TP, $TcPO_2$ (mmHg)
0	≥ 0.8	≥ 100	≥ 60
1	0.6-0.79	70-99	40-59
2	0.40-0.59	50-69	30-39
3	<0.40	<50	<30

Table 1C: Wound Infection foot Ischaemia Classification System: foot Infection category

Grade	Clinical Description	IDSA	IWGDF Class
0	Wound without purulence or manifestations of infection	uninfected	1
1	>2 manifestations of infection, erythema (< 2cm), pain, tenderness, warmth or induration) no local complications or systemic illness	mild	2
2	Infection in patient who is systemically stable but has ≥ 1 of; cellulitis (>2 cm), lymphangitis, spread beneath fascia, deep tissue abscess, gangrene, muscle, tendon, joint or bone involvement	moderate	3
3	Infection in patient with systemic or metabolic toxicity (SIRS/ sepsis)	severe	4

Table 1D: Wound Infection foot Ischaemia Classification System: Estimate risk of amputation at 1 year

	Ischemia – 0				Ischemia – 1				H	Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H		L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H		L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H		M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H		H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3		FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

Table 1E: Wound Infection foot Ischaemia Classification System: Estimate likelihood of benefit of/requirement of revascularisation

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

Key:

Very Low = VL = Class or Clinical Stage 1
Low = L = Class or Clinical Stage 2
Moderate = M = Class or Clinical Stage 3
High = H = Class or Clinical Stage 4

TREATMENT

Clinical question: In which persons with diabetes, PAD and a foot ulcer or gangrene using clinical findings, perfusion test findings, and/or classification systems, should revascularisation be considered?

Recommendation 11: In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who is being considered for revascularisation, evaluate the entire lower extremity arterial circulation (from aorta to foot) with detailed visualization of the below-knee and pedal arteries. Best Practice Statement

Rationale: As per our recommendations 1-4 clinical examination and bedside testing should be the first line testing undertaken to diagnose the presence of PAD. When a revascularisation is being considered further anatomical information on the arteries of the lower limb should be obtained to assess the presence, severity, and distribution of arterial stenoses or occlusions. In this process, adequate imaging of the tibial and pedal vessels is of critical importance, particularly in planning intervention in people with diabetes and a foot ulcer (17). Modalities that can be used to obtain anatomical information include: arterial colour duplex ultrasound, computed tomographic angiography, magnetic resonance angiography, or intra-arterial digital subtraction angiography (including anteroposterior and lateral views of the foot). The Writing Committee considered that each of the imaging techniques have their advantages and disadvantages and their use will depend heavily on the availability of equipment and local expertise, preferences of the individual and associated costs. For these reasons a Best Practice statement was formulated. Regarding their use in people with diabetes, the utility of some these techniques, such as CDUS and CTA, can be affected by (severe) MAC, which is frequently present in the smaller arteries of the leg in people with DFU. MRA images are incapable of defining the extent of calcification which may be important when planning revascularisation (17). Finally, as stated in the Global Vascular Guidelines, catheter digital subtraction angiography (DSA), represents the gold standard imaging technique, especially for the below knee and foot arteries (17). In many centres DSA is typically used when MRA or CTA are not available, fail to adequately define the arterial anatomy, or when an endovascular intervention is planned. Arterial imaging should allow complete anatomical staging from aorta to foot using, for example, TASC for aorto-iliac disease and the Global Anatomic Staging System (GLASS), described in the Global Vascular Guidelines, for infrainguinal and pedal disease (17).

Recommendation 12: In a person with diabetes, peripheral artery disease, a foot ulcer and clinical findings of ischaemia, a revascularisation procedure should be considered. Findings of ischaemia include absent pulses, monophasic or absent pedal Doppler waveforms, ankle pressure < 100 mm Hg or toe pressure < 60 mm Hg. Consult a vascular specialist unless major amputation is considered medically urgent. Best Practice Statement

Rationale: The natural history of people with diabetes, PAD, and a DFU or gangrene remains poorly defined, but in two studies reporting the outcomes of participants with diabetes and limb ischaemia who were not revascularised, the limb salvage rate was around 50% at 1 year (66, 94). Our analysis of the evidence for revascularisation suggests that revascularisation in appropriately selected people with diabetes and hemodynamically significant PAD, can improve perfusion, expedite wound healing and reduce major limb amputations(73). After a revascularization procedure, most studies report limb salvage rates of 80% to 85% and ulcer healing in >60% at 12 months (95). On the other hand,

performing a revascularisation is not without risks. As summarised in the systematic review performed by the IWGDF in 2019 (95), peri-operative or 30-day mortality was around 2% in people with diabetes undergoing either endovascular or surgical revascularisation (95). The highest risk group includes people with end-stage renal disease, who have a 5% perioperative mortality, 40% 1-year mortality and 1-year limb salvage rates of around 70% (95).

People with signs of ischaemia, e.g., as defined by WIfI and the Global Vascular Guidelines; absent pulses and monophasic or absent pedal Doppler waveforms, ankle pressure < 100 mm Hg or toe pressure < 60 mm Hg, are very likely to have significant PAD that could impact wound healing potential and amputation risk (17, 78). We judged in our systematic review the certainty of the evidence on the effects of revascularisation on wound healing and amputation risk as low, as many important factors that can affect outcomes were not reported such as the availability of vein conduit, wound care, offloading and sufficient anatomical details about the extent and severity of the lesions treated. Factors that influence the decision to revascularise include the degree of limb threat (e.g., WIfI classification), the amount of tissue loss, presence of infection, co-morbidities, feasibility of the different revascularisation options and their risk.

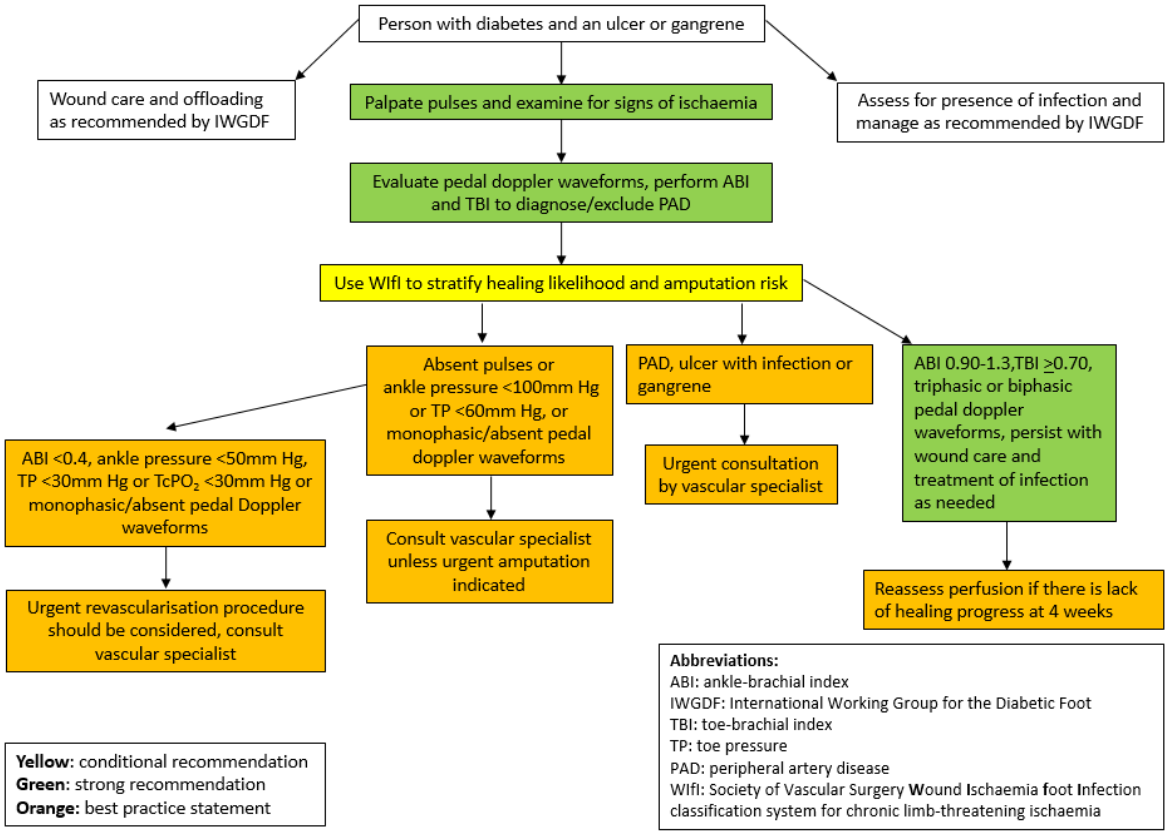
As discussed in other parts of the IWGDF Guidelines, restoration of perfusion in the foot is only part of the treatment required to optimise wound healing and to prevent or limit tissue loss, which should be provided by a multidisciplinary team (77). Any revascularisation procedure should be part of a comprehensive care plan that addresses other important issues including: prompt treatment of concurrent infection, regular wound debridement, biomechanical off-loading, control of blood glucose, assessment and improvement of nutritional status, as well as treatment of oedema and co-morbidities (77). The decision to perform a revascularisation procedure and which procedure is preferred depends therefore on several factors and in each individual the balance should be made between expected benefits, potential risks, harms and costs, in a shared decision-making process. For these reasons we made a Best Practice Recommendation. The care of persons with a DFU is frequently managed by health care professionals who are not specifically trained in the treatment of PAD. Care for people with PAD is differently organised in many countries, with different medical disciplines involved, such as vascular surgeons, angiologists, interventional radiologists, nephrologists, cardiac surgeons and cardiologists. For this reason, we used the term "vascular specialist consultation" in our recommendation, but whatever the organisation of care all people with diabetes and PAD should have access to both bypass surgery and endovascular procedures.

Recommendation 13: In a person with diabetes, peripheral artery disease, a foot ulcer, and severe ischaemia i.e. an ankle-brachial index <0.4, ankle pressure <50mmHg, toe pressure <30mmHg or transcutaneous oxygen pressure <30mmHg or monophasic or absent pedal Doppler waveforms, urgently consult a vascular specialist regarding possible revascularisation. Best Practice Statement

Rationale: Severe ischaemia is defined in The Global Vascular Guidelines (GVG) as an ABI <0.4, AP pressure <50mmHg, TP <30mmHg or $TcPO_2$ <30mmHg or monophasic or absent pedal Doppler waveforms (17, 78). Such perfusion deficits are, as also stated in the GVG, an indication for revascularisation, unless contra-indicated or technically not possible. There is retrospective evidence demonstrating that a delay in revascularisation of more than two weeks in people with diabetes results

in increased risk of limb loss (96). This is supported by observational research demonstrating that a shorter time to revascularisation (<8 weeks) is associated with higher probability of DFU healing and lower likelihood of limb loss (67). As shorter time to revascularisation was associated with higher probability of DFU healing and lower likelihood of limb loss we made a Best Practice Statement supporting urgent referral for vascular consultation in people with DFU and evidence of severe ischaemia (Figure 1).

Figure 1: Assessment and management pathway for a person with diabetes, peripheral artery disease and a foot ulcer with findings of ischaemia, infection or gangrene. (Colour code: yellow=conditional recommendation, green=strong recommendation, orange= best practice recommendation)



Recommendation 14: In a person with diabetes, peripheral artery disease and a foot ulcer with infection or gangrene involving any portion of the foot, urgently consult a vascular specialist in order to determine the timing of a drainage procedure and a revascularisation procedure. Best Practice Statement

Rationale: In the presence of PAD and infection or gangrene, an urgent revascularisation should be considered. In the prospective Eurodiale study participants with the combination of a foot infection and PAD had a 1-year major amputation rate as high as 44% (80). In addition, participants with higher WIfI infection grade had higher risk of amputation in several observational studies, as summarised in our systematic review on Classification Systems (97). Delay in treatment can lead to rapid tissue destruction

and life-threatening sepsis as described in the IWGDF/IDSA Guidelines on Management of Diabetic Foot Infections (98). In a person with a foot abscess or infection of a deep foot compartment that needs immediate drainage, or where there is gangrene that must be removed to control the infection, immediate surgery should be considered first (98). This should be accompanied by broad-spectrum antibiotic therapy, which is subsequently tailored according to tissue culture results, as "time is tissue" in these people. Once the sepsis is controlled and the person is stabilized, evaluation of the arterial tree should lead to consideration for prompt revascularisation (i.e., within a few days) in people with significant perfusion deficits. Once blood flow is improved and infection is controlled, a definitive operation may be required in order to create a functional foot, which may require soft tissue and bone reconstruction (99).Due to the risk of amputation in this clinical scenario, the likelihood that the person will value avoidance of amputation, and the need for appropriate prioritisation of intervention strategies to achieve this, the Writing Committee formulated a Best Practice Statement.

Recommendation 15: In a person with diabetes and a foot ulcer, when the wound deteriorates or fails to significantly improve (e.g. a less than 50% reduction in wound area within 4 weeks) despite appropriate infection and glucose control, wound care, and offloading, reassess the vascular status and consult with a vascular specialist regarding possible revascularisation. Best Practice Statement

Rationale: Multiple factors may contribute to delayed or non-healing of DFU, including presence of infection, wound size and depth, elevated foot pressures at the wound site and inadequate wound care. A number of studies have demonstrated that a reduction in percentage of wound area of more than 50% by four weeks after presentation is predictive of healing at 12 weeks (100-103). This has been shown to be the case independent of the ulcer size at baseline and supports review of treatment protocols where adequate wound reduction is not being achieved in the four-week timeframe. Presence of suspected CLTI or a DFU that is failing to adequately heal despite best practice care requires prompt consultation with a vascular specialist and assessment of whether a revascularisation procedure is indicated. There is no direct evidence supporting our recommendation which is a pragmatic statement based on indirect evidence and expert opinion. Given the risk of poor outcomes when PAD is left untreated in a person with a poorly healing ulcer, we have made a Best Practice Statement.

Recommendation 16: In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, avoid revascularisation when the risk–benefit ratio for the probability of success of the intervention is clearly unfavourable. Best Practice Statement

Rationale: Revascularisation should not be performed if there is no realistic chance of wound healing, when major amputation is inevitable, a functional foot is unlikely to be achieved, or when life expectancy is short and there is unlikely to be of benefit to the person. The Writing Committee considered that in such persons any revascularisation procedure is unlikely to be of benefit to the person and may cause harm. Many affected individuals pose high peri-procedural risk because of comorbidities. In particular, the following people may not be suitable for revascularisation: those who are very frail, have short life expectancy, have poor functional status, are bed bound, and/or have a large area of tissue destruction that renders the foot functionally unsalvageable and those who cannot realistically be expected to mobilize following revascularisation. There are occasional situations where an arterial inflow procedure is

performed to improve the likelihood of healing of a below knee amputation, so as to avoid an above knee amputation.

There is evidence from several observational studies of a 50% healing rate for ischaemic DFU in people with diabetes unsuitable for revascularisation and this should also be considered in determining choice of care (67, 94). The decision to proceed to primary amputation, or to adopt a palliative approach, should be made in conjunction with the person and the multidisciplinary team (104) including a vascular specialist unless an emergency procedure is indicated as discussed earlier. The Writing Committee considered that in these circumstances where healing is improbable a person is unlikely to value the outcomes from revascularisation over no revascularisation. Similarly in such circumstances the benefit of revascularisation will not outweigh the potential harms.

Clinical question: In people with diabetes, PAD and either a foot ulcer or gangrene how does endovascular revascularisation compare to open or hybrid revascularisation?

Recommendation 17: In a person with diabetes, peripheral artery disease and either a foot ulcer or gangrene who have an adequate single segment saphenous vein in whom infrainguinal revascularisation is indicated and who are suitable for either approach, we suggest bypass in preference to endovascular therapy (Conditional, Moderate)

Recommendation 18: A person with diabetes, peripheral artery disease (PAD) and a foot ulcer or gangrene, should be treated in centres with expertise in, or rapid access to, endovascular and surgical bypass revascularisation. In this setting, consider making treatment decisions based on the risk to and preference of the individual, limb threat severity, anatomic distribution of PAD, and the availability of autogenous vein. Best Practice Statement

Rationale: Once the decision to revascularise has been made, the next decision is whether an endovascular, an open (i.e., bypass or endarterectomy) procedure, or a combination of both (i.e. hybrid procedure) should be performed. Recommendation 18 highlights the complementary role of open and endovascular techniques in contemporary vascular practice. In particular, endovascular techniques have largely replaced open surgery in the management of aorto-iliac disease and also allow treatment of foot and pedal arch disease.

The majority of studies we identified in our systematic review on endovascular and bypass surgical outcomes were observational and retrospective case series, with a high risk of bias (105). The BEST CLI trial was a large randomised clinical trial with low risk of bias comparing an endovascular first with a surgical first approach. People with CLTI who were deemed appropriate for revascularisation for infrainguinal arterial occlusive disease were included (106). The primary outcome was above-ankle amputation of the index limb or a major reintervention in the index limb (new bypass, vein graft interposition revision, thrombectomy or thrombolysis) or death. It was designed in two parallel-cohort trials: (Cohort 1) people who had adequate single segment great saphenous vein (GSV) available for use as a bypass conduit, and (Cohort 2) people without adequate single segment GSV who required an alternate conduit. Treatment with a GSV bypass first approach was superior to endovascular therapy first for the primary outcome (hazard ratio [HR], 0.68; 95% confidence interval [CI] 0.59-0.79; P <0.001). In Cohort 2 the primary outcomes were similar between the two groups. Subgroup analysis of

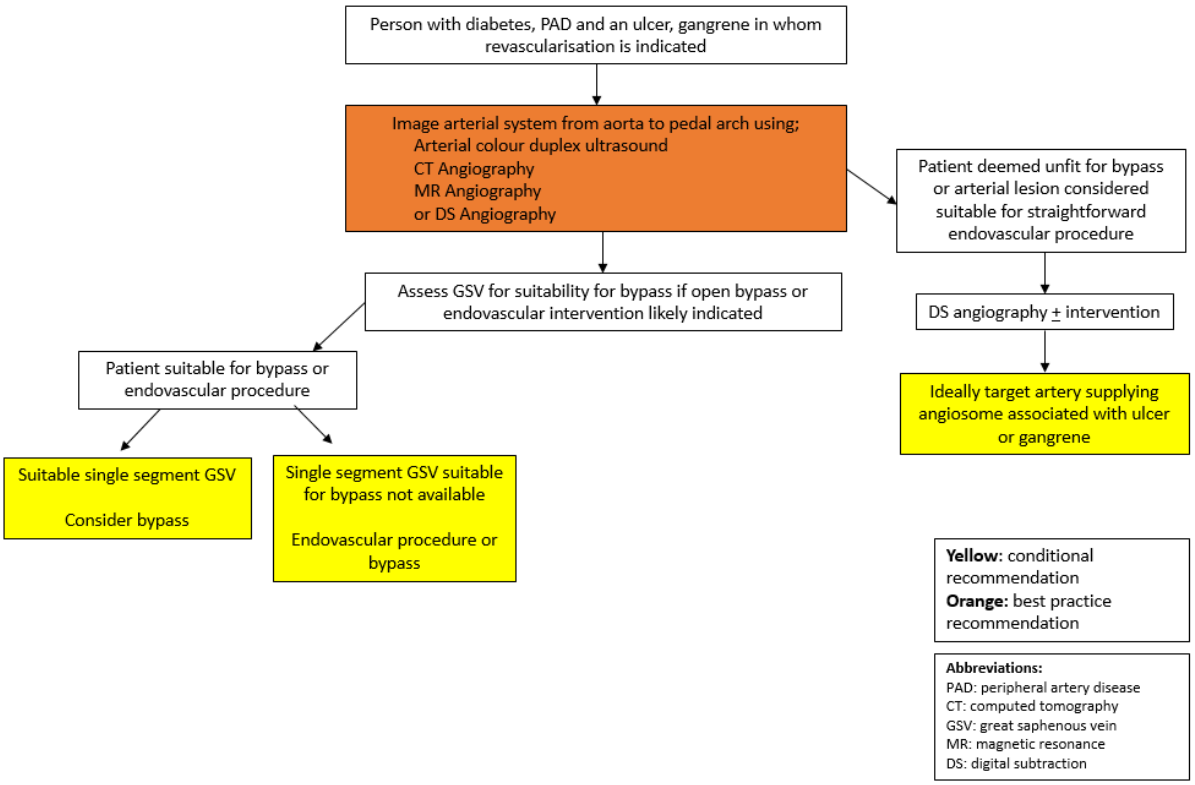
people in Cohort 1 favoured surgery in people with diabetes (HR 0.72; CI 0.61-0.86) with benefit comparable to those without diabetes (HR 0.57; CI 0.41-0.78). At the time of writing this guideline, further results of this study have not been published. Of note whole group data for Cohort 1 demonstrated a higher rate of major amputation in those undergoing an endovascular procedure compared with those having surgery (Surgery:74/709 (10.4%) Endovascular:106/711 (14.9%). Further sub-analysis may demonstrate this is relevant to those with diabetes and therefore this may affect an individual's preference for intervention. From the perspective of the person receiving treatment, the difference in length of hospital stay should be taken into account, which in our systematic review was longer in the bypass publications than in endovascular publications. In addition, people might prefer to have an endovascular approach given the more invasive approach of bypass surgery. Considering costs there are probably no major differences except the length of hospital stay however this is yet to be determined and may be an additional outcome of the BEST-CLI study. Subsequent analyses are also awaited to shed more light on the anatomical patterns and extent of disease treated, as well as which patterns of disease were not well represented or excluded. As BEST-CLI is currently the only randomised controlled trial (RCT) in this area, the certainty of the evidence for our recommendation was moderate. Given the important differences in outcomes in the BEST-CLI trial we recommend considering bypass surgery as first option in people with a suitable saphenous vein. We acknowledge that this recommendation can lead to some major changes in the policy of the many centres whichcurrently have an 'endovascular-first' approach for everyone.

Our recommendation may not be feasible in the short term in all countries due to the lack of equipment and expertise. Finally, it should be noted that in the BEST-CLI study, endovascular procedures could be performed in the iliac and common femoral artery to ensure optimal inflow into the bypass, emphasising that a centre treating PAD in people with a DFU should have the expertise to perform both endovascular and bypass procedures. In addition, in some centres the immediate availability of an endovascular approach might be a reason to opt for this treatment when an urgent revascularisation is needed or when the surgical risk is deemed too high. For these reasons and the moderate certainty of the evidence we made a Conditional recommendation.

In people with diabetes in whom a revascularisation is considered but who do not have a suitable single segment great saphenous vein for bypass surgery, the results in BEST-CLI were similar for endovascular and surgical bypass. This statement is in line with the results of our systematic review, in which the non-randomised and observational studies showed that the evidence was inadequate to establish whether an endovascular, open, or hybrid revascularisation technique is superior. Each of these techniques has its advantages and disadvantages. A successful distal venous bypass can result in a marked increase of blood flow to the foot, but general, spinal or epidural anaesthesia is usually necessary and a suitable vein, as a bypass conduit, should be present, as in the BEST-CLI trial. An endovascular procedure has several logistical advantages, but sometimes, very complex interventions are necessary to obtain adequate blood flow in the foot and a failed endovascular intervention may lead to worse outcomes when an open procedure is subsequently performed (107). Over the past few decades, there have been significant advancements in endovascular techniques; however, parallel to this, we have seen improvements in anaesthesia and perioperative care that have helped improve surgical outcomes. As there is no "one size fits all" approach to treatment for people with diabetes, PAD and foot ulceration or gangrene, it is important that a treating centre has the expertise and facilities to provide a range of

treatment options with availability of both endovascular and open techniques. We recommend that in each person requiring lower limb revascularization, all revascularisation techniques should be considered (Figure 2).

Figure 2: Approach to vascular intervention for a person with diabetes and a foot ulcer or gangrene. (Colour code: yellow=conditional recommendation, green=strong recommendation, orange= best practice recommendation)



Clinical Question: In people with diabetes, PAD and either a foot ulcer or gangrene how does direct angiosome revascularisation compare to indirect angiosome revascularisation?

Recommendation 19: In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, revascularisation procedures should aim to restore in-line blood flow to at least one of the foot arteries. Best Practice Statement

Rationale: In people with diabetes and a foot ulcer or gangrene in whom revascularisation is required, optimising blood flow to the foot is important to optimise the chance of healing the foot and avoiding amputation. Incomplete revascularisation (including treating inflow disease when distal disease is present or bypassing into "blind segment" arteries with no runoff), can result in delayed (or non-) wound healing and significant risk of amputation.

Bypass surgery is ideally performed to an outflow vessel that runs into the foot. However, bypasses performed to the peroneal artery (which rely on collateralisation to the foot) are most effective when

there is good collateralisation to the foot and a patent pedal arch is present (93). Pedal arch patency also seems to be associated with improved wound healing and reduced risk of major amputation (108).

Recommendation 20: In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who are undergoing an endovascular procedure, consider targeting the artery that on angiography that supplies the anatomical region of the ulcer, when possible or practical. (Conditional, Very low)

Rationale: Angiosomes are three-dimensional regions of tissue and skin supplied by a source artery. The six angiosomes of the foot and ankle are supplied by the posterior tibial artery (n=3), peroneal artery (n=2) and anterior tibial artery (n=1) (Figure 3). Communications between angiosomes include direct arterial-arterial connections, as well as "choke" vessels which link adjacent angiosomes (108-110). The effect/ influence of angiosome-based revascularisation on wound healing and prevention of amputation (major and minor) in the management of diabetes-related foot complications remains controversial.

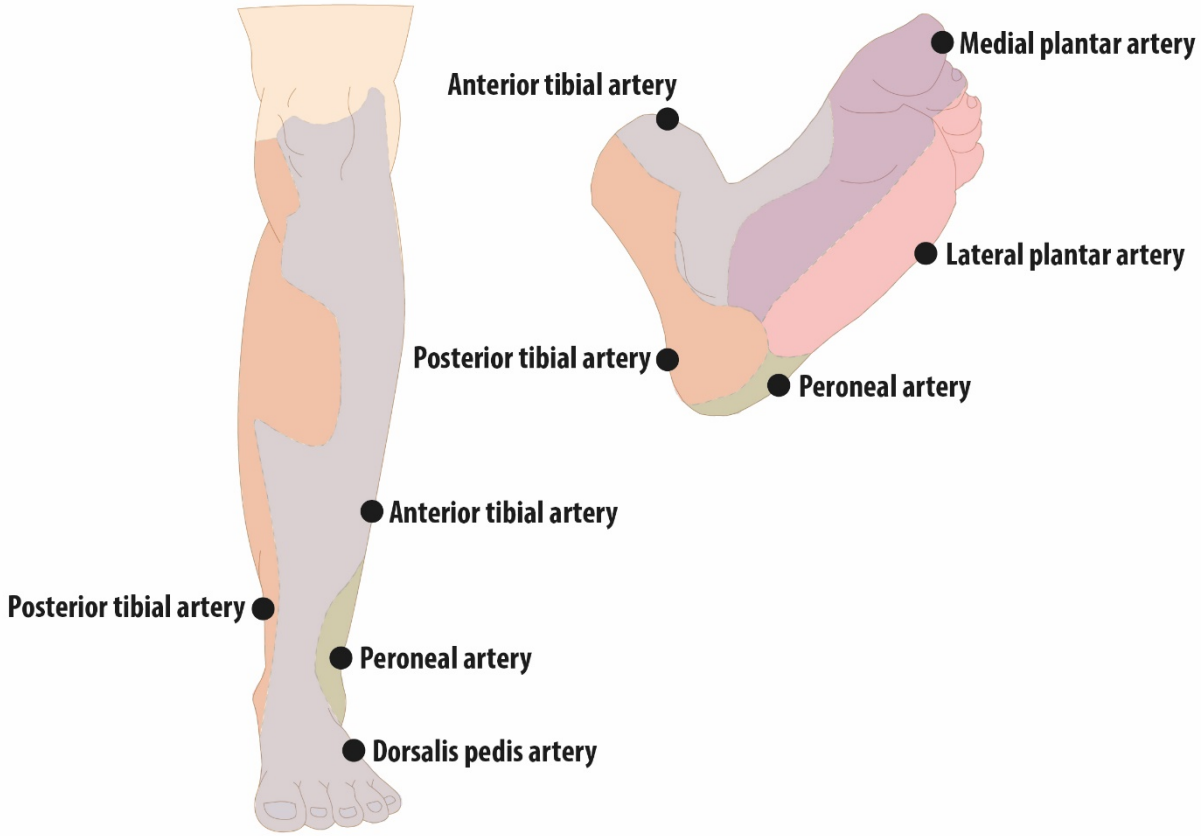
Direct revascularisation involves revascularisation of the tibial artery supplying the angiosome in which the tissue loss has occurred. The alternative to this is indirect revascularisation where the tibial artery treated is the artery in which successful in-line flow to the foot is most likely to be achieved by endovascular techniques or is deemed the best tibial outflow vessel for anastomosis in bypass surgery but does not directly supply the affected area of tissue loss. Our systematic review found that open vascular reconstruction procedures were equally effective whether direct or indirect revascularisation to the affected foot angiosome was performed (105).

In addition, healing and amputation outcomes for direct and indirect endovascular revascularisation shows that if direct revascularisation is possible, DFU healing time and major amputation may be reduced compared with indirect revascularisation. There is inadequate evidence to determine whether direct revascularisation is superior to indirect revascularisation to prevent minor amputation (111). Indirect revascularisation with collaterals was associated with wound healing and limb salvage outcomes which were similar to direct revascularisation outcomes and significantly better than the indirect without collateral cohorts (112-116).

The majority of included studies in our systematic review used endovascular procedures with data probably favouring direct revascularisation. For bypass procedures there was little difference in healing and amputation outcomes at 12 months between direct and indirect revascularisation (116-119). These studies had a high risk of bias, lacked randomisation (and it is unlikely that this will ever be possible) and were mostly retrospective. Baseline variables such as wound/foot staging (e.g., by WIfI) and extent of tissue loss were infrequently reported. Heterogeneity of the included studies was found to be high preventing meta-analysis of data. This is likely to be due to high variability in participants and wound stage (extent of tissue loss, severity of ischaemia, presence of infection). Comparison of primary outcomes (healing/ amputation) or adverse events is therefore problematic. Based on the available data it appears direct revascularisation may have improved outcomes and therefore we considered that this procedure is likely to be preferred by people receiving treatment to improve healing and prevent amputation. However, the Writing Committee considered there is likely to be important variability in patient values due to the lack of cear benefit of one approach over the other. Factors such as the severity of ischaemia and tissue loss (e.g., WIfI staging) and patient suitability for the procedure/presence of comorbidities, as well as availability of expertise and costs of the procedures

(which may vary between locations/countries) drives decision making in relation to the type of procedure considered appropriate with these factors also impacting. Several studies have noted that only a minority of foot and ankle wounds in their series corresponded to one angiosome. Kret et al, (120) found that only 36% of wounds in their series corresponded to a single distinct angiosome. Similarly, Aerden et al, (121) found it difficult to allocate people to direct revascularisation versus indirect revascularisation due to the presence of multiple wounds and large wounds that had more than one angiosome supplying them. In such cases it is the opinion of the Writing Committee that the best quality artery should preferentially be targeted. Many clinicians will consider attempting to treat the second vessel supplying the wound as well, although there is a lack of evidence to support this approach (105).

Figure 3: Angiosome distribution in the lower leg and foot.



Clinical question: In people with DFU do revascularisation perfusion outcomes predict healing, major amputation or the need for further revascularisation?

Recommendation 21: In a person with diabetes and either a foot ulcer or gangrene who has undergone revascularisation, objectively assess adequacy of perfusion e.g., using non-invasive bedside testing. Best Practice Statement:

Rationale: There are few available data examining the predictive capacity of post-revascularisation perfusion measures for healing or amputation outcomes or for the need for further revascularisation in people with diabetes. However, adequate perfusion is essential for wound healing and clinical examination is often too unreliable. Diabetes-related PAD is characterised by atherosclerotic plaque formation that is long and diffuse in nature and more likely to involve distal vascular beds. Frequently long-term patency is not achieved in endovascular treatment of tibial lesions (122).

Regular assessment of perfusion post-revascularisation should therefore be undertaken due to the risk of occlusion/ restenosis after intervention. This should be conducted in combination with regular assessment of the foot lesion to determine whether healing is indeed taking place. We recommend that revascularisation should aim to improve perfusion to the foot as much as possible, which will vary according to the individual. Due to the lack of data available determining the optimum time frame for follow-up and the likelihood that this may vary depending on the testing method being used, we have made a Best Practice Statement based on indirect evidence and expert opinion.

Recommendation 22: A person with diabetes, peripheral artery disease and either a foot ulcer or gangrene should be treated by a multidisciplinary team as part of a comprehensive care plan. Best Practice Statement

Rationale: As discussed in several parts of this guideline and in other IWGDF guidelines on the diagnosis and management of DFU, restoration of perfusion in the foot is only part of the treatment, which should be provided by multidisciplinary care team (77). Lack access to specialist care is associated with worse foot outcomes. In rural and remote locations and areas where specialist access is challenging referral pathways that address care access (e.g. through virtual referral pathways) are essential to establish to provide multidisciplinary care (123). Any revascularization procedure should therefore be part of a comprehensive care plan that addresses other important issues including: prompt treatment of concurrent infection, regular wound debridement, biomechanical offloading, control of blood glucose, cardiovascular risk reduction, and treatment of co-morbidities (123). Moreover, once the ulcer has healed the risk of recurrence is up to 50% over five years in several studies so preventive measures need to be taken and many people need long-term follow-up by a dedicated foot complication prevention team (23).

Clinical question: In a person with diabetes, PAD, and a foot ulcer, which medical treatments should be advised to prevent major adverse cardiovascular events (MACE), major adverse limb events (MALE) and death?

MACE* is defined as a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death.
MALE* is defined as the development of severe lower leg ischaemia leading to a vascular intervention or a major lower leg amputation.
* These definitions vary slightly between studies.

People with diabetes and PAD (with or without a foot ulcer) are at a very high cardiovascular risk. Cardiovascular risk factor goals should always be individualised taking life-expectancy, expected benefit, treatment burden, potential drug interactions and undesirable treatment effects into account. While taking these considerations into account the Writing Committee suggests the following treatment targets to reduce the risk of future major adverse limb and cardiovascular events:

Recommendation 23: In a person with diabetes and peripheral artery disease the following target levels should be:

- HbA1c < 8% (< 64 mmol/mol), but higher target HbA1c value may be necessary depending on the risk of severe hypoglycaemia
- Blood pressure < 140/ 90 mmHg but higher target levels may be necessary depending on the risk of orthostatic hypotension and other side-effects.
- Low density lipoprotein target of < 1.8 mmol/L (<70 mg/dL) and reduced by at least 50% of baseline. If high intensity statin therapy (with or without ezetimibe) is tolerated, target levels < 1.4 mmol/L (55 mg/dL) are recommended.

Best Practice Statement

Recommendation 24: A person with diabetes and symptomatic peripheral artery disease:

- should be treated with single antiplatelet therapy,
- treatment with clopidogrel may be considered as first choice in preference to aspirin
- combination therapy with aspirin (75 mg to 100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for people without a high bleeding risk.

Best Practice Statement

Recommendation 25: In a person with type 2 diabetes with peripheral artery disease:

- with an eGFR > 30 ml/min/1.73m2, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit should be considered, irrespective of the blood glucose level
- SGLT-2 inhibitors should not be started in drug-naïve people with a diabetes-related foot ulcer or gangrene and temporary discontinuation should be considered in people already using these drugs, until the affected foot is healed.

Best Practice Statement

Rationale: The Writing Committee decided to not write their own guidelines on pharmacological interventions in people with diabetes, PAD and a foot ulcer or gangrene in order to reduce cardiovascular risk or to prevent major limb events as defined above. There are already a number of guidelines on cardiovascular risk prevention in people with diabetes and cardiovascular disease, and thus another guideline would have little added value. We decided to base our Best Practice Statements on the Global Vascular Guidelines for CLTI produced by the ESVS, SVS and World Federation of Vascular Societies (WFVS) (17), as these address the specific population of people with CLTI. The advice on antiplatelet therapy is in line with the recent ESVS antithrombotic guidelines (124). When we felt it was applicable, we used the guidelines of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and other guidelines on peripheral artery disease (European Society of Cardiology [ESC]-ESVS, European Society of Vascular Medicine [ESVM], ESC-EASD, ESC- European Atherosclerosis Society [EAS]) (13-16, 18-20).

PAD runs a more aggressive course in those with diabetes mellitus compared with those without diabetes, with an elevated risk of lower leg amputation. In addition, the combination of diabetes and PAD is associated with a high risk of developing complications in other vascular beds. As discussed previously, persons with an ischaemic diabetes-related foot ulcer have an overall 5-year cardiovascular mortality around 50% (125). Therefore, according to the international guidelines of several major vascular and diabetes associations, these individuals should be considered as having a very high cardiovascular risk and should be treated as such. On the other hand, they usually have, in addition to peripheral neuropathy, other diabetes-related complications as well as several co-morbidities, resulting in a high burden of diseases and multiple medications (27). Many affected persons are elderly, frail and are living in vulnerable socio-economic circumstances with a low quality of life (126, 127). It is therefore essential that cardiovascular risk factor management in these people should be individualised, tailored and should be part of a shared decision-making process, taking life-expectancy, diabetes-related complications/co-morbidities, expected benefit, treatment burden, drug interactions and undesirable treatment effects into account. This care should be provided by health care worker(s) with sufficient expertise in treating cardiovascular risk factors and glycaemia, preferably by person(s) who are part of the multidisciplinary team for diabetes-related foot care.

Glycaemic goals

As stated in the ADA and ESC-EASD guidelines, near-normal glycaemia with HbA1c level below 7.0% (53 mmol/mol) will decrease microvascular complications (15, 19). Tighter glucose control initiated early in the course of diabetes in younger individuals leads to a reduction in macrovascular complications, i.e. cardiovascular outcomes, over a 20 year timescale. Such glucose control can have beneficial effects on microvascular complications in a shorter period of time. However, when blood glucose lowering agents are used that have the risk of severe hypoglycaemia, this can increase the risk of cardiovascular events and death, as detailed in the ADA and ESC-EASD guidelines (15, 18). As many people with a DFU and PAD also have atherosclerotic disease in other vascular beds, tight glucose control can be harmful. The risk of hypoglycaemia is markedLy lower when people are only treated with metformin, a sodium–glucose cotransporter 2 inhibitor or a glucagon-like peptide 1 receptor agonist. Tight glucose control is often not indicated in persons with PAD and a DFU due to the risk of hypoglycaemia outweighing the potential benefit. The ADA recommends in the 2022 Standards of Care to aim for an Hba1c < 8% (<

64 mmol/mol) in such persons and the ESC-EASD 2019 guideline for levels below 8- 9% (<64-75 mmol/L) (15, 18). However, the target chosen will depend on factors such as age, duration of diabetes, complications, co-morbidities and risk of hypoglycaemia. These target HbA1c levels are higher than the level formulated in the Global Vascular Guidelines for CLTI (< 7,0%, 53 mmol/mol), but as discussed above we concluded that the risk of such tight blood glucose control is too high in this specific population.

Blood pressure goals

The ESC-EASD guidelines state that RCTs have demonstrated the benefit (reduction of stroke, coronary events, and kidney disease) of lowering systolic BP to <140 mmHg and diastolic BP to <90 mmHg (15). Usually, multiple drugs are necessary to reach these levels in people with diabetes. In younger people (e.g., younger than 65 years) level below 130/80 mmHg can be considered if there are no contra-indications for such tight blood pressure control and the risk of orthostatic hypotension is low. Both the ADA and ESC-EASD stress the importance of individualised treatment as overly aggressive blood pressure lowering is not without risk in the usually elderly with a DFU and those with multiple diabetes-related complications and co-morbidities. Therefore, we recommend in these people blood pressures < 140/90 mmHg, but in younger individuals (e.g. < 65 years) and with a small risk of adverse effects of the treatment, lower target levels might be considered.

Lipid goals

The ADA and EASD guidelines recommend in persons with diabetes and atherosclerotic cardiovascular disease an LDL target of < 1.8 mmol/L (70 mmol/L) (18). In line with the 'the lower the better' approach, recent trials suggest that lower levels of LDL of < 1.4 mmol/L (55 mg/dL) can be beneficial in persons with a very high cardiovascular risk. Therefore, the recent ESC-EASD and ESC-EAS guidelines recommend that such very low LDL levels should be the target in these individuals (15, 16). In those with recurrent events within 2 years, even LDL levels < 1.0 mmol/L (40 mg/dL) are suggested as target in ESC-EAS guidelines (16). With statin therapy such as rosuvastatin 20-40 mg or atorvastatin 40-80 mg, marked reductions of LDL cholesterol can be achieved if these relatively simple treatments are tolerated. When the target is not reached ezetimibe can be added, which is available in combination tablets with both statins. These treatments have limited side effects in most (but not all) people and are relatively inexpensive. According to the recent ESC-EASD and ESC-EAS guidelines, an LDL-level below 1.0 mmol/L (40 mg/dL) can be the target in people with recurrent cardiovascular events (within 2 years), based on a limited number of RCT's in which relatively few participants with CLTI and diabetes were included. In order to reach the aforementioned very low LDL levels additional treatment with a PCSK9 inhibitor will be necessary in a proportion of people. PCSK9 inhibitors are monoclonal antibodies which have limited side-effects but have the drawback of high costs, parental administration and at present there is very limited evidence of the costs-effectiveness of PCSK9 inhibitors in people with diabetes, PAD and a foot ulcer or gangrene. In addition, the use of these expensive drugs is a problem for many countries in the world, and for these reasons we did not include a recommendation on LDL-level below 1.0 mmol/L (40 mg/dL) for our specific population, but we acknowledge that in several countries PCSK9 inhibitors are used to reach these goals in those with recurrent cardiovascular events.

In line with the other cardiovascular risk reduction interventions in these usually frail, multimorbid individuals, treatment and its goals should be based on shared decision making and should be individualised after careful weighting the benefits, harms and costs. The LDL (and other) treatment targets in our recommendation should not be interpreted as absolute goals but more as desired goals. Even if the goal is only partially met, it can result in a marked reduction in cardiovascular events in these very high-risk people. Although very low LDL levels are perhaps not achievable in all, LDL reductions up to 50% can be achieved in many with the aforementioned potent statins (and ezetimibe), with marked reduction in cardiovascular risk (13).

Additional therapies

Antiplatelet therapy

All guidelines strongly recommend treatment with a single antiplatelet agent in persons with cardiovascular disease -or more specifically chronic limb threatening ischaemia (CLTI). These drugs reduce the risk of cardiovascular events; in case of increased risk of gastric bleeding in aspirin treated individuals a proton pump inhibitor as additional treatment should be considered. There is less consensus which drug to choose, clopidrogel or aspirin. The ADA and ESC-EASD guideline advise in persons with diabetes and a cardiovascular event aspirin as first choice, but did not specify for the presence of PAD (15, 18). In the recent ESVM, ESC-ESVS and GVG Guidelines, clopidrogel is considered as the antiplatelet agent of choice in those with PAD. This recommendation is in particular based on 'The Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE)' trial, in which clopidrogel was more effective in reducing cardiovascular risk without an increased risk of bleeding (128). It should be noted that only a subset of participants in this trial had PAD of which only 21% had diabetes. Also, a meta-analysis did not show any benefit from aspirin for those with PAD (129). A post-hoc, sub-analysis of the CAPRIE trial showed that clopidogrel was superior to aspirin in reducing recurrent ischemic events in patients with diabetes (130). The relative risk reduction was comparable to those without diabetes, but due to the greater number of events, the absolute risk reduction was even larger. Given the potential benefit, we suggest in a conditional recommendation that clopidogrel may be considered as first choice, in line with the aforementioned Guidelines.

As an additional alternative to single antiplatelet therapy, combination therapy with aspirin (100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for persons with low bleeding risk to prevent cardiovascular events as well as reduce extremity ischaemic events in those with CLTI, as suggested by the Global Vascular Guidelines, ESVM and the ESC-EASD guidelines (13) (17, 20). This suggestion is based on the COMPASS trial in which this combination therapy was more effective than aspirin but was also associated with an increase of risk of clinically relevant bleeding, mostly gastrointestinal (131). In this trial approximately 38% had diabetes mellitus and the benefit of the combination therapy seemed similar in those with and without diabetes. Given this limited evidence base and the added treatment burden for this frequently vulnerable cohort, we made a Best Practice Statement. The ESVS antithrombotic guidelines recommend that those not at high risk of bleeding who undergo an endovascular intervention for lower extremity PAD may be considered for a 1-6 month course of dual antiplatelet therapy (aspirin plus clopidogrel) to reduce the risk of MACE and MALE followed by single antiplatelet therapy (132). Similarly, those undergoing endovascular intervention who are not at high risk of bleeding should be considered for aspirin (75-100 mg daily) and low-dose

rivaroxaban (2.5 mg twice daily) to reduce the risk of MACE and MALE (133, 134). If the bleeding risk is considered to be high, single antiplatelet therapy should be used post-intervention.

If clopidogrel is used in addition to aspirin and low-dose rivaroxaban after endovascular intervention, clopidogrel should only be used for <30 days as with longer-term use the bleeding risk is likely to outweigh the benefit (135).

The ESVS antithrombotic guidelines recommend that persons undergoing infrainguinal endarterectomy or bypass surgery who are not at high risk of bleeding should be considered for aspirin (75-100 mg daily) and low-dose rivaroxaban (2.5 mg twice daily) to reduce the risk of MACE and MALE. Those persons undergoing infrainguinal bypass surgery with autogenous vein who are not at high bleeding risk may be considered for treatment with vitamin K antagonist to improve graft patency (134, 136).

Those undergoing infrainguinal bypass with prosthetic should be considered for single antiplatelet therapy. Persons at high risk of bleeding undergoing lower extremity bypass surgery using autogenous or prosthetic conduit may be considered for single antiplatelet therapy to improve graft patency (134).

Arterial duplex scanning post-autologous vein bypass surgery is generally advised post-procedure to detect graft stenoses. The benefits of post-procedure surveillance following endovascular intervention remain uncertain; we suggest following local protocols.

Sodium–glucose cotransporter 2 inhibitors and a glucagon-like peptide 1 receptor agonists
In recent years it has become increasingly clear that several sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 receptor (GLP-1) agonists, which were originally developed to lower blood glucose levels, can have beneficial cardiovascular effects in persons with type 2 diabetes (18). These effects are independent of their blood glucose lowering effect. To what extent this benefit can also be observed in those with type 1 diabetes mellitus, in whom glucose management with these drugs only has a limited (SGLT-2 inhibitors) or no (GLP-1 agonists) role to play, remains to be established. In individuals with an eGFR < 30 ml/min/1.73m^2 these drugs are contra-indicated. Therefore, we advise to consider these drugs in type 2 diabetes mellitus and peripheral artery disease with an eGFR > 30 ml/min/1.73m^2 after careful review and possibly adjustment of other blood glucose lowering medication in order to prevent hypoglycaemia, but for SGLT2-inhibitors there are additional caveats.

The SGLT2-inhibitor canagliflozin was associated with an increased risk of amputation in an RCT. This was not a pre-specified endpoint and was not observed in the other SGLT2-inhibitors trials (137) or in long-term prospective studies, as concluded in the ADA-EASD 2022 consensus report (138). In addition, in post-hoc analyses, these drugs had beneficial cardiovascular and renal effects in persons with peripheral artery disease (139). However, individuals with foot ulcers were frequently excluded in SGLT2-inhibitor trials and there is a second caveat to be considered. Diabetes-related ketoacidosis is a rare but serious side effect of SGLT2-inhibitors and prolonged fasting, acute illness and the peri-operative period predispose to developing ketoacidosis. In these situations, the ADA-EASD recommend temporary discontinuation of the medication, i.e., 3 days prior to surgery (138). As those with PAD, a diabetes-related foot ulcer or gangrene have a high risk of developing a foot infection or to undergo one or more (urgent) surgical procedures, we suggest for pragmatic reasons that SGLT-2 inhibitors should

not be started in drug-naïve individuals and that temporary discontinuation should be considered in those already using these drugs, until the affected foot is healed.

POSTSCRIPT

The targets discussed in this text are based on reduction of cardiovascular events, but is should be noted that this is a composite end-point and the definition between trials differs. MALE is also sometimes differently defined and the evidence for reducing lower limb events in persons with diabetes, PAD and a foot ulcer by pharmacological treatment is scarce. For this reason we could not provide a specific recommendation on this topic.

FUTURE RESEARCH PRIORITIES

One of the main limitations of this Guideline is the lack of prospective randomized trials, inconsistency of classification and outcomes reported, and lack of separation of outcome for people with CLTI with and without diabetes. Data reporting on PAD in relation to diagnosis, prognosis and management overwhelmingly relate to the general population. There is a paucity of high-level evidence for diagnosis and management of those with DFU or gangrene with studies frequently including only persons with intact feet or inadequately detailing (or controlling for) confounding factors including presences of neuropathy, ulcer, infection, or other contributors to poor outcomes. Moreover, few studies in CLTI cohorts provide sub-analysis for those with diabetes although they are likely to make up the majority of the included population. As such, there is clearly a need for further research into this unique subgroup of individuals with diabetes, in order that outcomes around the world can be improved. The Writing Committee considers there are a number of priority areas for future research. Our systematic review of the prognostic capacity of bedside vascular testing to predict DFU healing and amputation outcomes demonstrated a lack of investigations of sufficient quality for several widely available tests including TBI and $TcPO_2$, with inconsistent use of measurement thresholds and a lack of data examining the effect of combining test outcomes. New technologies to develop optimal tools and measures of foot perfusion for people with DFU and PAD to guide revascularization therapies would be invaluable in guiding revascularisation strategies for individuals and for determining when more aggressive strategies are indicated.

FURTHER QUESTIONS

1. Which group of people with diabetes and a DFU, tissue loss or gangrene most benefit from urgent revascularisation, and who may benefit from an initial expectant management?

The working group has made a Best Practice Statement attempting to define which people are likely to benefit most from urgent vascular assessment and revascularisation. Further studies to clarify person- and limb-related factors are needed and such predictions may be facilitated by new prediction methods such as Machine Learning (140).

2. Do newer endovascular revascularisation adjuncts and techniques developed for infra-popliteal revascularisation positively impact on patency rates and person-centred endpoints (amputation-free survival, improved wound healing and health-related quality of life) in those with diabetes, PAD and a foot ulcer?

A number of new technologies have been developed to enhance patency of endovascular interventions, including drug-eluting balloons and stents, and bioresorbable vascular scaffolds/stents. Atherectomy and lithotripsy devices have been developed to deal with heavily calcified lesions. Venous arterialisation has also been introduced to attempt to revascularize those with "no option" for revascularisation (141, 142). The role and indications for these interventions in the general population with CLTI and in particular, those with diabetes, remains to be clarified.

3. Identify effective regenerative therapies (e.g. cell or gene-based) to improve foot perfusion in persons with DFU and PAD who are not candidates for standard revascularization.

Angiogenesis (formation of new blood vessels from existing ones) is important for the development of arterial collateral formation in response to arterial occlusion and also for wound healing. Diabetes (and hyperglycaemia) are associated with impaired angiogenesis. A number of cell-, gene- and protein-based therapeutic approaches have, and are, being trialled for both "no option" CLTI and wound healing in diabetes. There are currently no therapeutic therapies which have proven beneficial and trials are on-going (143).

CONTRIBUTION OF AUTHORS

The Writing Committee was chaired by R.F. (on behalf of the IWGDF), with R.H. (on behalf of the ESVS) and J.L.M (on behalf of the SVS) as co-chairs and supported by NCS (on behalf of the IWGDF). V.C. acted as scientific secretary. The three organisations involved were each tasked to select six well recognised experts in order to create an international, multidisciplinary, writing committee of eighteen members in total. Care was taken to have a global, multidisciplinary group that included disciplines such as vascular surgery, angiology, interventional radiology, vascular medicine, endocrinology, epidemiology and podiatry.

All members of the Writing Committee were involved in summarising the available evidence in the supporting systematic reviews, that are published separately, and in writing this guideline. Several members (the chairs, scientific secretary, N.S, and M.S.C.) were assigned to write individual sections of the guideline, and all authors reviewed and discussed during group meetings the evidence obtained, the evidence to decision items according to GRADE and each recommendation. All authors reviewed and agreed with the final document before societal review and subsequent submission for endorsement. All members of the working group undertook Level 1 GRADE training and the several working group members undertook Guideline Methodology training (McMaster University).

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REFERENCES

(1) Bus SA, Monteiro-Soares M, Game F, van Netten JJ, Apelqvist J, Fitridge R, Senneville E, Schaper NC; IWGDF Editorial Board. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diabetes Metab Res Rev. 2023;e3656.

(2) Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(3) [Current care guidelines: peripheral arterial disease]. Duodecim. 2010;126(12):1433-4.

(4) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009;339:b2535.

(5) Lucas NP, Macaskill P, Irwig L, Bogduk N. The development of a quality appraisal tool for studies of diagnostic reliability (QAREL). Journal of Clinical Epidemiology. 2010;63(8):854-61.

(6) Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. bmj. 2016;355.

(7) Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj. 2019;366.

(8) Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.

(9) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011;155(8):529-36.

(10) Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of internal medicine. 2013;158(4):280-6.

(11) Schünemann H, Brożek J, Guyatt G, Oxman A. The GRADE handbook. Cochrane Collaboration London, UK; 2013.

(12) Dewidar O, Lotfi T, Langendam MW, Parmelli E, Saz Parkinson Z, Solo K, et al. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. BMJ Evid Based Med. 2022.

(13) Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa. 2019;48(Suppl 102):1-79.

(14) Aboyans V, Ricco JB, Bartelink ML, Björck M, Brodmann M, Cohner T, et al. [2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)]. Kardiol Pol. 2017;75(11):1065-160.

(15) Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.

(16) Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.

(17) Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. Eur J Vasc Endovasc Surg. 2019;58(1s):S1-S109.e33.

(18) 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S144-s74.

(19) 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S83-s96.

(20) Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Rev Esp Cardiol (Engl Ed). 2018;71(2):111.

(21) Van Netten JJ, Bus SA, Apelqvist J, et al. Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev. 2023;e3654.

(22) Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119.

(23) Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376(24):2367-75.

(24) Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care. 1999;22(7):1036-42.

(25) Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964-74.

(26) Stoberock K, Kaschwich M, Nicolay SS, Mahmoud N, Heidemann F, Rieß HC, et al. The interrelationship between diabetes mellitus and peripheral arterial disease. Vasa. 2021;50(5):323-30.

(27) Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007;50(1):18-25.

(28) Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001;24(8):1433-7.

(29) Golledge J. Update on the pathophysiology and medical treatment of peripheral artery disease. Nat Rev Cardiol. 2022;19(7):456-74.

(30) Low Wang CC, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, et al. Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. J Am Coll Cardiol. 2018;72(25):3274-84.

(31) Ix JH, Miller RG, Criqui MH, Orchard TJ. Test characteristics of the ankle-brachial index and ankle-brachial difference for medial arterial calcification on X-ray in type 1 diabetes. J Vasc Surg. 2012;56(3):721-7.

(32) Leibson CL, Ransom JE, Olson W, Zimmerman BR, O'Fallon W M, Palumbo PJ. Peripheral arterial disease, diabetes, and mortality. Diabetes Care. 2004;27(12):2843-9.

(33) Yammine K, Hayek F, Assi C. A meta-analysis of mortality after minor amputation among patients with diabetes and/or peripheral vascular disease. J Vasc Surg. 2020;72(6):2197-207.

(34) Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3276.

(35) Aubert CE, Cluzel P, Kemel S, Michel PL, Lajat-Kiss F, Dadon M, et al. Influence of peripheral vascular calcification on efficiency of screening tests for peripheral arterial occlusive disease in diabetes--a cross-sectional study. Diabet Med. 2014;31(2):192-9.

(36) Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes care. 2005;28(9):2206-10.

(37) Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. Diabetes Care. 2002;25(1):113-20.

(38) Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. Jama. 2001;286(11):1317-24.

(39) Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. J Vasc Surg. 2016;63(2 Suppl):29S-36S.e1-2.

(40) Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69(11):e71-e126.

(41) Hart T, Milner R, Cifu A. Management of a Diabetic Foot. Jama. 2017;318(14):1387-8.

(42) Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. 2016;63(2 Suppl):3s-21s.

(43) National Institute for Health and Care Excellence: Guidelines. Diabetic foot problems: prevention and management. London: National Institute for Health and Care Excellence (NICE) copyright © NICE 2023; 2023.

(44) Chuter VH, Schaper NC, Mills J, Hinchliffe R, Azuma N, Behrendt C, et al. The effectiveness of bedside investigations for diagnosing peripheral artery disease among people with diabetes mellitus: a systematic review. Diabetes Metab Res Rev. 2023; in press.

(45) Casey S, Lanting S, Oldmeadow C, Chuter V. The reliability of the ankle brachial index: a systematic review. J Foot Ankle Res. 2019;12:39.

(46) Wennberg PW. Approach to the patient with peripheral arterial disease. Circulation. 2013;128(20):2241-50.

(47) Vriens B, D'Abate F, Ozdemir BA, Fenner C, Maynard W, Budge J, et al. Clinical examination and non-invasive screening tests in the diagnosis of peripheral artery disease in people with diabetes-related foot ulceration. Diabet Med. 2018;35(7):895-902.

(48) Babaei MR, Malek M, Rostami FT, Emami Z, Madani NH, Khamseh ME. Non-invasive vascular assessment in people with type 2 diabetes: Diagnostic performance of Plethysmographic-and-Doppler derived ankle brachial index, toe brachial index, and pulse volume wave analysis for detection of peripheral arterial disease. Prim Care Diabetes. 2020;14(3):282-9.

(49) Dinesh R, Vinod KV, Ramkumar G. Comparison of resting/postexercise ankle-brachial index and transcutaneous partial pressure of oxygen for noninvasive diagnosis of peripheral artery disease in type 2 diabetes mellitus. Medical Journal Armed Forces India. 2021.

(50) Fejfarova V, Matuska J, Jude E, Pithova P, Flekac M, Roztocil K, et al. Stimulation TcPO2 Testing Improves Diagnosis of Peripheral Arterial Disease in Patients With Diabetic Foot. Frontiers in Endocrinology. 2021;12 (no pagination).

(51) Hur KY, Jun JE, Choi YJ, Lee JH, Kim DJ, Park SW, et al. Color doppler ultrasonography is a useful tool for diagnosis of peripheral artery disease in type 2 diabetes mellitus patients with ankle-brachial index 0.91 to 1.40. Diabetes and Metabolism Journal. 2018;42(1):63-73.

(52) Normahani P, Poushpas S, Alaa M, Bravis V, Sounderajah V, Aslam M, et al. Diagnostic Accuracy of Point-of-care Tests Used to Detect Arterial Disease in Diabetes: TEsting for Arterial Disease in Diabetes (TrEAD) Study. Ann Surg. 2022;276(5):e605-e12.

(53) Park SC, Choi CY, Ha YI, Yang HE. Utility of toe-brachial index for diagnosis of peripheral artery disease. Archives of Plastic Surgery. 2012;39(3):227-31.

(54) Potier L, Halbron M, Bouilloud F, Dadon M, Le Doeuff J, Ha Van G, et al. Ankle-to-brachial ratio index underestimates the prevalence of peripheral occlusive disease in diabetic patients at high risk for arterial disease. Diabetes Care. 2009;32(4):e44-e.

(55) Bevilacqua NJ, Rogers LC, Armstrong DG. Diabetic foot surgery: classifying patients to predict complications. Diabetes Metab Res Rev. 2008;24 Suppl 1:S81-3.

(56) Hering J, Angelkort B, Keck N, Wilde J, Amann B. Long-term outcome of successful percutaneous transluminal angioplasty of the fibular artery in diabetic foot syndrome and single-vessel calf perfusion depends on doppler wave pattern at the forefoot. Vasa. 2010;39(1):67-75.

(57) Tsai CY, Chu SY, Wen YW, Hsu LA, Chen CC, Peng SH, et al. The value of Doppler waveform analysis in predicting major lower extremity amputation among dialysis patients treated for diabetic foot ulcers. Diabetes Res Clin Pract. 2013;100(2):181-8.

(58) Gershater MA, Löndahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia. 2009;52(3):398-407.

(59) Wallin L, Björnsson H, Stenström A. Fluorescein angiography for predicting healing of foot ulcers. Acta Orthop Scand. 1989;60(1):40-4.

(60) Zhang S, Wang S, Xu L, He Y, Xiang J, Tang Z. Clinical outcomes of transmetatarsal amputation in patients with diabetic foot ulcers treated without revascularization. Diabetes Therapy. 2019;10(4):1465-72.

(61) Ho CY, Shanahan CM. Medial Arterial Calcification: An Overlooked Player in Peripheral Arterial Disease. Arterioscler Thromb Vasc Biol. 2016;36(8):1475-82.

(62) Silvestro A, Diehm N, Savolainen H, Do DD, Vögelea J, Mahler F, et al. Falsely high ankle-brachial index predicts major amputation in critical limb ischaemia. Vasc Med. 2006;11(2):69-74.

(63) Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC. Diabetic foot disease: impact of ulcer location on ulcer healing. Diabetes Metab Res Rev. 2013;29(5):377-83.

(64) Kalani M, Brismar K, Fagrell B, Ostergren J, Jörneskog G. Transcutaneous oxygen tension and toe blood pressure as predictors for outcome of diabetic foot ulcers. Diabetes Care. 1999;22(1):147-51.

(65) Bunt TJ, Holloway GA. TcPO2 as an accurate predictor of therapy in limb salvage. Ann Vasc Surg. 1996;10(3):224-7.

(66) Elgzyri T, Larsson J, Thörne J, Eriksson KF, Apelqvist J. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. Eur J Vasc Endovasc Surg. 2013;46(1):110-7.

(67) Elgzyri T, Larsson J, Nyberg P, Thörne J, Eriksson KF, Apelqvist J. Early revascularization after admittance to a diabetic foot center affects the healing probability of ischemic foot ulcer in patients with diabetes. Eur J Vasc Endovasc Surg. 2014;48(4):440-6.

(68) Fagher K, Katzman P, Löndahl M. Transcutaneous oxygen pressure as a predictor for short-term survival in patients with type 2 diabetes and foot ulcers: a comparison with ankle-brachial index and toe blood pressure. Acta Diabetol. 2018;55(8):781-8.

(69) Manu CA, Slim H, Huang D, Wilkins CJ, Vas PRJ, Rashid H, et al. Isolated low toe-brachial index is associated with increased mortality and morbidity: a retrospective cohort study. J Wound Care. 2021;30(1):65-73.

(70) Mennes OA, van Netten JJ, van Baal JG, Slart R, Steenbergen W. The Association between Foot and Ulcer Microcirculation Measured with Laser Speckle Contrast Imaging and Healing of Diabetic Foot Ulcers. J Clin Med. 2021;10(17).

(71) Rajagopalan C, Viswanathan V, Rajsekar S, Selvaraj B, Daniel L. Diabetic foot ulcers - comparison of performance of ankle-brachial index and transcutaneous partial oxygen pressure in predicting outcome. Int J Diabetes Dev Ctries. 2018;38:179-84.

(72) Faris I, Duncan H. Skin perfusion pressure in the prediction of healing in diabetic patients with ulcers or gangrene of the foot. J Vasc Surg. 1985;2(4):536-40.

(73) Chuter VH, Schaper N, Mills J, Hinchliffe R, Azuma N, Behrendt C, et al. A systematic review of the prognostic capacity of lower limb vascular bedside investigations for diabetes-related foot disease outcomes. Diabetes Metab Res Rev. 2023; in press.

(74) Sharma S, Schaper N, Rayman G. Microangiopathy: Is it relevant to wound healing in diabetic foot disease? Diabetes Metab Res Rev. 2020;36 Suppl 1:e3244.

(75) McIllhatten A, Lanting SM, Chuter VH, Fitridge R. The prognostic capacity of measures of micovascular function on diabetes related foot ulcer healing: A systematic review. Diabetes Metab Res Rev. 2023.

(76) Fiordaliso F, Clerici G, Maggioni S, Caminiti M, Bisighini C, Novelli D, et al. Prospective study on microangiopathy in type 2 diabetic foot ulcer. Diabetologia. 2016;59(7):1542-8.

(77) Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, Monteiro-Soares M, Senneville E; IWGDF Editorial Board. Practical guidelines on the diagnosis and management of the diabetic foot. . Diabetes Metab Res Rev. 2023; e3657.

(78) Mills JL, Sr., Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischaemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220-34.e1-2.

(79) van Reijen NS, Ponchant K, Ubbink DT, Koelemay MJW. Editor's Choice - The Prognostic Value of the WIfI Classification in Patients with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2019;58(3):362-71.

(80) Andersen CA, McLeod K, Steffan R. Diagnosis and treatment of the invasive extension of bacteria (cellulitis) from chronic wounds utilising point-of-care fluorescence imaging. Int Wound J. 2022;19(5):996-1008.

(81) Fujii M, Terashi H, Yokono K, Armstrong DG. The Degree of Blood Supply and Infection Control Needed to Treat Diabetic Chronic Limb-Threatening Ischemia with Forefoot Osteomyelitis. J Am Podiatr Med Assoc. 2021;111(2).

(82) Mathioudakis N, Hicks CW, Canner JK, Sherman RL, Hines KF, Lum YW, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing but not major amputation in patients with diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg. 2017;65(6):1698-705.e1.

(83) Weaver ML, Hicks CW, Canner JK, Sherman RL, Hines KF, Mathioudakis N, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing better than direct angiosome perfusion in diabetic foot wounds. J Vasc Surg. 2018;68(5):1473-81.

(84) Hicks CW, Canner JK, Karagozlu H, Mathioudakis N, Sherman RL, Black JH, 3rd, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system correlates with cost of care for diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg. 2018;67(5):1455-62.

(85) Robinson WP, Loretz L, Hanesian C, Flahive J, Bostrom J, Lunig N, et al. Society for Vascular Surgery Wound, Ischemia, foot Infection (WIfI) score correlates with the intensity of multimodal limb treatment and patient-centered outcomes in patients with threatened limbs managed in a limb preservation center. J Vasc Surg. 2017;66(2):488-98.e2.

(86) Yang S, Gu Z, Lu C, Zhang T, Guo X, Xue G, et al. Neutrophil Extracellular Traps Are Markers of Wound Healing Impairment in Patients with Diabetic Foot Ulcers Treated in a Multidisciplinary Setting. Adv Wound Care (New Rochelle). 2020;9(1):16-27.

(87) Zhan LX, Branco BC, Armstrong DG, Mills JL, Sr. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. J Vasc Surg. 2015;61(4):939-44.

(88) Neagu C, Doran H, Buzea A, Agache A, Georgescu D, Patrascu T. Algorithm of Medical-Surgical Treatment in the Peripheral Arterial Disease of the Diabetic Patient. Maedica. 2020;15(3):310.

(89) Cheun TJ, Jayakumar L, Sideman MJ, Pounds LC, Davies MG. Outcomes of isolated inframalleolar interventions for chronic limb-threatening ischaemia in diabetic patients. J Vasc Surg. 2020;71(5):1644-52.e2.

(90) Hicks CW, Canner JK, Karagozlu H, Mathioudakis N, Sherman RL, Black JH, 3rd, et al. Quantifying the costs and profitability of care for diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg. 2019;70(1):233-40.

(91) Hicks CW, Canner JK, Sherman RL, Black JH, 3rd, Lum YW, Abularrage CJ. Evaluation of revascularization benefit quartiles using the Wound, Ischemia, and foot Infection classification system for diabetic patients with chronic limb-threatening ischaemia. J Vasc Surg. 2021;74(4):1232-9.e3.

(92) Pena G, Kuang B, Edwards S, Cowled P, Dawson J, Fitridge R. Factors Associated With Key Outcomes in Diabetes Related Foot Disease: A Prospective Observational Study. Eur J Vasc Endovasc Surg. 2021;62(2):233-40.

(93) Ricco JB, Gargiulo M, Stella A, Abualhin M, Gallitto E, Desvergnes M, et al. Impact of angiosome- and nonangiosome-targeted peroneal bypass on limb salvage and healing in patients with chronic limb-threatening ischaemia. J Vasc Surg. 2017;66(5):1479-87.

(94) Lepäntalo M, Mätzke S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg. 1996;11(2):153-7.

(95) Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral artery disease: A systematic review. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3279.

(96) Noronen K, Saarinen E, Albäck A, Venermo M. Analysis of the Elective Treatment Process for Critical Limb Ischaemia with Tissue Loss: Diabetic Patients Require Rapid Revascularisation. Eur J Vasc Endovasc Surg. 2017;53(2):206-13.

(97) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3648.

(98) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(99) Fisher TK, Scimeca CL, Bharara M, Mills JL, Sr., Armstrong DG. A stepwise approach for surgical management of diabetic foot infections. J Am Podiatr Med Assoc. 2010;100(5):401-5.

(100) Lavery LA, Barnes SA, Keith MS, Seaman JW, Jr., Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. Diabetes Care. 2008;31(1):26-9.

(101) Coerper S, Beckert S, Küper MA, Jekov M, Königsrainer A. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing--analysis of a single-center cohort of 704 diabetic patients. J Diabetes Complications. 2009;23(1):49-53.

(102) Snyder RJ, Cardinal M, Dauphinée DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage. 2010;56(3):44-50.

(103) Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care. 2003;26(6):1879-82.

(104) Dunning T. Integrating palliative care with usual care of diabetic foot wounds. Diabetes Metab Res Rev. 2016;32 Suppl 1:303-10.

(105) Chuter VH, Schaper NC, Mills J, Hinchliffe R, Azuma N, Behrendt C, et al. Outcomes of revascularisation procedures in people with diabetes-related foot ulcer and gangrene: A systematic review. Diabetes Metab Res Rev. 2023; in press.

(106) Farber A, Menard MT, Conte MS, Kaufman JA, Powell RJ, Choudhry NK, et al. Surgery or endovascular therapy for chronic limb-threatening ischaemia. New England Journal of Medicine. 2022;387(25):2305-16.

(107) Meecham L, Patel S, Bate GR, Bradbury AW. Editor's Choice - A Comparison of Clinical Outcomes Between Primary Bypass and Secondary Bypass After Failed Plain Balloon Angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. Eur J Vasc Endovasc Surg. 2018;55(5):666-71.

(108) Troisi N, Turini F, Chisci E, Ercolini L, Frosini P, Lombardi R, et al. Pedal arch patency and not direct-angiosome revascularization predicts outcomes of endovascular interventions in diabetic patients with critical limb ischaemia. Int Angiol. 2017;36(5):438-44.

(109) Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg. 1987;40(2):113-41.

(110) Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast Reconstr Surg. 2006;117(7 Suppl):261s-93s.

(111) Fossaceca R, Guzzardi G, Cerini P, Cusaro C, Stecco A, Parziale G, et al. Endovascular treatment of diabetic foot in a selected population of patients with below-the-knee disease: is the angiosome model effective? Cardiovasc Intervent Radiol. 2013;36(3):637-44.

(112) Acín F, Varela C, López de Maturana I, de Haro J, Bleda S, Rodriguez-Padilla J. Results of infrapopliteal endovascular procedures performed in diabetic patients with critical limb ischaemia and tissue loss from the perspective of an angiosome-oriented revascularization strategy. Int J Vasc Med. 2014;2014:270539.

(113) Alexandrescu VA, Brochier S, Limgba A, Balthazar S, Khelifa H, De Vreese P, et al. Healing of Diabetic Neuroischemic Foot Wounds With vs Without Wound-Targeted Revascularization: Preliminary Observations From an 8-Year Prospective Dual-Center Registry. J Endovasc Ther. 2020;27(1):20-30.

(114) Bekeny JC, Alfawaz A, Day J, Naz I, Attinger CE, Fan KL, et al. Indirect Endovascular Revascularization via Collaterals: A New Classification to Predict Wound Healing and Limb Salvage. Ann Vasc Surg. 2021;73:264-72.

(115) Zheng XT, Zeng RC, Huang JY, Pan LM, Su X, Wu ZH, et al. The Use of the Angiosome Concept for Treating Infrapopliteal Critical Limb Ischemia through Interventional Therapy and Determining the Clinical Significance of Collateral Vessels. Ann Vasc Surg. 2016;32:41-9.

(116) Špillerová K, Settembre N, Biancari F, Albäck A, Venermo M. Angiosome Targeted PTA is More Important in Endovascular Revascularisation than in Surgical Revascularisation: Analysis of 545 Patients with Ischaemic Tissue Lesions. Eur J Vasc Endovasc Surg. 2017;53(4):567-75.

(117) Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T. Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the angiosome important in selecting bypass target artery? Eur J Vasc Endovasc Surg. 2012;43(3):322-8.

(118) Lejay A, Georg Y, Tartaglia E, Gaertner S, Geny B, Thaveau F, et al. Long-term outcomes of direct and indirect below-the-knee open revascularization based on the angiosome concept in diabetic patients with critical limb ischaemia. Ann Vasc Surg. 2014;28(4):983-9.

(119) Neville RF, Attinger CE, Bulan EJ, Ducic I, Thomassen M, Sidawy AN. Revascularization of a specific angiosome for limb salvage: does the target artery matter? Ann Vasc Surg. 2009;23(3):367-73.

(120) Kret MR, Cheng D, Azarbal AF, Mitchell EL, Liem TK, Moneta GL, et al. Utility of direct angiosome revascularization and runoff scores in predicting outcomes in patients undergoing revascularization for critical limb ischaemia. Journal of vascular surgery. 2014;59(1):121-8.

(121) Aerden D, Denecker N, Gallala S, Debing E, Van den Brande P. Wound morphology and topography in the diabetic foot: hurdles in implementing angiosome-guided revascularization. Int J Vasc Med. 2014;2014:672897.

(122) Mustapha J, Finton SM, Diaz-Sandoval LJ, Saab FA, Miller LE. Percutaneous transluminal angioplasty in patients with infrapopliteal arterial disease: systematic review and meta-analysis. Circulation: Cardiovascular Interventions. 2016;9(5):e003468.

(123) McDermott KM, Srinivas T, Abularrage CJ, editors. Multidisciplinary approach to decreasing major amputation, improving outcomes, and mitigating disparities in diabetic foot and vascular disease. Seminars in Vascular Surgery; 2022: Elsevier.

(124) Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890-909.

(125) Hinchliffe RJ, Brownrigg JR, Andros G, Apelqvist J, Boyko EJ, Fitridge R, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes Metab Res Rev. 2016;32 Suppl 1:136-44.

(126) Siersma V, Thorsen H, Holstein PE, Kars M, Apelqvist J, Jude EB, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. Diabet Med. 2013;30(11):1382-7.

(127) Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. Qual Life Res. 2007;16(2):179-89.

(128) A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348(9038):1329-39.

(129) Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. Jama. 2009;301(18):1909-19.

(130) Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. American Journal of Cardiology. 2002;90(6):625-8.

(131) Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. J Am Coll Cardiol. 2018;71(20):2306-15.

(132) Twine CP, Kakkos SK, Aboyans V, Baumgartner I, Behrendt CA, Bellmunt-Montoya S, et al. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases. Eur J Vasc Endovasc Surg. 2023.

(133) Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. New England Journal of Medicine. 2020;382(21):1994-2004.

(134) Twine CP, Kakkos SK, Aboyans V, Baumgartner I, Behrendt C-A, Bellmunt-Montoya S, et al. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases. European Journal of Vascular and Endovascular Surgery. 2023.

(135) Hiatt WR, Bonaca MP, Patel MR, Nehler MR, Debus ES, Anand SS, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: impact of concomitant clopidogrel on efficacy and safety. Circulation. 2020;142(23):2219-30.

(136) Group DBOAoAS. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. The Lancet. 2000;355(9201):346-51.

(137) Arnott C, Huang Y, Neuen BL, Di Tanna GL, Cannon CP, Oh R, et al. The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial. Diabetes Obes Metab. 2020;22(10):1753-66.

(138) Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925-66.

(139) Barraclough JY, Yu J, Figtree GA, Perkovic V, Heerspink HJL, Neuen BL, et al. Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: Data from the CANVAS Program and CREDENCE trial. Diabetes Obes Metab. 2022;24(6):1072-83.

(140) Xie P, Li Y, Deng B, Du C, Rui S, Deng W, et al. An explainable machine learning model for predicting in-hospital amputation rate of patients with diabetic foot ulcer. Int Wound J. 2022;19(4):910-8.

(141) Ho VT, Gologorsky R, Kibrik P, Chandra V, Prent A, Lee J, et al. Open, percutaneous, and hybrid deep venous arterialization technique for no-option foot salvage. J Vasc Surg. 2020;71(6):2152-60.

(142) Shishehbor MH, Powell RJ, Montero-Baker MF, Dua A, Martínez-Trabal JL, Bunte MC, et al. Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia. New England Journal of Medicine. 2023;388(13):1171-80.

(143) Solly EL, Psaltis PJ, Bursill CA, Tan JTM. The Role of miR-181c in Mechanisms of Diabetes-Impaired Angiogenesis: An Emerging Therapeutic Target for Diabetic Vascular Complications. Front Pharmacol. 2021;12:718679.

Guidelines on offloading foot ulcers in persons with diabetes

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

Offloading mechanical tissue stress is arguably the most important of multiple interventions needed to heal diabetes-related foot ulcers. This is the 2023 International Working Group on the Diabetic Foot (IWGDF) evidence-based guideline on offloading interventions to promote healing of foot ulcers in persons with diabetes. It serves as an update of the 2019 IWGDF guideline.

We followed the GRADE approach by devising clinical questions and important outcomes in the PICO (Patient-Intervention-Control-Outcome) format, undertaking a systematic review and meta-analyses, developing summary of judgements tables and writing recommendations and rationales for each question. Each recommendation is based on the evidence found in the systematic review, expert opinion where evidence was not available, and a careful weighing of GRADE summary of judgement items including desirable and undesirable effects, certainty of evidence, patient values, resources required, cost effectiveness, equity, feasibility and acceptability.

For healing a neuropathic plantar forefoot or midfoot ulcer in a person with diabetes, use a non-removable knee-high offloading device as the first-choice offloading intervention. If contraindications or patient intolerance to non-removable offloading exist, consider using a removable knee-high or ankle-high offloading device as the second-choice offloading intervention. If no offloading devices are available, consider using appropriately fitting footwear combined with felted foam as the third-choice offloading intervention. If such non-surgical offloading treatment fails to heal a plantar forefoot ulcer, consider an Achilles tendon lengthening, metatarsal head resection, joint arthroplasty, or metatarsal osteotomy. For healing a neuropathic plantar or apex lesser digit ulcer secondary to flexbile toe deformity, use digital flexor tendon tenotomy. For healing rearfoot, non-plantar or ulcers complicated with infection or ischaemia, further recommendations have been outlined. All recommendations have been summarized in an offloading clinical pathway to help facilitate implementation of this guideline into clinical practice.

These offloading guideline recommendations should help healthcare professionals provide the best care and outcomes for persons with diabetes-related foot ulcers and reduce the person's risk of infection, hospitalisation and amputation.

LIST OF RECOMMENDATIONS

1a. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a non-removable knee-high offloading device as the first choice of offloading treatment to promote healing of the ulcer. (GRADE recommendation: Strong; Certainty of evidence: Moderate)

1b. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for which a non-removable knee-high offloading device is to be used, choose either a total contact cast or non-removable knee-high walker based upon local resources and the person's individual factors and acceptability. (Conditional; Moderate)

2. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a non-removable knee-high offloading device is contraindicated or not tolerated, consider using either a removable knee-high or ankle-high offloading device as the second choice of offloading treatment to promote healing of the ulcer, and encourage the person to use the device during all weight-bearing activities. (Conditional; Low)

3. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, do not use, and educate the person not to use conventional footwear or standard therapeutic footwear over an offloading device, to promote healing of the ulcer. (Strong; Low)

4. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for which offloading devices are not available, consider using felted foam in combination with appropriately fitting footwear as the third choice of offloading treatment to promote healing of the ulcer. (Conditional; Very Low)

5a. In a person with diabetes and a neuropathic plantar metatarsal head ulcer for which non-surgical offloading treatment fails, consider using Achilles tendon lengthening in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Moderate)

5b. In a person with diabetes and a neuropathic plantar metatarsal head ulcer for which non-surgical offloading treatment fails, consider using metatarsal head resection in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Low)

5c. In a person with diabetes and a neuropathic hallux ulcer for which non-surgical offloading treatment fails, consider using joint arthroplasty in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Low)

5d. In a person with diabetes and a neuropathic plantar ulcer on metatarsal heads 2-5 for which non-surgical offloading treatment fails, consider using a metatarsal osteotomy in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Very low)

6. In a person with diabetes and a neuropathic plantar or apex ulcer on digits 2-5, secondary to a flexible toe deformity, use a digital flexor tenotomy to promote and sustain healing of the ulcer. (Strong; Moderate)

7. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with either mild infection or mild ischaemia, consider using a non-removable knee-high offloading device to promote healing of the ulcer. (Conditional; Low)

8. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both mild infection and mild ischaemia, or with either moderate infection or moderate ischaemia, consider using a removable offloading device to promote healing of the ulcer. (Conditional; Low)
9. In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both moderate infection and moderate ischaemia, or with either severe infection or severe ischaemia, primarily address the infection and/or ischaemia, and use a removable offloading intervention over no offloading based on the person's individual factors, to promote healing of the ulcer. (Strong; Very low)
10. In a person with diabetes and a neuropathic plantar rearfoot ulcer, consider using a non-removable knee-high offloading device over a removable offloading device to promote healing of the ulcer. (Conditional; Very low)
11. In a person with diabetes and a non-plantar foot ulcer, use a removable offloading device, footwear modifications, toe spacers, orthoses, or digital flexor tenotomy, depending on the type and location of the foot ulcer, to promote healing of the ulcer. (Strong; Very low)
12. In a person with diabetes and a foot ulcer for which a knee-high or ankle-high offloading device is used, consider also using a shoe lift on the contralateral limb to improve the person's comfort and balance while walking in the device. (Conditional; Very low)

INTRODUCTION

Diabetes-related foot ulceration (DFU) is a leading cause of global disability, mortality and healthcare cost burdens (1-5). DFUs annually affect around 20 million people worldwide (2, 4), and without appropriate care, these foot ulcers can lead to infection, hospitalisation, amputation and death (1-5). Thus, healing of DFU is of paramount global importance (1-5).

The most common cause of DFU is high mechanical tissue stress on the foot of a person with diabetes and a loss of protective sensation (2, 6-8). Loss of protective sensation results from peripheral neuropathy and affects around half of all people with diabetes (2, 3, 9). Mechanical tissue stress is composed of plantar pressures and shear accumulated during repetitive cycles of weight-bearing activity (2, 6-8). Peripheral neuropathy can also lead to further changes in gait, foot deformity and soft tissue, all of which can further elevate mechanical tissue stress (7, 8, 10). Once a DFU forms, healing is chronically delayed if the area is not effectively offloaded (2, 6, 11).

Multiple interventions are typically required to effectively heal a DFU, including local wound management, management of any infection and peripheral artery disease, and offloading (12, 13). For this, a collaborative team approach is needed from different specialities, as well as an engaged and empowered patient (13). The first three of those interventions are covered in other parts of the International Working Group of the Diabetic Foot (IWGDF) Guidelines (13-16). In people with neuropathic DFUs, offloading has been found to be arguably the most important of these interventions for effective healing (11-13, 17, 18). There is a long-standing clinical tradition of using different offloading devices, footwear, surgery, and other offloading interventions to heal DFUs (6, 19-22). Previous IWGDF Guidelines have shown that sufficient evidence is available to support the use of non-removable knee-high offloading devices to heal plantar forefoot ulcers, over all other offloading interventions (11, 13, 19). It also identified that more high-quality studies are needed to confirm the promising effects of other offloading interventions to heal DFUs, in order to better inform practitioners about effective treatments (11, 19).

Over the past four years, a number of new trials have been performed in the area of offloading that add to the evidence base for treating people with DFU (23-29). Ulcer healing is still recognised as the key critically important outcome for people with DFU. However, other outcomes of importance to people with DFU are receiving more attention and also require careful consideration when developing recommendations in new offloading guidelines, such as effects on plantar pressure, weight-bearing activity, adherence, adverse effects, quality of life, and costs.

This new 2023 guideline aims to update the previous 2019 IWGDF guideline on offloading DFUs by following the best practice GRADE approach for guideline development to consider all new evidence and important outcomes so as to provide contemporary evidence-based international recommendations and rationale for offloading DFUs (19). This guideline is part of a series of new 2023 IWGDF guidelines including those on ulcer classification, peripheral artery disease, infection, wound healing, prevention, and Charcot foot (14-16, 30-32).

WHAT'S NEW

We have made several changes in this updated 2023 offloading guideline when compared to the previous 2019 offloading guideline. The main changes are the following:

- Used a more thorough GRADE methodological approach to the guideline and the systematic review supporting it, by performing meta-analyses, grading effect sizes, grading certainty (quality) of evidence with 'very low' as an option, developing summary of findings tables and developing summary of judgement tables.
- Added new clinical questions on the topics of ankle-high offloading devices, plantar digital foot ulcers, combination of interventions, educational and psychological interventions, and offloading for the contralateral limb.
- Added new important outcomes, including sustained healing, balance and the specific adverse effects/events of new lesions, falls, infections and amputations.
- Removable knee-high and ankle-high offloading devices are now grouped into one recommendation for second-choice offloading device treatment, rather than separate recommendations for second and third-choice treatment, respectively, effectively upgrading ankle-high offloading devices. This is based on added evidence in the last 4 years and the more thorough GRADE approach used.
- Added four new recommendations for specific surgical offloading interventions rather than grouping surgical interventions into one recommendation.
- Added a new recommendation on offloading for the contralateral limb.
- Updated the strength of recommendation in two recommendations and the certainty of evidence in nine recommendations based on using the more thorough GRADE approach.

METHODS

In this guideline we have followed the key steps of the GRADE evidence-to-decision approach, including: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes in the PICO-format (Patient-Intervention-Comparison-Outcome), iii) performing systematic reviews and rigorous appraisals of all available evidence that address the questions, iv) assessing key summary of judgements items for each question, v) developing recommendations and their rationale based on these summary of judgements, and vi) consulting external stakeholders on each step (33, 34). The methodology for this guideline is summarised below; we refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (35).

First, a multidisciplinary working group of independent international experts in offloading DFU (the authors of this guideline) was invited by the IWGDF Editorial Board to develop and author this guideline. International experts were defined as those having significant experience in clinical practice and/or studying offloading DFU and published on the topic in the previous four years. The working group comprised members from exercise and human movement science, orthopaedic surgery, podiatry, prosthetics and orthotics, endocrinology, and rehabilitation science disciplines from Europe, North America, Asia and Australia.

Second, the working group devised important clinical questions and associated outcomes, building on the last version of the guideline, to be answered using the GRADE approach. The questions and outcomes were reviewed and prioritised with the help of six external clinical experts and two persons with lived DFU experience from various geographical regions, and the IWGDF Editorial Board. The aim was to ensure the questions and outcomes were of relevance to a wide range of healthcare professionals and patients so as to provide the most useful clinical information on offloading interventions to treat foot ulcers in people with diabetes. The working group classified the outcomes as critically important or important, aligning with international DFU standards (12, 36) or the expert opinion of the working group if standards did not exist.

Third, we systematically reviewed the literature and appraised all studies addressing the above agreed upon clinical questions. Each assessable outcome for each question was meta-analysed if appropriate, and had effect sizes and certainty of evidence (CoE) assessed using the Cochrane and GRADE Handbooks. Finally, we developed summary of findings tables, including evidence statements, for each assessable outcome for each question which we presented in full in the systematic review. The systematic review supporting this guideline is published separately (11).

Fourth, based on the systematic review, summary of findings tables and expert opinion, teams of two members of the working group developed summary of judgements tables for each question following GRADE (see online supplemental information). The summary of judgement items assessed included desirable and undesirable effects, balance of effects, CoE, values, costs, cost-effectiveness, equity, acceptability and feasibility. Definitions for these items can be found in the summary of judgements table in the online supplemental information. After careful weighing up of the summary of judgements, the team proposed to the working group a direction, strength, CoE and wording of recommendation(s) and

rationale to address the question concerned. CoE was rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Rationale for each recommendation was also provided and based on the summary of judgements tables (33, 34).

Fifth, summary of judgements tables and recommendations for each question were extensively discussed in online meetings with the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention, and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the online supplemental information.

Finally, all recommendations, with their rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same clinical experts and persons with lived DFU experience who reviewed the clinical questions, as well as by members of the IWGDF Editorial Board. The working group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline manuscript.

CONFLICT OF INTEREST STATEMENT

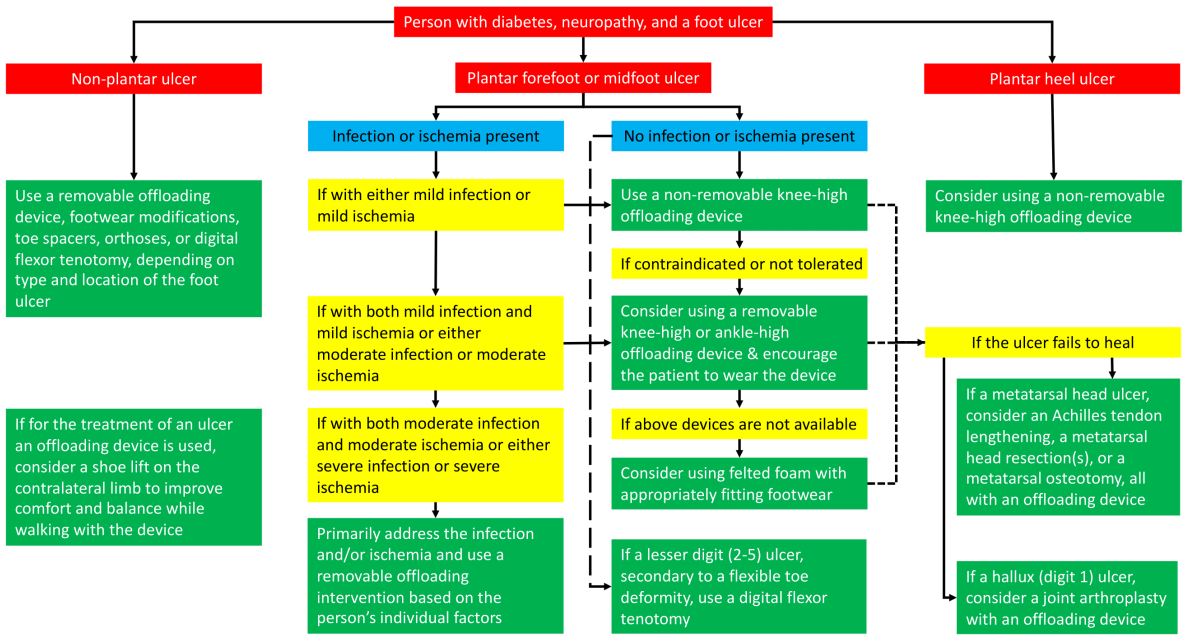
The offloading guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and these can be found at *www.iwgdfguidelines.org*. No company was involved in the development or review of the guideline. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting in-person.

RESULTS

Overall, 14 clinical questions, each with up to 13 (critically) important outcomes, were finalised and addressed by this guideline. The accompanying systematic review identified 194 eligible studies, performed 35 meta-analyses and developed 17 summary of findings tables with 128 evidence statements to collectively address these questions (11). Based on the systematic review and expert opinion of the group, 20 summary of judgements tables were completed (see supplemental information) with 16 recommendations developed that addressed the clinical questions. A clinical pathway, using a diagrammatic overview and incorporating all 16 recommendations, summarises the recommended approach to offloading treatment to heal a DFU (Figure 1).

Note, different offloading interventions are mentioned in this guideline and they are discussed according to the following categories: offloading devices, footwear, other offloading techniques, and surgical offloading techniques. We refer readers to the glossary at the end of this guideline for the definitions and descriptions of each of these offloading interventions and categories. Furthermore, many of the offloading devices and interventions recommended require specific training, skills, and experience to apply properly. The specific skills and training are not described in the studies performed and may differ between centres and countries. We suggest that the person applying the offloading should be a properly trained healthcare professional who according to their national or regional standards has the knowledge, expertise, and skills necessary to treat DFU.

Figure 1: Flow diagram on the recommended offloading treatment for a person with diabetes and a foot ulcer



RECOMMENDATIONS

OFFLOADING DEVICES

Clinical question 1: In a person with diabetes and a plantar forefoot or midfoot ulcer, should non-removable offloading devices be used over removable offloading devices?

Recommendation 1a: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, use a non-removable knee-high offloading device as the first choice of offloading treatment to promote healing of the ulcer. (GRADE recommendation: Strong; CoE: Moderate)

Rationale: Non-removable knee-high offloading devices are devices that extend up the leg to a level just below the knee and cannot be readily removed by the patient, such as total contact casts (TCCs) and non-removable walkers (see Glossary for definitions). They should also incorporate a foot-device interface that helps reduce peak pressure at the ulcer location. For TCCs, foot-device interfaces are typically accommodated within the TCC method via the hand-moulding of the TCC to the shape of the plantar surface to redistribute pressure over the foot. For walkers, the foot-device interfaces typically consists of prefabricated (which may be of a modifiable modular design) or custom insoles. Additionally, felted foam may be added around the perimeter of the ulcer as part of the foot-device interface in order to further reduce pressure and promote healing of the ulcer. Lastly, we suggest persons use a walking aid if stability is compromised by wearing the device and risk of falling is high.

Our systematic review and meta-analyses identified 10 randomised controlled trials (RCTs) and 6 other controlled studies, with 4 non-controlled studies also adding relevant evidence for this question (11). We judged the overall desirable effects (benefits) to be moderate, based on our meta-analysis finding non-removable knee-high devices likely cause moderate increases in the critical outcome of proportions of ulcers healed compared to removable offloading devices (risk ratio (RR) 1.24, 95% CI 1.09-1.41; Moderate CoE) and may also cause moderate decreases in infections (RR 0.58, 0.34-0.99; Low CoE) and amputations (RR 0.53, 0.19-1.50; Very low CoE). Whereas we judged the overall undesirable effects (harms) to be small, we found non-removable knee-high devices may also cause moderate increases in new lesions compared to removable devices (RR 1.77, 0.89-3.54; Low CoE), small decreases in patient satisfaction (mean difference (MD) 0.21 lower on 10-point scale, 1.47 lower to 1.05 higher; Very low CoE) and little-to-no difference for falls (RR NA; Very low CoE). However, the evidence was very uncertain for falls as one other controlled study also noted two persons using bilateral TCCs discontinued use because of falls. Therefore, we judged the balance of effects clearly favours non-removable offloading devices over removable offloading devices, based on a moderate CoE for our critical outcome of ulcers healed.

Findings for other important surrogate outcomes for ulcers healed, such as adherence, activity and plantar pressure, provide potential rationale for this improved ulcers healed rate. The principal advantage of non-removable devices over removable offloading devices is enforced adherence, with our meta-analysis finding non-removable devices may cause large decreases in non-adherence (RR 0.07, 0.01-0.79; Very low CoE). Additionally, another review found some evidence that a reduction in weight-bearing activity may benefit ulcer healing (37), with our meta-analysis finding non-removable versus removable devices may cause small decreases in weight-bearing activity (MD 671 less daily steps, 95%

CI 1,680 less to 338 more; Very low CoE). Finally, plantar pressure reductions are well-known to be associated with improved healing, with our meta-analysis finding non-removable versus removable devices may cause small increases in plantar pressure (MD 39 kPa higher, 95% CI 7 less to 84 more; Very low CoE). However, we note that in our meta-analysis, we compared TCCs to removable knee-high walkers that can be made non-removable, and thus, in our judgement plantar pressure reductions in reality should be similar between non-removable and removable walkers (11). Therefore, in our judgement, non-removable compared to removable offloading devices result in similar plantar pressure reductions, small reductions in weight-bearing activity and large increases in adherence and hence heal more ulcers.

In terms of costs of initial treatment, our systematic review found non-removable compared to removable devices may cause small increases in initial treatment costs (MD €14.60 higher, 95% CI 7.68 lower to 136.88 higher; Very low CoE). However, conversely in terms of cost-effectiveness over the full duration of treatment, our systematic review found non-removable versus removable devices may be moderately more cost-effective (MD NA; N=2; n=2,053; Low CoE).

Additionally, although a lack of evidence was identified, our expert opinion judgement is that health equity is likely reduced with the use of non-removable devices compared to removable devices due to implementation of such interventions likely being limited in some low-, and middle-income countries by patients' ability to pay for them and access to healthcare professionals with the skills and resources to provide the interventions. Thus, based on this and multiple published surveys showing low use of non-removable offloading devices in clinical practice, and in particular TCCs (20, 22, 38, 39), we judged using non-removable offloading devices to be probably not equitable or acceptable to many patients and clinicians (20, 21). However, we judged implementation of such non-removable offloading as probably feasible, in the context of comparing to other removable devices, as most removable knee-high devices could readily be converted to a non-removable format using cast tape, straps or other methods.

In summary, based on our judgements that non-removable compared to removable devices should produce moderate desirable effects and small undesirable effects, and with moderate certainty of supporting evidence for critical outcomes, we consider the balance of effects strongly favour non-removable offloading devices. Furthermore, our judgements were that there should only be a small increase in initial costs for the resources required for non-removable devices, but over the treatment duration non-removable devices should be moderately more cost-effective and feasible to implement. However, in terms of the impact on health equity and acceptability, our judgements were removable devices may be favoured. Thus, after weighing up all important summary of judgement items we consider a strong recommendation in favour of non-removable offloading devices is justified and based on moderate CoE. However, in cases where the plantar ulcer is on the lesser digits and secondary to flexible toe deformity present, we refer to recommendation 6.

Clinical question 2: In a person with diabetes and a plantar forefoot or midfoot ulcer, should a total contact cast be used over another non-removable knee-high offloading device?

Recommendation 1b: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for which a non-removable knee-high offloading device is to be used, choose either a total contact cast or

non-removable knee-high walker based upon local resources and the person's individual factors and acceptability. (Conditional; Moderate)

Rationale: When choosing a non-removable knee-high offloading device, two modalities are generally used, a TCC or a prefabricated removable walker that is rendered non-removable. Both are used in clinical practice, which justifies the question regarding which is more effective and preferred for offloading plantar forefoot and midfoot DFUs.

Our systematic review and meta-analyses identified 5 RCTs and 1 other controlled study, with 6 non-controlled studies also adding relevant evidence for this question (11). We judged the overall desirable effects to be small, based on our meta-analysis finding TCCs likely make little-to-no difference compared to non-removable knee-high walkers in proportions of ulcers healed (RR 1.05, 95% CI: 0.92-1.19; Moderate CoE), infections (RR 1.00, 0.07-14.90; Low CoE) and amputations (RR 1.05, 0.07-15.68; Low CoE). Whereas we judged the overall undesirable effects to be small, TCCs may also cause small increases in plantar pressure compared to non-removable walkers (MD 39 kPa more; 95% CI: 5-73; Low CoE), large increases in new lesions (i.e. abrasions, ulcers; RR 2.04, 95% CI: 0.70-5.96; Low CoE), moderate increases in falls but the evidence is very uncertain (RR 1.47, 95% CI: 0.16-13.18; Very low CoE), and small decreases in patient satisfaction (MD -1.60 lower on 10-point scale, 2.91-0.29 lower; Low CoE). Therefore, we judged the balance of effects did not favour either TCCs or non-removable walkers, based on a moderate CoE for our critical outcome of ulcers healed.

In terms of initial costs, our meta-analysis found TCCs and non-removable walkers may cause little-to-no difference in initial costs (MD €0.77 lower, €11.62 lower to €10.09 higher; Very low CoE), but that TCCs were likely to be moderately less cost-effective over the treatment duration than non-removable walkers (MD €564.79 higher, 781.57-348.01 higher; Moderate CoE), with the results of one health technology assessment that could not be pooled also pointing in that direction (40). An additional consideration that has been reported in the literature which may impact provider preference between the two types of devices is application time. TCCs were found to take longer to apply and remove than a non-removable knee-high walker (MD 13 minutes longer, $p<0.001$; MD 4.8 minutes longer, $p<0.0001$, respectively) (41, 42).

Additionally, based on our expert opinion only as no evidence existed, we judged equity to probably be reduced with TCCs compared to non-removable walkers as they are likely to only be available to those willing to pay for ongoing TCC materials, have access to clinicians with the skills and resources to provide TCCs and may require more consultations than non-removable walkers. For similar reasons to those in Recommendation 1, we judged TCCs were probably less acceptable compared to non-removable walkers based on multiple published surveys finding they are not commonly used in clinical practice. Finally, we judged TCCs were probably not as feasible to implement as non-removable walkers for similar above cost, resource and skill reasons.

In summary, many of the important outcomes favour non-removable walkers, but TCC show slightly better effect sizes for some of the critically important outcomes (i.e. ulcers healed and amputation). Based on our judgements that TCCs compared to removable devices may produce small desirable effects and small undesirable effects, and with moderate certainty of supporting evidence for critical outcomes, we consider the balance of effects does not favour one device over the other. We have

therefore made a conditional recommendation that healthcare professionals may choose to use either a TCC or non-removable knee-high walker for people with a neuropathic plantar forefoot or midfoot ulcer and the certainty of the evidence is moderate. The choice between a TCC or non-removable knee-high walker should ultimately be dependent upon the resources available, technician skills, patient preferences, and the appropriateness of the device to fit the level of any foot deformity present (i.e. using a TCC with a severely deformed foot).

Clinical question 3: In a person with diabetes and a plantar forefoot or midfoot ulcer, should removable knee-high offloading devices be used over removable ankle-high offloading devices?

Recommendation 2: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for whom a non-removable knee-high offloading device is contraindicated or not tolerated, consider using either a removable knee-high or ankle-high offloading device as the second choice of offloading treatment to promote healing of the ulcer, and encourage the person to wear the device during all weight-bearing activities. (Conditional; Low)

Rationale: There are circumstances when a non-removable knee-high offloading device is contraindicated (e.g. heavily exudating wound or moderate infection) or not acceptable to the person with a plantar forefoot or midfoot ulcer. This can include when the person declines to wear the device or the person's circumstances do not support its use, such as unable to use the device as part of the person's job. A removable knee-high or ankle-high offloading device may be a solution to overcome these issues, such as removable knee-high walker or healing sandal, respectively (see Glossary for definitions) (11). Again, when using a removable offloading device an appropriate foot-device interface should be used and a walking aid should also be considered (see Recommendation 1 for details).

Our systematic review and meta-analyses identified 4 RCTs and 2 other controlled studies, with 7 non-controlled studies adding relevant evidence for this question (11). We judged the overall desirable effects to be small, based on our meta-analysis finding removable knee-high compared to removable ankle-high offloading devices may cause little-to-no difference in proportions of ulcers healed (RR 1.00, 95% CI 0.86-1.16; Low CoE) and infections (RR 1.00, 0.51-1.94; Low CoE), but small decreases in plantar pressure (MD 42 kPa lower, 95% CI 68-12 lower; Low CoE) and new lesions (RR 0.87, 0.42-1.82; Very low CoE), and moderate decreases in weight-bearing activity (MD 969 daily steps, 95% CI 2,004 lower to 67 higher; Very low CoE). Whereas, we also judged the overall undesirable effects to be small, finding removable knee-high may also cause small decreases in patient satisfaction compared to ankle-high devices (MD -0.6 lower on 10-point scale, 1.8 lower to 0.7 higher, Very low CoE), and moderate increases in non-adherence (RR 1.66, 95% CI 1.10-2.52; Low CoE), falls (RR 2.00, 95% CI 0.13-30.34; Very low CoE) and amputations (RR 1.96, 95% CI 0.52-7.34; Very low CoE), but the evidence is very uncertain. Therefore, we judged the balance of effects did not favour either removable knee-high or removable ankle-high offloading devices, based on a low CoE for our critical outcome of ulcers healed.

Interestingly, the evidence to support either the use of knee-high or ankle high devices for other important surrogate outcomes for ulcers healed, including plantar pressure reduction, weight bearing activity, and adherence, is inconsistent. Our meta-analysis indicates that knee-high devices reduce more plantar pressure and weight-bearing activity, but also reduce adherence compared to ankle-high devices.

The lower levels of adherence could explain why the mechanistic effects of a reduction in plantar pressure and weight bearing activity observed in knee-high devices does not lead to an improvement in ulcer healing rates. If people with a plantar forefoot or midfoot ulcers can be encouraged to wear a knee-high device, then given the observed reduction in plantar pressure and activity this may translate into better ulcer healing rates compared to an ankle-high device.

One RCT (11) found one-off material costs for knee-high devices were higher than for ankle-high devices (MD NA; US$150-200 v $25-75; p=NR; Very low CoE). However, one large cost-effectiveness analysis (40), using evidence from several trials and expert opinion, found knee-high devices to be more cost-effective than removable ankle-high devices (MD NA; $1,629 v $1,934; p=NR; Low CoE). However, the variety of different types of devices included in the intervention and comparator groups increases the uncertainty around the cost effectiveness of individual devices.

Additionally, based on our expert opinion only as no evidence existed, we judged there would probably be no impact on equity as there is a balance between costs and cost-effectiveness between removable knee-high and ankle-high devices, they are likely similarly available in low-, middle- and high-income countries and the clinical skills to apply both devices is also similar. However, we judged knee-high devices were probably less acceptable over ankle-high devices due to the slightly lower participant satisfaction or acceptability of knee-high devices and multiple published surveys of clinical practice suggested the healthcare professional's acceptability to using removable knee-high devices is also slightly lower than ankle-high devices (20, 21). Finally, we judged removable knee-high devices were probably as feasible to implement as removable ankle-high devices based on our expert opinion.

In summary, based on our judgements that removable knee-high devices compared to removable ankle-high devices may produce small desirable effects and small undesirable effects, and with low certainty of supporting evidence for critical outcomes, we consider the balance of effects does not favour one device over the other. We have therefore made a conditional recommendation that healthcare professionals should use a person-centred approach to prescribing either a knee-high or ankle-high offloading device, taking into consideration offloading capacity and adherence levels to wearing the device. A device with less pressure reduction worn more regularly may be equally or more effective at healing a plantar forefoot or midfoot ulcer than a device with high levels of pressure reduction worn less frequently. Thus, people should be educated on the benefit of adherence to using a removable offloading device during all weight-bearing activity to improve the effectiveness of the device to heal their ulcer.

Please note, this means in contrast to the 2019 IWGDF guideline, removable knee-high and ankle-high offloading devices are now grouped into one recommendation for second-choice of offloading treatment, rather than separate recommendations for second and third-choice treatment, respectively, as in 2019. Effectively that means an upgrade for ankle-high offloading devices to second-choice of offloading treatment, and is based on the current available evidence as well as on analysis and interpretation using the more thorough GRADE approach.

Clinical question 4: In a person with diabetes and a plantar forefoot or midfoot ulcer, should removable above ankle-high offloading devices be used over removable below ankle-high offloading devices?

Recommendation: No recommendation made.

Rationale: Ankle-high offloading devices can range in height from above the ankle such as ankle-high walkers, to below the ankle such as postoperative healing shoes, and all are used in clinical practice for treating plantar forefoot and midfoot DFU (see Glossary for further definitions and examples).

We considered there was insufficient evidence to answer this question, based on our systematic review finding of no controlled studies that compared above ankle-high to below-ankle-high devices for the critical outcome of ulcers healed and most other important outcomes, such as weight-bearing activity, adherence, new lesions, falls, infections, amputations or costs. Furthermore, as ankle-high offloading has already been incorporated in an earlier recommendation, we considered there was limited priority to develop a specific recommendation on types of ankle-high offloading to address this specific question if it were to be based mainly on expert opinion.

Otherwise, there was some evidence from repeated measures studies on other important outcomes of plantar pressure, quality of life and balance. Studies compared a variety of different above ankle-high cast walkers to below ankle-high offloading devices which made specific comparisons challenging. Three repeated measures studies (11), found little-to-no difference in plantar pressure reduction between the two different height devices. One of these studies also found removable above ankle-high compared to below ankle-high devices may make little-to-no effect on balance. There is evidence from one repeated measures study (11) though, that found removable above ankle-high compared to below ankle-high devices may increase patient comfort. However, all the current research is limited to repeated measures studies in surrogate populations for people with DFU. Thus, a larger evidence base is needed on this clinical question in particular regarding the critical outcome of ulcers healed, before any recommendation can be made.

FOOTWEAR

Clinical question 5: In a person with diabetes and a plantar forefoot or midfoot ulcer, should footwear be used over offloading devices?

Recommendation 3: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer, do not use, and educate the person not to use conventional footwear or standard therapeutic footwear over an offloading device, to promote healing of the ulcer. (Strong; Low)

Rationale: Conventional footwear is off-the-shelf footwear that does not have any intended therapeutic effect; whereas standard therapeutic footwear is off-the-shelf footwear with some intended therapeutic effect, such as extra-depth footwear, but is not custom-made footwear (see Glossary for more detail).

Unlike with offloading devices, all controlled studies that investigated conventional or standard therapeutic footwear did so as the comparator/control to another offloading intervention, such as an offloading device. Therefore, for our systematic review and meta-analysis we compared offloading device interventions to therapeutic footwear controls and have used this evidence to inform this clinical question.

Our systematic review and meta-analyses identified 5 RCTs for this question, with 5 non-controlled studies adding relevant evidence (11). We judged the overall desirable effects to be small for therapeutic footwear, based on our meta-analysis finding offloading devices may increase new lesions compared to therapeutic footwear (RR 1.60, 0.07-37.75; Very low CoE). Whereas, we judged the overall undesirable effects to be large for therapeutic footwear, finding offloading devices may moderately increase the proportions of ulcers healed compared to therapeutic footwear (RR 1.39, 95% CI 0.89-2.18; Low CoE), plus non-removable knee-high offloading devices had larger effects again on ulcers healed compared to therapeutic footwear (RR 1.98, 95% CI 0.99-3.93). Further, offloading devices may cause large decreases in plantar pressure (MD 239 kPa lower, 317-160 lower; Low CoE), infections (RR 0.15, 0.03-0.79; Low CoE) and amputations (RR 0.18, 0.01-3.56; Very low CoE) compared to therapeutic footwear, and little-to-no difference in patient satisfaction (MD 2.8 of 100mm VAS lower, 10.6 lower to 4.9 higher; Very low CoE). Therefore, we judged the balance of effects to strongly favour offloading devices over therapeutic footwear based on a low CoE for our critical outcome of ulcers healed.

We found offloading devices may cause small increases in material costs compared to therapeutic footwear ($20 vs $7; Very low CoE), but one large cost-effectiveness analysis (40), found offloading devices compared to therapeutic footwear likely causes large increases in cost-effectiveness (MD NA; $877 v $1934; Moderate CoE).

Additionally, based on our expert opinion only as no evidence existed, we judged therapeutic footwear would probably increase health equity compared to offloading devices as footwear is more likely to be available and cheaper in low-income countries. Further, we considered therapeutic footwear would be probably acceptable and feasible in most places.

In summary, based on our judgements that therapeutic footwear compared to offloading devices may produce small desirable effects but large undesirable effects, and with low certainty of supporting evidence for critical outcomes, we consider the balance of effects does not favour therapeutic footwear and instead favours offloading devices. Thus, we

we have made a strong recommendation against the use of conventional or standard therapeutic footwear for treating plantar forefoot or midfoot DFUs in preference of a wide range of options for offloading devices, when these are available. This recommendation is based on low CoE.

OTHER OFFLOADING INTERVENTIONS

Clinical question 6: In a person with diabetes and a plantar forefoot or midfoot ulcer, should any other non-surgical offloading intervention be used over another non-surgical offloading intervention?

Recommendation 4: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer for which offloading devices are not available, consider using felted foam in combination with appropriately fitting footwear as the third choice of offloading treatment to promote healing of the ulcer. (Conditional; Very Low)

Rationale: Other offloading interventions are defined as any intervention undertaken with the intention of relieving mechanical stress from a specific region of the foot, that is not an offloading device, footwear, or surgical procedure. Despite many practice surveys reporting high use of other offloading interventions, such as felted foam and wheelchairs (21, 22), there has been limited evidence to support other offloading interventions to heal DFUs (11). Our systematic review identified 3 RCTs and 2 other controlled studies, with 5 non-controlled studies adding relevant evidence for this question (11). The other offloading intervention with most controlled studies was felted foam, however wheelchairs, botulinum toxin injections, gait retraining and foam wound dressings also had controlled studies (11). We note no controlled studies were identified for offloading interventions such as bedrest, crutches, callus debridement, foot-related exercises, or knee scooters.

Felted foam was the only intervention defined as an other offloading intervention for which our systematic review found any potentially favourable evidence on the critical outcome of healed ulcers. Our systematic review found wheelchairs were not favoured over wheelchairs in combination with removable offloading devices as they may cause moderate decreases in the proportions of ulcers healed (RR 0.77, 0.59-1.00; Low CoE) and large increases in amputations (RR 12.24, 95% CI 0.69 to 216.92; Very low CoE). Further, whilst our systematic review found gait retraining, botulinum toxin injections, and foam wound dressings may reduce plantar pressure based on (very) low CoE, we considered plantar pressure evidence alone was not sufficient to justify completing summary of judgements or recommendations. Therefore, we only performed summary of judgements for this clinical question on felted foam, and specifically the use of felted foam in combination with a removable ankle-high offloading device compared to the removable ankle-high offloading device alone.

Our systematic review and meta-analyses identified 2 RCTs and one other controlled study on felted foam (11). We judged the desirable effects for felted foam with removable ankle-high offloading device intervention compared to the device alone to be small, based on our systematic review finding little-to-no difference in the proportions of ulcers healed (RR 0.97, 0.82-1.19; Very low CoE), but moderate decreases in plantar pressure outcomes (MD 98 kPa lower, 151-45 lower; Very low CoE). Furthermore, we judged the undesirable effects to be trivial, finding the intervention may result in little-to-no difference in new lesions (RR 1.00, 0.07-14.85; Very low COE) and infections (RR 1.07, 0.41-2.77; Very low CoE). Therefore, we judged the balance of effects probably favours the felted foam with a removable ankle-high offloading device intervention over the device alone, however, based on very low CoE. We also note the systematic review found whether the felted foam is applied to the foot or the device may make little-to-no difference.

In terms of the other important judgements for this felted foam intervention, there was no evidence identified in our systematic review for resources required, cost-effectiveness or health equity. However, based on our expert opinion, we judged the additional resources required for the use of felted foam to be negligible. While felted foam is an additional cost and requires frequent replacement (at least weekly), from an offloading treatment perspective we judged that felted foam is inexpensive to purchase, in low-, middle- and high-income countries, and requires little additional skill to apply. For the same reasons, we judged health equity to be probably increased. Multiple published surveys of offloading practices around the world show the use of felted foam to be high in many countries (21,

22). Therefore, we also considered felted foam to have a positive impact on acceptability and feasibility to implement.

Unfortunately, as identified in clinical questions 1-5, offloading devices are not always feasible to use in all parts of the world due to lack of availability, whereas felted foam and footwear are typically available everywhere. Therefore, we also considered whether felted foam with appropriately fitting footwear may also be an acceptable option for offloading DFU when no offloading devices are available. Whilst our systematic review identified no evidence, based on our expert opinion we considered that felted foam used with appropriately fitting footwear compared to footwear alone may promote healing of the ulcer in a similar mechanistic manner to how felted foam used in combination with ankle-high offloading devices may promote healing over the use of the device alone. We define appropriately fitting footwear as footwear that provides sufficient room for the patients' foot shape and the additional felted foam. Thus, this recommendation would enable some form of offloading treatment for people with a plantar forefoot or midfoot DFU when offloading devices as recommended in Recommendation 1 to 3 are not available. However, we stress that this would be a last resort non-surgical offloading option and that felted foam should not be used as a single treatment modality.

In summary, we consider a conditional recommendation in favour of the intervention of felted foam in combination with a removable ankle-high device compared to a removable ankle-high device alone is justified, based on a probably favourable balance of effects, resources required, equity, acceptability and feasibility. This conditional recommendation is based on very low CoE, and thus, not all patients will be best served by this recommendation, so there is a need to carefully consider the patients circumstances, preferences and values when considering implementing this recommendation. However, because ankle-high offloading devices already have a conditional recommendation as a second-choice offloading treatment (see Recommendation 2), and based on the evidence probably favouring the added use of felted foam for this clinical question, we have incorporated the felted foam consideration under the foot-device interface consideration as outlined in Recommendations 1 and 2. For this Recommendation 4 though, and based on our expert opinion, we have recommended to consider only when offloading devices are not available, that felted foam may be used in combination with appropriately fitting footwear, as a third choice of non-surgical offloading treatment to promote healing of the ulcer.

SURGICAL OFFLOADING INTERVENTIONS

Clinical question 7: In a person with diabetes and a plantar forefoot or midfoot ulcer, should any surgical offloading intervention be used over other offloading interventions?

Recommendation 5a: In a person with diabetes and a neuropathic plantar metatarsal head ulcer for which non-surgical offloading treatment fails, consider using Achilles tendon lengthening in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Moderate)

Recommendation 5b: In a person with diabetes and a neuropathic plantar metatarsal head ulcer for which non-surgical offloading treatment fails, consider using metatarsal head resection in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Low)

Recommendation 5c: In a person with diabetes and a neuropathic hallux ulcer for which non-surgical offloading treatment fails, consider using joint arthroplasty in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Low)

Recommendation 5d: In a person with diabetes and a neuropathic plantar ulcer on metatarsal heads 2-5 for which non-surgical offloading treatment fails, consider using a metatarsal osteotomy in combination with an offloading device to promote and sustain healing of the ulcer. (Conditional; Very low)

Rationale: Surgical offloading interventions have been traditionally used for plantar forefoot and midfoot DFU that are considered hard-to-heal with non-surgical offloading interventions (11). These surgical interventions change the structure and function of the foot and therefore provide a more permanent offloading solution for areas of elevated mechanical tissue stress, even when the patient is not adherent to using an offloading device. However, surgical offloading also potentially comes with increased risk of complications (11).

Regarding Achilles tendon lengthening, we identified 2 RCTs and 5 non-controlled studies (11). We judged the overall desirable effects to be moderate, based on systematic review finding Achilles tendon lengthening in combination with a TCC likely causes small increases in the proportion of ulcers healed compared to a TCC alone (RR 1.10, 0.96-1.27; Moderate CoE), and may cause large increases in sustained healing once healed (RR 3.41, 1.42-8.18, Moderate CoE), large decreases in forefoot plantar pressure (MD 218 kPa lower, 410-26 lower; Low CoE), moderate decreases in new lesions (RR 0.71, 0.22-2.28; Very low CoE) and large decreases in amputations (RR 0.35, 0.01-8.38; Very low CoE). Whereas we judged the overall undesirable effects as moderate, with large increases in new rearfoot ulcers (RR 9.56, 0.54-170.46; Moderate CoE), falls (RR 5.31, 0.27-106.46; Low CoE) and infections (RR 3.19, 0.13-75.43; Low CoE). Thus, we judged our balance of effects probably favours Achilles tendon lengthening in combination with TCC over TCCs alone only if non-surgical offloading treatment has already failed.

For resources required, cost-effectiveness, equity, acceptability and feasibility, our systematic review identified no supporting evidence and hence our judgments were based on expert opinion. We judged the resources required as moderate, as the Achilles tendon lengthening intervention requires additional resources such as operating theatres, skilled surgeons, hardware, post-operative care, etc. Conversely, we judged cost-effectiveness probably favours the intervention, based on a moderate desirable effect outweighing the initial moderate resources required. We judged the impact of health equity as probably reduced as the Achilles tendon lengthening intervention is unlikely to be available everywhere in the world, is probably not acceptable to some patients and healthcare professionals, except if non-surgical offloading interventions consistently fail, and the feasibility of Achilles tendon lengthening may vary based on the local resources available.

In summary, we consider a conditional recommendation in favour of the Achilles tendon lengthening in combination with an offloading device compared to an offloading device alone is justified when non-surgical offloading interventions have failed based on moderate desirable effects and despite moderate undesirable effects. If non-surgical treatment has already failed, the balance of effects at that point may favour the surgical intervention. We judged the CoE for this recommendation to be moderate based on

finding that the critical outcomes of ulcers healed and sustained healing have moderate certainty of supporting evidence.

Regarding metatarsal head (MTH) resection, we identified one RCT, 2 other controlled studies and 7 non-controlled studies. We judged the desirable effects to be moderate, based on our meta-analysis finding MTH resection in combination with offloading devices compared to offloading devices alone may cause moderate increases in proportion of ulcers healed (RR 1.33, 1.12-1.58; Low CoE) and sustained healing (RR 1.21, 1.09-1.35; Low CoE), moderate decreases in infections (RR 0.55, 0.25-1.19; Very low CoE) and amputations (RR 0.68, 0.28-1.66; Very low CoE), and large decreases in plantar pressure (MD 511 kPa lower, 607-415 lower; Very low CoE). We judged the undesirable effects to be small, based on moderate increases in new transfer lesions (RR 1.50, 0.46-4.86; Very low CoE) and large decreases in weight-bearing activity (MD 2.2 lower on 4-point scale, 3.2-1.2 lower; Low CoE). Although some persons may experience improved wound healing in association with a reduction in activity, excessively large reductions are likely to yield declines in individuals' general health. We also emphasize that the indication for MTH resection may include management of infection, such as osteomyelitis or joint infection, as well as surgical offloading of a prominent metatarsal head. This makes the comparison to conservative treatment difficult as the magnitude of the undesirable effect may also vary due to the joint in question. It is expected that there is a higher risk of undesirable effects in the first metatarsal phalangeal joint than in the second to fifth metatarsals. Overall, we judged our balance of effects probably favours MTH resection in combination with an offloading device over a device alone.

We found MTH resection may also cause moderate decreases in quality of life during healing (MD 1.2 lower on 4-point discomfort scale, 2.1-0.3 lower; Low CoE) but moderate increases in quality of life after healing (MD 2.5 higher on 10-point global satisfaction scale, 0.4-4.6 higher; Low CoE), and small increases in cost-effectiveness, but evidence is very uncertain. Based primarily on expert opinion, we considered equity and acceptability to be probably reduced, and the and the feasibility of the intervention may vary based on the local resources available.

In summary, we consider a conditional recommendation in favour of the MTH resection in combination with an offloading device or footwear when non-surgical offloading interventions have failed, and the CoE for this recommendation as low.

As both Achilles tendon lengthening and MTH resection have a conditional recommendation in favor of the intervention to treat a neuropathic plantar MTH ulcer, the question arises as to when to perform one over the other. Based on our expert opinion, Achilles tendon lengthening is indicated in the case of someone with such an ulcer and an equinus position of the foot. When osteomyelitis of the metatarsal head or infection in the metatarsophalangeal (MTP) joint is identified, as proven by either Magnetic Resonance Imaging (MRI) or the ulcer permitting a probe to reach the bone or joint (15), MTH resection or joint arthroplasty should be considered. In the case of previous MTH resection or osteotomies and a transfer ulcer to another metatarsal head, we suggest either an Achilles tendon lengthening alone, or in combination with an MTH resection when infection or osteomyelitis is identified.

Regarding joint arthroplasty, we identified 2 controlled studies and 4 non-controlled studies. We judged the desirable effects to be moderate, based on our meta-analysis finding metatarsal-phalangeal joint

arthroplasty in combination with a non-removable offloading device may cause a small increase in proportion of ulcers healed over devices alone (RR 1.07, 0.89-1.28; Low CoE) and sustained healing (RR 1.19, 0.67-2.12; Low CoE), and large decreases in amputations (RR 0.48, 0.05-4.85; Very low CoE). Whereas, we judged the undesirable effects to be small, based on little-to-no differences for infections (RR 0.95, 0.44-2.05; Low CoE) and new lesions (RR NA; Very low CoE), but the evidence is very uncertain as zero new lesions were reported when in our expert opinion we would expect some new lesions and other outcomes such as falls weren't reported. Thus, we judged the balance of effects probably favours joint arthroplasty in combination with a non-removable offloading device over a device alone if non-surgical offloading treatment fails. We also emphasize that the indication for joint arthroplasty is for a hallux ulcer with limited range of motion of the first metatarsal-phalangeal joint. In case of other deformities with a hallux ulcer, joint arthroplasty may not be indicated. Otherwise, we consider based on only expert opinion the costs to be moderate, equity probably reduced, low acceptability and the feasibility of the intervention may vary based on the local resources available.

In summary, we consider a conditional recommendation in favour of the metatarsal-phalangeal joint arthroplasty in combination with a non-removable offloading device when non-surgical offloading interventions have failed, and the CoE for this recommendation as low based on the low CoE for the critical outcomes of ulcers healed and sustained healing.

Regarding metatarsal osteotomy, we identified one controlled study and 5 non-controlled studies. We judged the desirable effects to be moderate, based on our meta-analysis finding metatarsal osteotomy in combination with a non-removable offloading device may cause shorter time-to-healing (RR NA; 51.3 vs 159.3 days time-to-healing; p=0.004; Low CoE), large decreases in amputations (RR 0.17, 0.02-1.24; Very low CoE), and moderate decreases in plantar pressure (MD 136 kPa lower, 144-128 lower; Very low CoE) over non-surgical care (11). Whereas, we judged the undesirable effects to be small, based on our systematic review finding little-to-no difference for sustained healing, and very uncertain effects on infections and new lesions, based on only non-controlled studies. We therefore judged the desirable effects as moderate and the undesirable effect as small, and thus a balance of effects probably in favour of the metatarsal osteotomy. Furthermore, we considered the costs as moderate, equity and acceptability probably reduced, and the feasibility of the intervention may vary based on the local resources available.

In summary, we consider a conditional recommendation in favour of the metatarsal osteotomy over conservative care, and the CoE for this recommendation as low based on the low CoE for the critical outcomes of ulcers healed. However, we highlight this conditional recommendation is limited to metatarsals 2-5. This is due in our expert opinion to the increased risk of undesirable effects when performing the osteotomy on the first ray. Additionally, in case of infection in the distal part of the metatarsals or in the MTP joint, consider using a MTH resection instead (recommendation 5b). Otherwise please refer to the comments in Recommendation 5b regarding the combined use of the Achilles tendon lengthening combined with MTP joint resection or metatarsal osteotomy.

We decided not to put forward a recommendation for the use of joint arthrodesis, based on the limited available evidence. The only controlled study regarding joint arthrodesis in combination with offloading devices compared to offloading devices alone is based on a population of people with Charcot midfoot

deformity and DFUs and that study found little-to-no difference in healing (43). That paper is included in the guideline on the Charcot foot (32), and hence, we have considered a recommendation was not justified.

Overall, there is some evidence to support surgical offloading in combination with offloading devices over offloading devices alone to improve ulcers healed and time-to-healing of plantar forefoot or midfoot DFU that prove to be hard-to-heal with non-surgical treatment, and much more evidence for sustained healing. However, the number of controlled studies for each surgical intervention is still low, the quality of these studies is generally low and the comparator is often not a gold standard treatment, and therefore we consider the CoE for most of the above recommendations to be low. For these and other reasons, we rate the strength of these recommendations as conditional, and recommend these interventions only when non-surgical offloading treatment fails in healing the foot ulcer. We also highlight that surgical offloading is contraindicated when severe ischaemia is present.

Recommendation 6: In a person with diabetes and a neuropathic plantar or apex ulcer on digits 2-5, secondary to a flexible toe deformity, use a digital flexor tenotomy to promote and sustain healing of the ulcer. (Strong; Moderate)

Rationale: A tenotomy of the flexor tendon of digits of the foot has been used to treat plantar or apex ulcers on flexible claw or hammer toe deformities. The recommendation for a digital flexor tenotomy procedure is limited to digits 2-5, based on our expert opinion that ulcers on the first toe are instead likely caused by other deformities or by limited joint motion, which are conditions that may contribute to the non-healing of the ulcer if a digital flexor tenotomy would be performed on the first toe.

Our systematic review identified 1 RCT and 13 non-controlled studies (11). We judged the desirable effects to be moderate, based on our systematic review finding digital flexor tenotomies in combination with removable ankle-high offloading devices likely causes large increases in proportion of ulcers healed (RR 2.43, 1.05-5.59; Moderate CoE) and sustained healing (RR 2.52, 0.70-9.01; Moderate CoE), and may cause large decreases in infections (RR 0.33, 0.02-7.14; Low CoE) and plantar pressure at the ulcer site (MD 398 kPa lower, 524-28 lower; Low CoE) in comparison to devices alone. The non-controlled studies also showed an overall healing rate of 97% in a mean 29.5 days (44) for digital flexor tenotomy which further supported the intervention findings in the RCT. Whereas, we judged the undesirable effects to be small, based on our systematic review finding of zero transfer lesions in the RCT, but that digital flexor tenotomy caused small increases in transfer lesions in most non-controlled studies (23), and little-to-no difference in balance and amputations again based on zero events. We also found digital flexor tenotomies in combination with ankle-high devices may cause small increases in patient satisfaction compared to devices alone (7.7 vs 3.9 on 10cm VAS scale; p=NR; Very low CoE). Therefore, with moderate desirable and small undesirable effects, we judged the balance of effects to be in favour of the digital flexor tenotomy in combination with ankle-high offloading devices over devices alone.

Furthermore, based on our expert opinion, we judged any additional resources and costs required to be negligible to small, as the tenotomy is a relatively straightforward procedure that can be performed in an outpatient clinic. As such, it is a surgery that requires little additional resources, and may be cost-effective based on our findings on balance of effects in favour of digital flexor tenotomy and our

judgement that initial costs would be small. We furthermore judged equity to be probably increased based on our expert opinion that tenotomies have negligible to small additionally required costs, require little extra surgical skill and are readily available around the world. We also judged tenotomies to be probably acceptable to most people for the above reasons and feasible to implement.

In summary, we previously considered digital flexor tenotomy to be a promising intervention for people with hammertoes and recalcitrant lesser digital ulcers that failed non-surgical treatment. However, based on the outcomes from a recent RCT (23), we now consider a strong recommendation in favour of digital flexor tenotomy as a first line of treatment is justified for neuropathic plantar or apex ulcer on digits 2-5, secondary to a flexible toe deformity. This is based on the clear balance of effects in favour of tenotomies over conservative care, and the CoE for this recommendation is graded as moderate based on the moderate CoE for the critical outcomes of ulcers healed and sustained healing. However, when digital flexor tenotomies are not available, we refer to the offloading device recommendations for plantar ulcers (Recommendations 1-4) or non-plantar ulcers (Recommendation 9) for treating a neuropathic plantar or apex ulcer on digits 2-5.

OTHER ULCERS

Clinical question 8: In a person with diabetes and a plantar forefoot or midfoot ulcer complicated by infection or ischaemia, should any one offloading intervention be used over another offloading intervention?

Recommendation 7a: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with either mild infection or mild ischaemia, consider using a non-removable knee-high offloading device to promote healing of the ulcer. (Conditional; Low)

Recommendation 7b: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both mild infection and mild ischaemia, or with either moderate infection or moderate ischaemia, consider using a removable offloading device to promote healing of the ulcer. (Conditional; Low)

Recommendation 7c: In a person with diabetes and a neuropathic plantar forefoot or midfoot ulcer with both moderate infection and moderate ischaemia, or with either severe infection or severe ischaemia, primarily address the infection and/or ischaemia, and use a removable offloading intervention over no offloading based on the person's individual factors to promote healing of the ulcer. (Strong; Very low)

Rationale: Many plantar ulcers seen in clinical practice are not purely neuropathic, but have some level of infection and/or ischaemia present. Due to the neuropathic origin and mechanical stress that often caused and continues to affect these ulcers, these infected and ischaemic ulcers still require some form of offloading treatment. However, healthcare professionals should be more cautious about what kind of offloading treatment to use if ulcers are complicated by infection or ischaemia. Although greater caution is warranted in selecting an appropriate means to offload the mechanical stress in these more complicated ulcers, the same arguments and indications for recommendations 1 to 6 are generally

applicable. Here, we will only report some specific aspects about the offloading treatment at different levels of infection and ischaemia, with data from our systematic review included.

Our systematic review identified one controlled study, supported by 3 non-controlled studies, that found non-removable knee-high devices versus removable devices may cause large increases in proportion of infected ulcers healed (adjusted OR 2.53, 1.19-5.35; Low CoE) (11). In our expert opinion, we consider such an outcome is likely in all plantar forefoot or midfoot DFUs complicated by either mild infection or mild ischaemia, or mild-to-moderate amounts of exudate (11). The improved healing is likely to be associated with increased levels of adherence for non-removable versus removable devices. It is possible that if removable devices were worn more frequently, there would be similar levels of healing between the devices. Furthermore, in our expert opinion, the presence of mild infection or mild ischaemia should not affect the resources required, cost-effectiveness, equity, acceptability and feasibility considerations for non-removable versus removable offloading devices as outlined in the rationale for Recommendations 1 and we refer the reader to those judgements. We do stress that when the ulcer is infected or ischaemic, it should be monitored more regularly via at least weekly visits to a healthcare professional, to enable the device to be removed and the ulcer and any infection checked. However, clearly more research is needed to investigate the use of non-removable knee-high devices compared to removable devices for healing a plantar forefoot or midfoot DFU complicated by either mild infection or mild ischaemia.

Non-removable offloading should not be used when both mild infection and mild ischaemia, moderate infection or ischaemia, or heavy exudate is present and these conditions require frequent inspection or wound care, potentially daily (11). Removable offloading devices can be considered for healing these ulcers, and we recommend any removable offloading device as per Recommendation 2, although note that one controlled study found removable knee-high devices may cause moderate increases in ulcers healed in people with infection compared to removable ankle-high devices (26). However, if the ulcer does not require daily inspection or wound care, but only removal of the device with certain indications (e.g. fever present) or otherwise at weekly clinic visits, a knee-high removable device may be rendered non-removable to promote adherence and efficacy. This should only be provided as long as the circumferential wrapping or other closure technique used can be removed and applied at any time, by a homecare professional or a trained partner.

If a neuropathic plantar forefoot or midfoot ulcer is complicated by both moderate infection and moderate ischaemia, or by severe infection or severe ischaemia, then the infection or ischaemia treatment should be planned first before determining the appropriate offloading intervention. This may mean the person remain fully non-weight-bearing during a period that the infection or ischaemia treatment prohibits the use of offloading. However, in cases where a person will be weight-bearing prior to resolution of the infection or severe ischaemia, the best offloading option that will work in conjunction with infection and/or ischaemia interventions should be implemented. As no evidence exists for offloading these severe infection or ischaemic complications, in our expert opinion, the choice of removable offloading intervention needs to consider a patient's individual factors, such as, their function, ambulatory status, and activity level. When the infection and ischaemia status improve, the recommendations for mild to moderate infection or ischaemia apply (Recommendations 7a and 7b), or, when the infection or ischaemia are resolved, the recommendations for non-complicated foot ulcers

apply (Recommendations 1- 6). Again, further research is needed to investigate the efficacy of offloading devices to heal these plantar DFU complicated by moderate-to-severe infection or ischaemia.

In summary, based on the lack of evidence for desirable and undesirable effects, patient preferences and costs, the strength of recommendations 7a-7b are conditional. However, we have made a strong recommendation for 7c based on our expert opinion that offloading compared to no offloading in these situations should provide a clear balance of effects in favour of offloading. The overall CoE for recommendations 7a-7b is low based on the limited controlled studies and very low for 7c that is only based on expert option that these plantar ulcers still require offloading for healing (11).

Clinical question 9: In a person with diabetes and a plantar digital ulcer, should any one offloading intervention be used over another offloading intervention?

Recommendation: No recommendation.

Rationale: We considered this question was not different enough from already existing questions 1 through 8 to assess the literature, write summary of judgements and write a specific recommendation for this question. Thus, we refer to earlier Recommendations 1 through 6 already addressing this question.

Clinical question 10: In a person with diabetes and a plantar rearfoot ulcer, should any one offloading intervention be used over another offloading intervention?

Recommendation 8: In a person with diabetes and a neuropathic plantar rearfoot ulcer, consider using a non-removable knee-high offloading device over a removable offloading device to promote healing of the ulcer. (Conditional; Very low)

Rationale: Neuropathic plantar rearfoot ulcers are less prevalent than forefoot ulcers (45), but are considered more of a challenge to offload and heal (11). However, there is little evidence available on offloading interventions to treat plantar rearfoot ulcers (11), and when studies were available, they did not specifically report outcomes for the subgroup of plantar rearfoot ulcers, such as in one large RCT, where 28% of rearfoot DFU were on the plantar surface (46).

Our systematic review and meta-analysis identified 1 RCT, 1 controlled study, and 5 non-controlled studies for this question (11). We judged the desirable effects to be moderate, based on our meta-analysis finding non-removable knee-high devices may cause large increases in plantar rearfoot ulcers healed compared to removable devices (RR 5.00, 0.30-83.69; Very low CoE), shorter time-to-ulcer healing (MD NA; 69 vs 107 days), and little-to-no difference in rearfoot plantar pressure (MD 20 kPa lower, 70 lower to 111 higher; Very low CoE), but the evidence is very uncertain. There was no data on other outcomes and thus we are reliant on our expert opinion judgement that undesirable effects may be small based on the evidence in Recommendation 1. Therefore, with moderate desirable and small undesirable effects, we judged the balance of effects to probably favour non-removable over removable offloading devices for plantar rearfoot ulcers, but based on a very low CoE for our critical outcome of ulcers healed. We do not intend to make a recommendation around the specific choice of non-

removable device (e.g. TCC or non-removable walker) to offload plantar rearfoot DFUs as there is insufficient evidence to support one over the other.

If a non-removable device is contraindicated, our meta-analysis found removable knee-high versus ankle-high offloading devices may cause large increases in proportions ulcers healed (RR 5.60, 0.87-36.22; Very low CoE), and small decreases in rearfoot plantar pressure (MD 36 kPa lower, 69-4 lower; Very low CoE), but the evidence is very uncertain. There were no data on the other important outcomes, such as weight-bearing activity, adherence, new lesions, falls, infections, quality of life, costs, cost-effectiveness, or balance for using offloading interventions to treat plantar rearfoot DFUs. We did not provide expert opinion on those outcomes, as we lack sufficient experience with treating rearfoot ulcers in people with diabetes, being uncommon in clinical practice. For resources required, equity, acceptability and feasibility, considerations for non-removable versus removable offloading devices should be similar regardless of the site of ulceration and have been discussed under clinical question 1. There is no data on the cost effectiveness of different offloading devices to heal plantar rearfoot DFUs.

In summary, the balance of effects probably favours non-removable over removable offloading devices for plantar rearfoot ulcers, with the CoE for this recommendation being very low based on the very low CoE for the critical outcome of ulcers healed. Therefore, we make a conditional recommendation in favour of non-removable offloading devices based on a very low CoE.

Clinical question 11: In a person with diabetes and a non-plantar foot ulcer, should any one offloading intervention be used over another offloading intervention?

Recommendation 9: In a person with diabetes and a non-plantar foot ulcer, use a removable offloading device, footwear modifications, toe spacers, orthoses, or digial flexor tenotomy, depending on the type and location of the foot ulcer, to promote healing of the ulcer. (Strong; Very low)

Rationale: Non-plantar foot ulcers also require offloading, when pressure or friction on that region of the foot is a likely cause of the ulcer, such as from tightly fitting footwear or rubbing between toes. Overall, our systematic review identified no controlled studies reporting outcomes addressing this question on how to offload non-plantar foot ulcers, despite these ulcers being prevalent and needing relief from mechanical stress (11, 45). Our systematic review did identify 2 RCTs and 1 other controlled trial that reported baseline non-plantar DFU characteristics, but they did not report outcomes for this question (11). One of the RCTs, a large high-quality RCT compared a custom-made fiberglass heel cast in addition to usual care ("usual care was not standardised") with usual care in patients that mostly (72%) had non-plantar rearfoot DFUs (the other 28% had plantar rearfoot ulcers), but did not subgroup the outcomes for non-plantar rearfoot DFUs (46). The study found no differences in proportion ulcers healed, adverse events or patient preferences, but did find the heel cast had higher overall costs.

Therefore, until new evidence becomes available, our recommendation is based entirely on expert opinion. Our expert opinion is to choose the best modality based on the principle that it prevents any tissue stress or contact with the ulcer and is an appropriate fit for the rest of the foot so as not to produce new lesions. A number of different interventions can be used to reduce pressure on a non-plantar ulcer, depending on the type and location of the ulcer. For example, appropriately fitting footwear or footwear modifications can reduce pressure on ulcers on the foot margins and dorsal foot,

toe spacers can reduce pressure on interdigital ulcers and specific ankle-foot orthoses may reduce pressure on ulcers on the back of the rearfoot or medial/lateral foot when lying in bed. Furthermore, a digital flexor tenotomy may be used to reduce pressure on and promote healing of dorsal ulcers on deformed toes (23, 47).

Further research is needed to investigate offloading interventions for healing a non-plantar foot ulcer. Due to the paucity of data, we rate the CoE for this recommendation as very low. However, we consider this a strong recommendation, based on our opinion that the use of these offloading interventions compared with using no offloading intervention would promote DFU healing, reduce tissue stress and be of preference to the patient, and that should outweigh any undesirable effects of the intervention.

GENERAL QUESTIONS

Clinical question 12: In a person with diabetes and a foot ulcer, should a combination of offloading interventions be used over a single offloading intervention?

Recommendation: No recommendation.

Rationale: In the multidisciplinary treatment of DFUs, typically a combination of multiple treatments are provided at once for improved effect on ulcer healing, for example offloading, wound dressings, debridement, revascularisation or antibiotics for infection (13). In a similar manner, a combination of offloading treatments to improve the effect on DFU healing may be provided, and justifies the question whether such combined offloading interventions should be used over a single offloading intervention to heal DFUs.

Our systematic review identified that nearly all studies primarily investigating surgical offloading interventions (e.g. Achilles tendon lengthening, digital flexor tenotomies, etc.) or other offloading interventions (e.g. felted foam, wheelchairs) did so in combination with an offloading device or footwear, and compared outcomes to a single intervention control (11). In contrast, our systematic review identified no studies that primarily investigated offloading devices or footwear, in combination with another offloading intervention.

Therefore, all the available evidence on the effect of a combination of interventions has already been considered in earlier clinical questions and recommendations made and we refrain from making a specific recommendation on this clinical question. We refer the reader to clinical questions 6, 7a-f and 11 for the combination of either a surgical or other offloading intervention in combination with an offloading device or footwear for the recommendations on combination interventions.

Clinical question 13: In a person with diabetes and a foot ulcer, should educational or psychological interventions along with an offloading intervention be used over an offloading intervention alone?

Recommendation: No recommendation.

Rationale: Our systematic review did not identify any studies investigating educational or psychological interventions for the purpose of enhancing the use of an offloading intervention (11). Furthermore, we considered there is insufficient expert opinion to be able to make any appropriately-informed judgements on the balance of effects of educational or psychological interventions along with an offloading intervention. Therefore, we were unable to make a specific recommendation to address this question. However, despite this lack of evidence, we consider this question is an important one. We encourage clinical researchers to conduct studies that investigate educational or psychological interventions intended to improve outcomes of offloading interventions, especially since educational and psychological interventions have shown promise in other areas of diabetes and diabetes-related foot disease, such as for self-care and footwear adherence for ulcer prevention (48-52).

Clinical question 14: In a person with diabetes and a foot ulcer, should an offloading intervention for the contralateral limb along with an offloading intervention for the ipsilateral limb be used over only an offloading intervention for the ipsilateral limb?

Recommendation 10: In a person with diabetes and a foot ulcer for which a knee-high or ankle-high offloading device is used, consider also using a shoe lift on the contralateral limb to improve the person's comfort and balance with walking in the device. (Conditional; Very low)

Rationale: People with a DFU who are provided with a knee-high or ankle-high offloading device may experience discomfort or issues with postural balance or gait stability when the thickness of the device's sole produces a leg-length discrepancy. For these cases, a contralateral lift may be indicated to reduce this leg-length discrepancy and improve gait. Furthermore, consideration should be given to using a walking aid if stability is compromised by wearing the device and risk of falling is high.

Our systematic review identified only 1 repeated measures study addressing this question and it investigated a contralateral shoe lift with an ipsilateral removable offloading device intervention versus the same ipsilateral offloading device alone (11). We judged the desirable effects for the intervention to be small based on little-to-no differences in plantar forefoot pressure found for removable knee-high device in combination with a contralateral shoe lift compared to the device alone (MD 1 kPa lower, 17 lower to 20 higher; Very low CoE) and removable ankle-high device in combination with a contralateral shoe lift compared to the device alone (MD 6 kPa lower, 10 lower to 22 higher; Very low CoE). However, moderate increases in perceived comfort (MD 2.2 higher, 0.1-4.3 higher; Very low CoE) and small improvements in balance were found in the groups with the removable device in combination with the contralateral shoe lift compared to the device alone. Additionally, we judged the undesirable effects to be trivial. Based on our expert opinion, we considered the additional costs of such an intervention to be negligible, the intervention would probably have no impact on equity, and would probably be acceptable and feasible. Thus, we considered a conditional recommendation in favour of such a contralateral shoe lift was justified based on the balance of effects favouring the contralateral shoe life, and a CoE for this recommendation of very low.

KEY CONSIDERATIONS FOR FUTURE RESEARCH

1. In the large number of studies conducted on the efficacy of non-removable offloading devices (TCC or non-removable walkers), many different versions, types and methods of devices and casts have been used. These different versions of devices, and the skills of the technician or healthcare professional to apply them, may potentially lead to different outcomes and varied costs as indicated in our systematic review. However, more trials are still needed comparing these different versions, types and methods of non-removable offloading devices with each other, so that more informed clinical decisions can be made in future on which are most effective to treat DFU and different DFU types.
2. Likewise, there are many different removable offloading devices, including knee-high devices and ankle-high offloading devices such as ankle-high walkers, forefoot offloading shoes, cast shoes, healing sandals, post-operative healing shoes, custom-made temporary shoes, etc. These removable devices can be prefabricated or custom-made, extend to the knee, just above-ankle or below-ankle, and incorporate different mechanical features and also may lead to different outcomes. Again more trials are needed to compare these different versions, types and methods of removable offloading devices with each other, so that more informed clinical decisions can be made in future on which are most effective to treat DFU and different DFU types. Note, this need for more trials also includes the comparison between knee-high and ankle-high removable devices since both are included as the recommended treatment in Recommendation 2.
3. Many RCTs on offloading interventions do not directly measure the degree to which the mechanical tissue stress on the ulcer has been changed by the offloading intervention. Such measurements improve our understanding of the role of offloading in healing, as do several other outcomes. While we acknowledge based on the above evidence provided that more high-quality RCTs on the primary outcome of ulcer healing are needed, the focus can be strengthened by measuring the factors impacting on the mechanical tissue stress levels that lead to different healing outcomes, such as plantar pressure, shear stress, weight-bearing activity (including steps and standing duration), and adherence to using offloading interventions or a combined plantar tissue stress measure (53, 54). If such combined plantar tissue stress measures are able to detect objective thresholds for effective healing, this may enable the development of future smart offloading treatments designed to meet such threshold targets (53, 55).
4. In developing the recommendations for this guideline, we have made an overall judgement that a reduction in weight bearing activity is beneficial to ulcer healing based on one other review (37) and our expert opinion. We acknowledge that in making this judgement we still do not fully appreciate if reducing weight-bearing activity is a desirable or undesirable effect on different DFU and health outcomes. Thus, we recommend more research is done to determine the effect that weight-bearing activity in combination with offloading interventions has on important outcomes, such as healing ulcers, adverse events, quality of life, and general health outcomes. An ideal offloading intervention would adequately offload a foot ulcer for effective healing while allowing the person to maintain or even increase activity levels to contribute to an improvement in overall general cardiovascular health and quality of life.
5. Offloading studies have focused almost exclusively on the treatment of non-complicated neuropathic plantar forefoot ulcers. Little data are still available on the value of offloading in healing

plantar foot ulcers complicated by infection or ischaemia, rearfoot ulcers, or non-plantar ulcers, even though these ulcers together are now arguably more common than purely neuropathic plantar forefoot and midfoot ulcers. Whilst promisingly there have been some new trials investigating offloading interventions in these more complicated DFU populations since 2019 (26, 27, 29), still comparatively little research has been done in these DFU sub-populations. Again, we stress that properly designed studies on offloading ulcers other than the non-complicated neuropathic plantar forefoot or midfoot ulcer are urgently needed.

6. Adherence to an intervention is crucial in healing foot ulcers. It is consistently reported that those who do not adhere to an offloading intervention present with worse healing outcomes. A stronger focus is required, both in research and in clinical practice, on the objective measurement and improvement of offloading treatment adherence, and understanding people's thoughts, views, emotions and practices around adhering to using offloading devices to treat foot ulcers (56, 57).
7. Surgical offloading has primarily been used to heal foot ulcers in selected patients, typically where non-surgical offloading interventions have failed. The evidence for several surgical interventions is mostly based on only a few older controlled studies. More high-quality RCTs on surgical offloading procedures in comparison to first-choice offloading devices are still required to determine the effectiveness of surgical interventions on the healing of both non-complicated and complicated foot ulcers. For digital flexor tenotomy, a recent RCT has added to the evidence base for this intervention (23), affecting the strength and CoE, and providing an example of what impact well-controlled studies can have in this area.
8. Information on undesirable effects (such as new lesions, falls, infections, amputations), quality of life and costs, equity, acceptability, and feasibility is critical in clinical decision making on offloading treatment. By incorporating the GRADE methodology and multiple meta-analyses pooling these outcomes, the 2023 guidelines are much more considerate of these outcomes than prior iterations in the analysis of the literature on offloading interventions. Still most RCTs are underpowered for these important outcomes. When trials report these outcomes using the same definitions there is the possibility of pooling data in meta-analyses as we have been able to do in our systematic review to better address these outcomes in the overall judgement. We recommend future trials continue to ensure they collect these outcomes based on standard definitions as recommended by Jeffcoate et al. and van Netten et al (12, 36) and on the summary of judgements tables as provided by GRADE.
9. Costs and cost-effectiveness have also received little attention in offloading studies, despite the fact that reimbursement through insured care is more and more dependent on proven cost-effectiveness. Very few additional cost studies have been performed since our previous guidelines in 2019 (58), so more attention is still warranted in view of the continuing pressure on healthcare cost containment.
10. Most interventions discussed are investigated in studies from high-income countries with relatively temperate climates. Whilst promisingly there have been some trials investigating offloading interventions in low and middle-income countries and countries with tropical climates published since 2019 (59-61), there is still a need for more specific guidance on approaches to ulcer healing in lower-income countries where climate and/or resources may be a factor in choice of offloading device, adherence to wearing the device and its efficacy.

11. We encourage our colleagues, whether working in multidisciplinary diabetic foot clinics or in a solo practice, to consider developing some form of surveillance (e.g., registries, pathways) to monitor interventions and outcomes and attempt to improve their outcomes (e.g. through bench marking, best practice and research) for cohorts of persons with diabetes who have a foot ulcer (62-64).
12. We encourage our research colleagues to consider these key considerations and conduct well-designed studies according to published reporting standards (12) in areas of offloading in which we find gaps in the evidence base so to better inform the diabetic foot community in the future on effective offloading treatment for persons with diabetes and a foot ulcer.

CONCLUDING REMARKS

The large global disease and economic burdens caused by DFU can be considerably reduced when evidence-based treatment is implemented by health-care professionals and multidisciplinary teams. Offloading interventions are arguably one of the, if not the, most important interventions with the highest certainty of evidence available for healing neuropathic DFUs and reducing the global burden of these ulcers. Following the recommendations for evidence-based offloading treatments of people with diabetes and a foot ulcer in this guideline should help healthcare professionals and teams improve important outcomes for persons with a diabetes-related foot ulcer.

GLOSSARY

Achilles tendon lengthening: a surgical procedure used to lengthen a tight Achilles tendon and increase motion at the ankle joint (65).

Adverse events/effects in relation to offloading treatment: general or local complications related directly or indirectly to the intervention regardless of whether they are serious. These include but are not limited to: falls; new pre-ulcerative lesion formation (i.e. abrasions, callus and blisters); new DFU formation; acute Charcot foot; infection; hospital admissions; amputation; and death.

Adherence to offloading intervention: The extent to which a person's behaviour corresponds with agreed recommendations for treatment from a healthcare provider, expressed as quantitatively as possible; usually defined as the proportion of time using the prescribed offloading intervention of the total time in which the intervention is prescribed to be used (e.g. % of the total weight bearing time that the patient was wearing the prescribed offloading device).

Ambulatory activity: defined as the weight-bearing dynamic activity, often expressed as average daily steps or strides.

Ankle-high offloading device: an offloading device that extends no higher up the leg than just above the ankle and can be further sub-grouped into above ankle-high and below ankle-high offloading devices. Includes ankle-high walker, forefoot offloading shoe, cast shoe, healing sandal, post-operative healing shoe, and custom-made temporary shoe.

Above ankle-high offloading device: an offloading device that extends up the leg to just above the ankle, typically includes ankle-high walkers.

Below ankle-high offloading device: an offloading device that extends no higher up the leg then just below the ankle, and typically includes forefoot offloading shoe, cast shoe, healing sandal, postoperative healing shoe, custom-made temporary shoe.

Cast shoe: a removable plaster or fibreglass cast that extends to just below or at the ankle joint, moulded around the shape of the foot with total contact of the entire plantar surface.

Complicated DFU: a plantar DFU that is complicated by infection and/or ischaemia.

Conventional footwear: off-the-shelf footwear with no specific properties for fitting or intended therapeutic effect.

Custom-made insole: An insole that is custom-made to the individual's foot using a 2D or 3D impression of the foot, and that is often built-up in a multi-layer construction. This may also incorporate other features, such as a metatarsal pad or metatarsal bar. The insole is designed to conform to the shape of the foot, providing cushioning and redistribution of plantar pressure. The term "insole" is also known as "insert" or "liner"

Custom-made (medical grade) footwear: Footwear uniquely manufactured for one person, when this person cannot be safely accommodated in prefabricated (medical grade) footwear. It is made to accommodate deformity and relieve pressure over at-risk sites on the plantar and dorsal surfaces of the foot. In-depth assessment, multiple measurements, impressions or a mould, and a positive model of a person's foot and ankle are generally required for manufacture. This footwear includes a custom-made insole. Also known as "bespoke footwear" or "orthopaedic footwear".

Custom-made temporary shoe: a unique, usually handmade shoe that is manufactured in a short time frame and is used temporarily to treat a foot ulcer. The shoe is built on a positive model of the patient's foot to accommodate deformity and relieve pressure over the ulcer site on the plantar surface of the foot.

Diabetes-related foot ulcer (DFU): see IWGDF definitions and criteria document (36).

Digital flexor tenotomy: a surgical division of a tendon,(66) in this case a digital flexor tendon.

DFU healing: defined as number or percentage of healed DFUs by a fixed time (e.g., % of DFUs healed in 12 weeks of intervention), or time-to-healing a DFU.

Extra-depth footwear: Prefabricated footwear constructed with additional depth and volume to accommodate deformity such as claw/hammer toes and/or to allow for space for a thick insole. Usually a minimum of 5 millimetres (~3/16") depth is added compared to off-the-shelf footwear. Even greater depth is sometimes provided in footwear that is referred to as double depth or super extra-depth.

Footwear: defined broadly as any shoe-gear and including insoles.

Forefoot offloading shoe: prefabricated shoe especially designed for relieving forefoot locations. The footwear has a specific shape with a wedge design raising the forefoot above the rearfoot, a rocker outsole, and minimal support of the forefoot. These shoes are usually worn unilaterally.

Half-shoe: prefabricated shoe designed to offload the forefoot. The anterior part of the shoe is cut out, leaving the rearfoot and the midfoot as the only weight-bearing surfaces.

Healed DFU: see IWGDF definitions and criteria document (36).

Heel-relief shoe: shoe designed to offload the rearfoot. The rearfoot part is missing from the footwear, and its sole arrangement is constructed in such a way that the rearfoot is not loaded when walking.

In-shoe (semi-)rigid orthoses: device put inside the shoe to achieve pressure reduction or alteration in the function of the foot. Can be prefabricated or custom-made

Joint arthrodesis: a surgical procedure that involves the fusion of two bones in a joint to relieve pain and improve stability.(66)

Joint arthroplasty: a surgical procedure that involves the repair or reconstruction of a damaged joint to increase range of motion, relieve pain, and improve mobility.(66)

Knee-high offloading device: an offloading device that extends up the leg to a level just below the knee (e.g., knee-high total contact cast (TCC), knee-high removable walker).

Lesion: Any abnormality associated with damage to the skin, nails, or deep tissues of the foot, such as abrasions, blisters, callus, maceration, subcutaneous haemorrhage, transfer lesions, ulcers (36).

Metatarsal head resection: a surgical removal of part of a bone, organ or structure,(66) in this case a metatarsal head.

Metatarsal osteotomy: a surgical procedure in which a bone is divided or a piece of bone is excised (as to correct a deformity),(66) in this case a metatarsal.

Non-plantar: see IWGDF definitions and criteria document (36).

Non-removable offloading device: an offloading device that cannot be removed by the patient (e.g., TCC, removable knee-high walker rendered non-removable (non-removable walker), etc.).

Non-surgical offloading intervention: any intervention undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot that does not involve a surgical procedure (includes offloading devices, footwear, and other offloading techniques).

Non-removable walker: prefabricated removable, mostly knee-high, walker rendered non-removable to the patient, by a healthcare professional circumferentially wrapping with a layer(s) of fiberglass cast material or other closure technique such as a tie wrap. Such a device is also known as "instant total contact cast". Manufacturers may also provide means to make the walker non-removable such as incorporating locking mechanisms into the walker

Offloading: the relief of mechanical stress (pressure) from a specific region of the foot.

Offloading device: any custom-made or prefabricated device designed with the intention of relieving mechanical stress (pressure) from a specific region of the foot (e.g., total contact cast (TCC), (non-)removable walker, knee-high walker, ankle-high walker, ankle foot orthoses, healing sandal, cast shoe, forefoot offloading shoe, etc.). Note that this excludes footwear.

Offloading intervention: any intervention undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot (includes surgical offloading techniques, offloading devices, footwear, and other offloading techniques).

Other offloading techniques: any other technique undertaken with the intention of relieving mechanical stress (pressure) from a specific region of the foot that is not a surgical offloading technique, offloading device or footwear (e.g. bed rest, crutches, wheelchairs, offloading dressings, felted foam/padding, callus debridement, gait retraining, foot-related exercises, patient education, etc.).

PICO: the PICO process is a technique used to frame evidence-based clinical questions. PICO stands for: (P): Population; (I): Intervention; (C): Control; (O): Outcome.

Plantar: see IWGDF definitions and criteria document (36).

Plantar pressure: see IWGDF definitions and criteria document (36).

Post-operative healing shoe: prefabricated shoe with roomy and soft upper worn after an operation of the foot.

Removable offloading device: an offloading device that can be removed by the patient (e.g. removable walker, forefoot offloading shoe, cast shoe, healing sandal, etc.).

Rocker outsole: rigid outsole with a sharp transition that aims to rock the shoe forward. during late support to allow walking without extension of the metatarsal-phalangeal joints.

Shoe modification: modification to an existing shoe with an intended therapeutic effect, for example, pressure relief.

Standard therapeutic footwear: off-the-shelf shoe with intended therapeutic effect but without any customization to the patient's foot.

Surgical offloading intervention: a surgical procedure or technique undertaken with the intention of relieving mechanical stress from a specific region of the foot, and includes Achilles tendon lengthening, metatarsal head resection, osteotomy, arthroplasty, arthrodesis, ostectomy, exostectomy, external fixation, flexor tendon transfer or tenotomy, silicone injections, tissue augmentation.

Sustained healing: Days since a person has achieved a healed ulcer and gone without another foot ulcer at the same location (also known as ulcer-free days or remission at that same location) (36).

Therapeutic footwear: Generic term for footwear designed to have a therapeutic effect that cannot be provided by or in a conventional shoe. Custom-made shoes or sandals, custom-made insoles, extra-depth shoes, and custom-made or prefabricated medical grade footwear are examples of therapeutic footwear.

Toe orthosis: an in-shoe orthosis to achieve some alteration in the function of the toe.

Total contact cast (TCC): a custom-made, well-moulded, minimally padded, knee-high non-removable fiberglass or plaster cast that maintains total contact with the entire plantar surface and lower leg. The cast is often worn with an attachable sole that protects the cast and facilitates walking.

Ulcers healed: Intact skin, meaning complete epithelialization without any drainage of a previous foot ulcer site, and typically stated within a certain prespecified time frame (e.g. ulcers healed within 3 months).(36)

Ulcer area reduction: defined as the proportion of ulcer area reduction from baseline over a given period of time (e.g., % ulcer area reduction at 4 or 6 weeks from the start of the observation period) (1).

Uncomplicated DFU: non-infected, non-ischaemic neuropathic DFU.

CONFLICT OF INTEREST STATEMENTS

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Full conflict of interest statements of all authors can be found online at *www.iwgdfguidelines.org*.

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AUTHOR CONTRIBUTIONS

SAB performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 5, 8, 11, and 14, and wrote the manuscript. DGA and KKM performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical question 7, and critically reviewed and edited the manuscript. RTC and CG performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 1-4, and 10, and critically reviewed and edited the manuscript. GJ performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 5, 8, 11, and 14, and critically reviewed and edited the manuscript. VV and PAL performed qualitative assessments, completed summary of judgements, and wrote recommendations for clinical questions 6, 9, 12 and 13, and critically reviewed and edited the manuscript.

SAB acted as chair of the working group and PAL as secretary and they take full responsibility for the content of the manuscript.

REFERENCES

(1) Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24.

(2) Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. New England Journal of Medicine. 2017;376(24):2367-75.

(3) Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers. Diabetes Care. 2018;41(4):645-52.

(4) Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964-74.

(5) Lazzarini PA, Cramb SM, Golledge J, Morton JI, Magliano DJ, Van Netten JJ. Global trends in the incidence of hospital admissions for diabetes-related foot disease and amputations: a review of national rates in the 21st century. Diabetologia. 2023;66(2):267-87.

(6) Bus SA. The Role of Pressure Offloading on Diabetic Foot Ulcer Healing and Prevention of Recurrence. Plast Reconstr Surg. 2016;138(3 Suppl):179S-87S.

(7) Lazzarini PA, Crews RT, Van Netten JJ, Bus SA, Fernando ME, Chadwick PJ, et al. Measuring Plantar Tissue Stress in People With Diabetic Peripheral Neuropathy: A Critical Concept in Diabetic Foot Management. Journal of Diabetes Science and Technology. 2019;0(0):1932296819849092.

(8) Fernando ME, Crowther RG, Pappas E, Lazzarini PA, Cunningham M, Sangla KS, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. Plos One. 2014;9(6):e99050.

(9) Lazzarini PA, Pacella RE, Armstrong DG, Van Netten JJ. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabetic Medicine. 2018;35:1297-9.

(10) Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: A systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. Clinical Biomechanics (Bristol, Avon). 2013;28(8):831-45.

(11) Lazzarini PA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Effectiveness of offloading interventions for people with diabetes-related foot ulcers: a systematic review and meta-analysis. Diab Metab Res Rev. 2023;e3650.

(12) Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. The Lancet Diabetes & Endocrinology. 2016;4(9):781-8.

(13) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease. Diab Metab Res Rev. 2023;e3657.

(14) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023;in press.

(15) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev 2023;in press.

(16) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3644.

(17) Zhang Y, Cramb S, McPhail SM, Pacella R, van Netten JJ, Cheng Q, et al. Factors Associated With Healing of Diabetes-Related Foot Ulcers: Observations From a Large Prospective Real-World Cohort. Diabetes Care. 2021;44(7):e143-e5.

(18) Zhang Y, Cramb S, McPhail SM, Pacella R, van Netten JJ, Cheng Q, et al. Multiple factors predict longer and shorter time-to-ulcer-free in people with diabetes-related foot ulcers: Survival analyses of a large prospective cohort followed-up for 24-months. Diabetes Res Clin Pract. 2022;185:109239.

(19) Bus SA, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3274.

(20) Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care. 2008;31(11):2118-9.

(21) Raspovic A, Landorf KB. A survey of offloading practices for diabetes-related plantar neuropathic foot ulcers. J Foot Ankle Res. 2014;7:35.

(22) Quinton T, Lazzarini P, Boyle F, Russell A, Armstrong D. How do Australian podiatrists manage patients with diabetes? The Australian diabetic foot management survey. Journal of Foot and Ankle Research. 2015;8(1):16.

(23) Asko Andersen J, Rasmussen A, Engberg S, Bencke J, Frimodt-Moller M, Kirketerp-Moller K, et al. Flexor Tendon Tenotomy Treatment of the Diabetic Foot: A Multicenter Randomized Controlled Trial. Diabetes Care. 2022;45(11):2492-500.

(24) Potier L, Francois M, Dardari D, Feron M, Belhatem N, Nobecourt-Dupuy E, et al. Comparison of a new versus standard removable offloading device in patients with neuropathic diabetic foot ulcers: a French national, multicentre, open-label randomized, controlled trial. BMJ Open Diabetes Res Care. 2020;8(1).

(25) Sahu B, Prusty A, Tudu B. Total contact casting versus traditional dressing in diabetic foot ulcers. J Orthop Surg (Hong Kong). 2018;26(3):2309499018802486.

(26) Berhane T, Jeyaraman K, Hamilton M, Falhammar H. Pressure relieving interventions for the management of diabetes-related foot ulcers: a study from the Northern Territory of Australia. ANZ J Surg. 2022;92(4):723-9.

(27) Hochlenert D, Fischer C. Ventral Windowed Total Contact Casts Safely Offload Diabetic Feet and Allow Access to the Foot. Journal of diabetes science and technology. 2022;16(1):137-43.

(28) Elbarbary AH, Sallam EM, Ismail AM. Metatarsal Head Resection Versus a Removable Mechanical Device for Offloading of the Neuropathic Diabetic Plantar Forefoot Ulcer. The international journal of lower extremity wounds. 2022;21(4):535-43.

(29) Fejfarova V, Pavlu J, Bem R, Woskova V, Dubsky M, Nemcova A, et al. The Superiority of Removable Contact Splints in the Healing of Diabetic Foot during Postoperative Care. J Diabetes Res. 2019;2019:5945839.

(30) Bus SA, Sacco ICN, Monteiro-Soares M, Raspovic A, Paton J, Rasmussen A, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3651.

(31) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;in press.

(32) Wukich DK, Schaper NC, Gooday C, Bal A, Bem R, Chabra A, et al. Guidelines on the diagnosis and treatment of charcot neuro-osteoarthropathy in persons with diabetes (IWGDF 2023). Diab Metab Res Rev. 2023;in press.

(33) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. Bmj. 2016;353:i2089.

(34) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(35) Bus SA, Game F, Monteiro-Soares M, Van Netten JJ, Apelqvist J, Fitridge R, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;e3656.

(36) Van Netten JJ, Bus SA, Apelqvist J, Chen P, Chuter VH, Fitridge R, et al. Definitions and criteria for diabetes-related foot disease (2023 update). Diab Metab Res Rev. 2023;e3654.

(37) Jarl G, van Netten JJ, Lazzarini PA, Crews RT, Najafi B, Mueller MJ. Should weight-bearing activity be reduced during healing of plantar diabetic foot ulcers, even when using appropriate offloading devices? Diabetes Res Clin Pract. 2021;175:108733.

(38) Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabetic Medicine: A Journal Of The British Diabetic Association. 2008;25(6):700-7.

(39) Raspovic A, Landorf K. A survey of offloading practices for diabetes-related plantar neuropathic foot ulcers. Journal of Foot and Ankle Research. 2014;7(1):35.

(40) Health Quality Ontario. Fibreglass Total Contact Casting, Removable Cast Walkers, and Irremovable Cast Walkers to Treat Diabetic Neuropathic Foot Ulcers: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17(12):1-124.

(41) Piaggesi A, Macchiarini S, Rizzo L, Palumbo F, Tedeschi A, Nobili LA, et al. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers - A randomized prospective trial versus traditional fiberglass cast. Diabetes Care. 2007;30(3):586-90.

(42) Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005;28(3):555-9.

(43) Wang Y, Zhou J, Yan F, Li G, Duan X, Pan H, et al. Comparison of Arthrodesis with Total Contact Casting for Midfoot Ulcerations Associated with Charcot Neuroarthropathy. Med Sci Monit. 2015;21:2141-8.

(44) Bonanno DR, Gillies EJ. Flexor Tenotomy Improves Healing and Prevention of Diabetes-Related Toe Ulcers: A Systematic Review. J Foot Ankle Surg. 2017;56(3):600-4.

(45) Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007;50(1):18-25.

(46) Jeffcoate W, Game F, Turtle-Savage V, Musgrove A, Price P, Tan W, et al. Evaluation of the effectiveness and cost-effectiveness of lightweight fibreglass heel casts in the management of ulcers of the heel in diabetes: a randomised controlled trial. Health Technol Assess. 2017;21(34):1-92.

(47) Mens MA, van Netten JJ, Busch-Westbroek TE, Bus SA, Streekstra GJ, Wellenberg RHH, et al. Biomechanical and musculoskeletal changes after flexor tenotomy to reduce the risk of diabetic neuropathic toe ulcer recurrence. Diabet Med. 2022;39(4):e14761.

(48) Keukenkamp R, Merkx MJ, Busch-Westbroek TE, Bus SA. An Explorative Study on the Efficacy and Feasibility of the Use of Motivational Interviewing to Improve Footwear Adherence in Persons with Diabetes at High Risk for Foot Ulceration. J Am Podiatr Med Assoc. 2018;108(2):90-9.

(49) Binning J, Woodburn J, Bus SA, Barn R. Motivational interviewing to improve adherence behaviours for the prevention of diabetic foot ulceration. Diabetes Metab Res Rev. 2019;35(2):e3105.

(50) Kaczmarek T, Kavanagh D, Lazzarini PA, Warnock J, Van Netten JJ. Training diabetes healthcare practitioners in motivational interviewing: a systematic review. Health Psychology Review. 2021:1-27.

(51) van Netten JJ, Seng L, Lazzarini PA, Warnock J, Ploderer B. Reasons for (non-)adherence to self-care in people with a diabetic foot ulcer. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2019;27(5):530-9.

(52) Ploderer B, Clark D, Brown R, Harman J, Lazzarini PA, Van Netten JJ. Self-Monitoring Diabetes-Related Foot Ulcers with the MyFootCare App: A Mixed Methods Study. 2023;23(5):2547.

(53) Lazzarini PA, Jarl G. Knee-High Devices Are Gold in Closing the Foot Ulcer Gap: A Review of Offloading Treatments to Heal Diabetic Foot Ulcers. Medicina. 2021;57(9):941.

(54) Jarl G, Rusaw DF, Terrill AJ, Barnett CT, Woodruff MA, Lazzarini PA. Personalized Offloading Treatments for Healing Plantar Diabetic Foot Ulcers. J Diabetes Sci Technol. 2023;17(1):99-106.

(55) Ababneh A, Finlayson K, Edwards H, Lazzarini PA. Factors associated with adherence to using removable cast walker treatment among patients with diabetes-related foot ulcers. BMJ Open Diabetes Research & Care. 2022;10(1):e002640.

(56) Ababneh A, Finlayson K, Edwards H, van Netten JJ, Lazzarini PA. Differences in adherence to using removable cast walker treatment during daytime and nighttime weight-bearing activities in people with diabetes-related foot ulcers. Therapeutic Advances in Endocrinology and Metabolism. 2023;14:20420188221142457.

(57) Zhang Y, Carter HE, Lazzarini PA, Cramb S, Pacella R, van Netten JJ, et al. Cost-effectiveness of guideline-based care provision for patients with diabetes-related foot ulcers: A modelled analysis using discrete event simulation. Diabetic Medicine. 2023;40(1):e14961.

(58) Berhane T, Jeyaraman K, Hamilton M, Falhammar H. Pressure relieving interventions for the management of diabetes-related foot ulcers: a study from the Northern Territory of Australia. ANZ journal of surgery. 2022;92:723-9.

(59) Elbarbary AH, Sallam EM, Ismail AM. Metatarsal Head Resection Versus a Removable Mechanical Device for Offloading of the Neuropathic Diabetic Plantar Forefoot Ulcer. The international journal of lower extremity wounds. 2020:1534734620971106.

(60) Sahu B, Prusty A, Tudu B. Total contact casting versus traditional dressing in diabetic foot ulcers. Journal of Orthopaedic Surgery. 2018;26(3).

(61) Yelland AC, Meace C, Knighton P, Holman N, Wild SH, Michalowski J, et al. Impact of case-mix adjustment on observed variation in the healing of diabetic foot ulcers at 12 weeks using data from the National Diabetes Foot Care Audit of England and Wales: A cohort study. Diabet Med. 2023;40(1):e14959.

(62) National Library of Medicine. MedlinePlus Bethesda (MD): National Library of Medicine (US); 2023 [Available from: *www.medlineplus.gov*.

(63) Merriam-Webster. Dictionary by Merriam-Webster Springfield, MA, USA: Merriam-Webster, Incorporated; 2023 [Available from: *www.merriam-webster.com*

Guidelines on interventions to enhance healing of foot ulcers in people with diabetes

IWGDF 2023 update

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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ABSTRACT

Principles of wound management, including debridement, wound bed preparation and newer technologies involving alternation of wound physiology to facilitate healing, are of utmost importance when attempting to heal a chronic diabetes-related foot ulcer. However, the rising incidence and costs of diabetes-related foot ulcer management necessitates that interventions to enhance wound healing of chronic diabetes-related foot ulcers are supported by high quality evidence of efficacy and cost effectiveness, when used in conjunction with established aspects of gold-standard multidisciplinary care. This is the 2023 International Working Group on the Diabetic Foot (IWGDF) evidence-based guideline on wound healing interventions to promote healing of foot ulcers in persons with diabetes. It serves as an update of the 2019 IWGDF guideline.

We followed the GRADE approach by devising clinical questions and important outcomes in the PICO (Patient-Intervention-Control-Outcome) format, undertaking a systematic review, developing summary of judgements tables and writing recommendations and rationale for each question. Each recommendation is based on the evidence found in the systematic review and, using the GRADE summary of judgement items including desirable and undesirable effects, certainty of evidence, patient values, resources required, cost effectiveness, equity, feasibility and acceptability, we formulated recommendations which were agreed by the authors and reviewed by independent experts and stakeholders.

From the results of the systematic review and evidence-to-decision making process we were able to make 29 separate recommendations. We made a number of conditional supportive recommendations for the use of interventions to improve healing of foot ulcers in people with diabetes. These include the use of sucrose octasulfate dressings, the use of negative pressure wound therapies for post-operative wounds, the use of placental derived products, the use of the autologous leucocyte/platelet/fibrin patch, the use of topical oxygen therapy, and the use of hyperbaric oxygen, although in all cases it was stressed that these should be used where best standard of care was not able to heal the wound alone and where resources were available for the interventions.

These wound healing recommendations should support improved outcomes for people with diabetes and ulcers of the foot, and we hope that widescale implementation will follow. However, although the certainty of much of the evidence on which to base the recommendations is improving, it remains poor overall and we encourage, not more, but better quality trials including those with a health economic analysis, into this area.

LIST OF RECOMMENDATIONS

All recommendations should be considered to be adjunctive to best standard of care when best standard of care alone has failed to heal the ulcers. This should include sharp debridement and basic wound dressings, which according to the IWGDF Practical Guidelines, should be dressings to absorb exudate and maintain a moist wound healing environment (1).

1. Do not use autolytic, biosurgical, hydrosurgical, chemical or laser debridement over standard of care. (GRADE Strength of recommendation: Strong; Certainty of evidence: Low)
2. Do not routinely use enzymatic debridement as opposed to standard of care (i.e. sharp debridement) to improve wound healing outcomes in people with diabetes and a foot ulcer. (Strong; Low)

2a. In specific situations where the availability of sharp debridement may be limited by access to resources and/ or availability of skilled personnel, consider using enzymatic debridement. (Conditional; Low)

3. Do not use any form of ultrasonic debridement over standard of care (i.e. sharp debridement). (Strong; Low)
4. Do not use surgical debridement in those for whom sharp debridement can be performed outside a sterile environment. (Strong; Low)
5. We recommend the frequency of sharp debridement should be determined by the clinician based on clinical need. (Strong; Low)
6. Do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes-related foot ulcers. (Strong; Moderate)
7. Do not use honey (or bee related products) for the purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
8. Do not use collagen or alginate dressings for the purpose of wound healing of diabetes-related foot ulcers. (Strong; Low)
9. Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to the best standard of care, in non-infected, neuro-ischaemic diabetes-related foot ulcers which have had insufficient change in ulcer area with best standard of care including appropriate offloading for at least 2 weeks. (Conditional; Moderate)
10. Do not use topical phenytoin for the purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
11. Do not use any dressing based or topical applications impregnated with herbal remedies for the sole purpose of wound healing in diabetes-related foot ulcers. (Strong; Low)
12. Consider the use of hyperbaric oxygen as an adjunct therapy in neuro-ischemic or ischemic diabetes-related foot ulcers where standard of care alone has failed and where resources already exist to support this intervention. (Conditional; Low)
13. Consider the use of topical oxygen as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention. (Conditional; Low)

14. Do not use other gases (e.g. cold atmospheric plasma, ozone, nitric oxide, CO2) in comparison to standard of care for wound healing in people with diabetes-related foot ulcers. (Strong; Low)
15. Do not use any interventions reported in the field of physical therapies for wound healing in the management of diabetes-related foot ulcers. (Strong; Low)
16. We suggest not using cellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)
17. We suggest not using acellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)
18. Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in patients with diabetes-related foot ulcers. (Strong; Low)
19. With the exception of the autologous leucocyte, platelet and fibrin patch we suggest not using autologous platelets therapy (including blood bank derived platelets) as an adjunct therapy to standard of care. (Conditional; Low)
20. Consider the use of autologous leucocyte, platelet and fibrin patch for diabetes-related foot ulcers as an adjunctive therapy to standard of care, where best standard of care alone has been ineffective, and where the resources and expertise exist for the regular venepuncture required. (Conditional; Moderate)
21. We suggest not using other cell therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)
22. We suggest not using growth factor therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)
23. Consider the use of placental derived products as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed. (Conditional; Low)
24. Do not use pharmacological agents promoting perfusion and angiogenesis to improve wound healing outcomes over standard of care. (Strong; Low)
25. Do not use pharmacological agents that supplement vitamins and trace elements to improve wound healing outcomes over standard of care. (Strong; Low)
26. Do not use pharmacological agents that stimulate red cell production or protein supplementation to improve wound healing outcomes over standard of care. (Strong; Low)
27. Do not use other pharmacological agents to improve wound healing outcomes over standard of care. (Strong; Low)
28. Consider the use of Negative Pressure Wound Therapy as an adjunct therapy to standard of care for the healing of postsurgical diabetes-related foot wounds. (Conditional; Low)

28a. Do not use Negative Pressure Wound Therapy as an adjunct therapy to standard of care for the healing of non-surgically related diabetes foot ulcers. (Strong; Low)

29. We do not recommend any specific educational and lifestyle support programmes over standard of care to improve healing of diabetes-related foot ulcers. (Strong; Low)

INTRODUCTION

Diabetes-related foot ulcer management remains challenging and costly, posing high financial burdens on healthcare economies and having impacts on morbidity, mortality and quality of life. Principles of wound management, including debridement, wound bed preparation and newer technologies involving alternation of wound physiology to facilitate healing, are thus of utmost importance when attempting to heal a chronic diabetes-related foot ulcer. However, the rising incidence and costs of diabetes-related foot ulcer management necessitates that interventions promoted to enhance wound healing of chronic diabetes-related foot ulcers are adequately supported by high quality evidence promoting efficacy and cost-effectiveness, when used in conjunction with established aspects of gold-standard multidisciplinary care (2-4).

Since 2008, the International Working Group of the Diabetic Foot (IWGDF) have commissioned evidence-based guidelines, updated every four years, with a chapter focusing on interventions to enhance wound healing. Up until 2019, each systematic review and guideline represented an update of previous search results. However, updated standards (5) for assessment of diabetes-related foot ulcer healing therapies have resulted in better quality studies in recent years. To enable consistent benchmarking across newer and older studies alike, the aim of developing this edition of the guidelines and systematic review was thus to undertake a complete search and re-evaluation of the literature, describing trials of interventions intended to improve wound healing of foot ulcers in people with diabetes (6, 7).

WHAT'S NEW

We have made several changes to the recommendations included in this updated 2023 wound healing interventions guideline compared to the previous 2019 wound healing interventions guideline. The main changes are as follows:

- Instead of a 4-yearly update we performed a new systematic review of wound healing interventions and re-evaluated previous interventions in line with newest benchmarking and risk of bias assessments according to GRADE methodology (7)
- We only evaluated RCTs to ensure only evidence at the highest level was included
- We increased the number of outcomes critical to decision making in wound healing, including sustained healing, resource utilisation, quality of life, maintenance of function and ability to perform activities of daily living, new infection and mortality
- We added new clinical questions on behavioural, educational and pharmacological interventions
- We changed categorisation of dressings, autologous products and skin substitutes
- We have 29 new recommendations with six interventions receiving conditional positive recommendations

METHODS

In this guideline we have followed the key steps of the GRADE evidence-to-decision framework, including: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes in the PICO-format (Patient-Intervention-Comparison-Outcome), iii) performing systematic reviews and rigorous appraisals of all available evidence that address the questions, iv) assessing key summary of judgements items for each question, v) developing recommendations and their rationale based on these summary of judgements, and vi) consulting external stakeholders on each step (8, 9). The methodology for this guideline is summarised below; we refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document (10).

First, a multidisciplinary working group of independent international experts in wound healing for diabetes-related foot ulcers (the authors of this guideline) was invited by the IWGDF Editorial Board to develop and author this guideline. International experts were defined as those having significant experience in practising or studying the healing of diabetes-related foot ulcers. The working group comprised members from, podiatric surgery, podiatry, and endocrinology disciplines from the USA, Caribbean, Europe, Asia and Australia.

Second, the working group devised important clinical questions and associated outcomes, building on the last version of the guideline, to be answered using the GRADE approach. The questions and outcomes were reviewed and prioritised with the help of fifteen external clinical experts and two persons with lived diabetes-related foot ulcer experience from various geographical regions, and the IWGDF Editorial Board. The aim was to ensure the questions and outcomes were of relevance to a wide range of healthcare professionals and people with the disease so as to provide the most useful clinical information on wound healing interventions to treat foot ulcers in people with diabetes. The working group classified the outcomes as critically important or important, aligning with international diabetes-related foot ulcer standards (5, 11) or the expert opinion of the working group if standards did not exist.

Interventions (topical and systemic therapeutic agents) included were those previously addressed in the previous guidelines (6) where it was known that trials had been performed to address our clinical questions. In addition the working group agreed interventions not previously looked at, including educational and behavioural interventions designed to aid wound healing were important additions. We did not include offloading interventions, or systemic interventions designed to treat infection or interventions that were designed to improve limb perfusion unless they were pharmacological in nature and reported wound healing, as these interventions were included in other working group guidelines (12-14).

Third, we systematically reviewed the literature and appraised all studies addressing the above agreed upon clinical questions. Unlike previous versions of the guidelines, in view of the huge increase in the volume of literature and the need to assess only the evidence of the highest quality in formulating guidelines, we included only randomised controlled trials (RCTs) in our systematic review. We

considered as a comparator best standard of care, defined as those described in the practical guidelines (1), that is, local debridement, offloading, revascularisation, treatment of infection where appropriate.

For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and any evidence of publication bias (where appropriate) (15). We then rated the quality of evidence as 'high', 'moderate' or 'low' according to GRADE methodology (8). Finally, we developed summary of findings tables, including evidence statements, for each assessable outcome for each question which we presented in full in the systematic review. The systematic review supporting this guideline is published separately (7)

Fourth, based on the systematic review, summary of findings tables and expert opinion, teams of two members of the working group developed summary of judgements tables for each question following GRADE (see Supporting Information S1). The summary of judgement items assessed included desirable and undesirable effects, balance of effects, certainty of evidence, values, resource use, cost-effectiveness, equity, acceptability and feasibility. Definitions for these items can be found in the Summary of Judgements table in the Supporting Information S1. For the resources required, the group considered potential financial and/or human resources directly linked to the implementation of the intervention in clinical practice and any specific expertise required. Where such information was missing, the group made a pragmatic decision based on their clinical expertise. The group defined equity in this context as the ability of all people with a diabetes-related foot ulcer (i.e. on a societal level) to have equitable access to the procedures required for the intervention application.

Acceptability to stakeholders was based on expert opinion and consideration of the balance of effects and any resources required by the users themselves. Feasibility was determined based on the groups' experience and the ease of use of the interventions

After careful weighing of the summary of judgements, the team proposed to the working group a direction, strength, certainty of evidence and wording of recommendation(s) and rationale to address the question concerned. Certainty of evidence was rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Rationale for each recommendation was also provided and based on the summary of judgements tables (see Supporting Information S1) (8, 9).

Fifth, summary of judgements tables and recommendations for each question were extensively discussed in online meetings with the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention, and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members were needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the supplementary material.

Finally, all recommendations, with the rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same clinical experts and persons with lived experience who reviewed the clinical questions, as well as by members of the IWGDF Editorial Board. The working

group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guideline manuscript.

To aid consideration of the literature the interventions were grouped into nine broad categories of i) debridement ii) dressings and topical applications iii) oxygen and other gases iv) therapies involving physical alteration of wound bed properties v) skin substitutes vi) autologous and other cellular products including growth factors and placental-derived products vii) pharmacological interventions viii) negative pressure and ix) educational and psychological interventions. Ten outcomes were identified as critical to decision making in wound healing, which were a) Complete wound healing; b) Time to healing; c) Sustained healing; d) Reduction in ulcer area; e) Amputation (major or minor); f) Quality of life; g) Maintenance of function and ability to perform activities of daily living; h) New infection; i) Resource utilisation; and j) death/mortality.

RECOMMENDATIONS

Overall, nine clinical questions, each with up to 10 outcomes critical to decision making were addressed by this guideline. This has led to the formulation of 29 separate recommendations. The accompanying systematic review (7) has been published and we developed 27 summary of judgement tables (available as online-only Supporting Information S1).

We considered the interventions to be adjunctive to best standard of care when best standard of care alone has failed to heal the ulcers. This should include basic wound dressings, which according to the IWGDF Practical Guidelines should be dressings to absorb exudate and maintain a moist wound healing environment (1). Additionally, these should be of the lowest acquisition cost for the local health care economy.

INTERVENTION: DEBRIDEMENT

Clinical question 1: In people with diabetes-related foot ulcers, is enzymatic debridement, autolytic debridement, biosurgical debridement, ultrasonic debridement, hydrosurgical abrasion or chemical debridement more effective for achieving wound healing compared to best standard of care (including sharp debridement)?

Debridement involves the removal of dead and devitalised tissue (necrosis and slough) from wounds in order to create a clean wound bed and is designed to promote wound healing. There are several different types of debridement including physical (e.g. surgical, sharp, hydro-debridement, or gaseous debridement), biological (larvae), autolytic (hydrogels) or biochemical (enzymes). Although there is unequivocal consensus amongst experts in support of the need for regular wound debridement to facilitate healing, high quality evidence to justify debridement in general, and to identify the best form of debridement is limited. For types of debridement, we found ten RCTs that met our prespecified inclusion criteria as described in our systematic review (16-25). There were five RCTs (16-20) of enzymatic debridement, 3 RCTs (21-23) of low frequency ultrasonic debridement, 1 RCT (24) of surgical debridement and 1 RCT (26) on frequency of sharp debridement. However we found no RCTs of other types of debridement.

Recommendation 1: Do not use autolytic, biosurgical, hydrosurgical, chemical or laser debridement over standard of care. (GRADE Strength of recommendation: Strong; Certainty of evidence: Low)

Rationale: No publications of RCTs were found on the use of autolytic, biosurgical, hydrosurgical, chemical or laser debridement that met our prespecified inclusion criteria, or had sufficient cost effectiveness data to warrant their use. Thus we were unable to make a recommendation supporting their use.

ENZYMATIC DEBRIDEMENT

Recommendation 2: Do not routinely use enzymatic debridement as opposed to standard of care (i.e. sharp debridement) to improve wound healing outcomes in people with diabetes and a foot ulcer. (Strong; Low)

Recommendation 2a: In specific situations where the availability of sharp debridement may be limited by access to resources and/ or availability of skilled personnel, consider using enzymatic debridement. (Conditional; Low).

Rationale: We found five RCTs on clostridial collagenase ointment (16-20) all of which were compared to standard of care (i.e. sharp debridement). All were exploratory RCTs that were designed to generate hypotheses and were not designed to provide a statistically significant outcome. All had significant methodological limitations, were mainly unblinded and at high risk of bias. Outcomes were assessed at different time points, between 4 to 6 weeks, with limited long-term follow up and different definitions of healing making comparisons between studies difficult.

Overall, the evidence behind the use of enzymatic debridement is limited and the certainty of evidence is low. This reflects the methodological limitations of the studies and the resultant high risk of bias. Overall, the balance of effects did not favour either enzymatic debridement or sharp debridement in terms of complete wound healing, or wound area reduction. One specific type of enzymatic debridement, topical clostridium collagenase, would probably have higher resource implications but there was low certainty of evidence of the required resources, and no formal cost effectiveness data were found. Due to the additional resources required to provide topical clostridium collagenase, we considered that equity may be reduced, particularly in low and middle income regions. However we also recognise that in some lower income regions access to standard of care (i.e. sharp debridement) may be limited as this requires skilled personnel, training programmes and sterile instruments. Hence, in health care systems where such skills are not available, alternative methods with enzymatic debriding agents could be considered.

ULTRASONIC DEBRIDEMENT

Recommendation 3: Do not use any form of ultrasonic debridement over standard of care (i.e. sharp debridement). (Strong; Low)

Rationale: We found three RCTs (21-23) of low frequency ultrasonic debridement compared to standard of care (i.e. sharp debridement). All three studies were at high risk of bias with none being blinded. Only one (21) suggested any differences between groups in time to healing, but this result should be treated with caution given the high risk of bias of the study. None showed any differences in absolute healing in the timescales of the follow-up of the studies. The other two studies (22, 23) presented either no difference between the two groups or did not present any between group analyses.

One of the three identified RCTs showed small desirable effects in regards to wound healing outcomes. Thus, ultrasonic debridement may be associated with decreased time to wound healing versus standard

of care, albeit with low certainty evidence, thus these findings should be interpreted with caution. No differences in complete wound healing or sustained healing were reported between groups. Thus, overall, the balance of effects does not favour either the intervention or control. The intervention, ultrasonic debridement, has a higher resource implication although with low certainty of evidence of the required resources and no formal cost effectiveness data found. From the limited data available it is uncertain as to whether the higher costs incurred could be offset by the small desirable effects in terms of decreased time to healing in the intervention group; although it seems unlikely, given the low certainty of the evidence of the beneficial effect. Due to the additional resources required to provide ultrasonic debridement, equity is probably reduced, particularly in lower income regions; however, the intervention is probably acceptable to patients and its use in a health care system was thought to be feasible. Due to all the above reasons, but mostly the low certainty of evidence of benefit and an absence of cost effectiveness data, we do not recommend the use of ultrasonic debridement over standard of care, that is, sharp debridement.

SURGICAL DEBRIDEMENT

Recommendation 4: Do not use surgical debridement in those for whom sharp debridement can be performed outside a sterile environment. (Strong; Low)

Rationale: We found one RCT (24) of surgical debridement compared to standard of care (i.e. sharp debridement), which reported two of our critical outcomes, time to healing and sustained healing but was assessed as being at high risk of bias; and any positive benefits reported should be treated with caution.

Overall, we considered that the balance of effects did not favour either the intervention or control. The intervention, surgical debridement, has a higher resource implication with large costs albeit with low certainty of the evidence of the required resources, and no formal cost effectiveness data were found. From the limited data available it is uncertain as to whether the higher costs incurred could be offset by the small desirable effects in terms of greater sustained healing in the intervention group although this seems unlikely. Due to the additional resources required to provide surgical debridement equity was felt to be reduced, particularly in low income regions, however the intervention is probably acceptable to patients and feasible. For all the above reasons but particularly the low certainty of evidence of benefit, we do not recommend the routine use of surgical debridement in those for whom sharp debridement can be performed outside of a sterile environment. However, in the absence of high-quality evidence the opinion of the expert group was that a) people with diabetes-related foot ulcers that can be managed appropriately with sharp debridement in an outpatient setting should not be taken to theatre for unnecessary surgical debridement as this approach is more expensive, resource intensive and might actually delay debridement if it could be undertaken at the chairside. b) People with diabetes-related foot ulcers with limb or life threatening features (e.g extensive necrosis, collections, or gas forming infections) must always be referred urgently for a surgical opinion to assess the need for surgical intervention to avoid the risk of further deterioration and worse outcomes (see Recommendation 18 of the 2023 Infection Guidelines) (14). The type of debridement modality, that is, sharp versus surgical

should be made by an experienced clinician based upon clinical severity and the presence or absence of any limb-threatening features.

FREQUENCY OF SHARP DEBRIDEMENT

Recommendation 5: We recommend the frequency of sharp debridement should be determined by the clinician based on clinical need. (Strong; Low)

Rationale: We found one RCT (25) at high risk of bias that investigated frequency of sharp debridement, weekly versus fortnightly. This one study, involving 61 participants per group, reported no statistically significant difference in wound healing outcomes, wound closure or healing times at 12 weeks between groups. The certainty of the evidence is low, as this is based on one unblinded study at high risk of bias Overall, we felt that the balance of effects does not favour either the weekly or fortnightly sharp debridement. No formal cost effectiveness data were found. From the limited data, it is uncertain as to whether there would be a difference in costs based on frequency of sharp debridement given all participants were attending clinics weekly. Sharp debridement, regardless of frequency is acceptable to patients and feasible. Due to limited evidence we do not recommend a specific frequency of debridement. The frequency should thus be determined by the clinician based on clinical need.

INTERVENTION: DRESSINGS

Clinical question 2: In people with diabetes-related foot ulcers, are dressings or applications with surface antimicrobial properties, honey or those that influence chronic wound biology more effective for achieving wound healing compared to basic contact dressings and best standard of care?

We identified 50 published RCTs related to our interventions and reporting our outcomes of choice which informed these guidelines. All but four studies reviewed were considered at high or moderate risk of bias. The duration of treatment and follow-up period varied widely between the studies reviewed (24 hours to 34 weeks) and many studies provided limited description of the ulcer and patient characteristics, but typically recruited superficial ulcers or non-infected ulcers. Additionally, most studies recruited individuals without peripheral artery disease (PAD) or with mild PAD (in most studies, but not all, defined as Ankle Brachial Index (ABI) 0.7 to 0.9, Transcutaneous Oxygen pressure ($TcPO_2$) 30 - 50mmHg). Therefore, the certainty of evidence and assessment of balance of effect in favour of the intervention in addition to generalizability to the typical diabetes-related foot ulcers seen in clinical practice was hard to determine. Furthermore, we also noted a significant lack of clear descriptions of standard of care provision including the type and quality of offloading provided, type and impact of any additional supportive interventions undertaken, such as revascularization.

Given this is a large group of interventions, we have broken down the key recommendations into smaller sections, based on the groups of types of products and applications currently available.

TOPICAL ANTIMICROBIAL OR ANTISEPTIC DRESSINGS

Recommendation 6: Do not use topical antiseptic or antimicrobial dressings for wound healing of diabetes-related foot ulcers (Strong; Moderate)

Rationale: We found 12 studies (27-38) evaluating anti-septic or antimicrobial dressings or topical antiseptic applications. Five evaluated the use of silver impregnated dressings in comparison with usual care (27-30, 37) but all were considered at high or moderate risk of bias. Four of these showed no significant improvement in terms of complete healing (27-30), or percentage area wound reduction.

We found three studies investigating the use of iodine impregnated dressings (31-33). Apart from one (32), all were at high risk of bias. This, the only study with blinding regarding the evaluation of outcomes, showed no difference in the incidence of outcomes of importance when compared with usual care. Thus, any positive benefits reported by the other studies should be treated with caution.

One study on Diperoxochloric Acid (34) was found which evaluated the impact of this intervention in hospitalised patients. Although with double blinding, usual care was not well defined and the clinical significance of the apparent positive results are not clear.

We identified two studies of topical gentamicin (35, 36) which fulfilled our inclusion criteria, although both were considered at high risk of bias, and only one reported apparent superiority of the intervention on wound healing after minor amputations. Thus, any apparent benefit on wound healing is of low certainty.

We identified only one non-blind study on a superoxidised solution (38). Although no differences were reported in complete wound healing a shorter time to heal and lower rates of reinfection were reported at 6 months in the intervention arm. The study was however at high risk of bias and thus we have low confidence in this result.

The evidence to support positive impact on wound healing of surface antiseptics or antimicrobials is thus inconsistent, and where present, the effect size was small with low certainty of evidence. There was significant heterogeneity in the type and size of diabetes-related foot ulcers recruited and the standard of care provided, making comparison between studies using the same type of dressing/application difficult. Thus the balance of effects was felt not to be in favour of the intervention. Although costs were thought to be moderate/low and equity, feasibility and acceptability were not thought to be affected, given the low certainty of evidence of benefit, we do not recommend the use of any of these products for the sole purpose of promoting wound healing of diabetes foot ulcers.

HONEY OR BEE PRODUCTS

Recommendation 7: Do not use honey (or bee related products) for the purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: We found six RCTs (28, 39-43) of interventions containing topical bee or honey products which reported some of our outcomes of importance. All were deemed at high risk of bias and any positive results on wound healing should be treated with caution. The only blinded study of a royal jelly found no difference in healing over 12 weeks (40). No studies reporting data on amputation, cost effectiveness or quality of life were found.

Overall, therefore, the certainty of any positive benefit of the topical use of honey or bee related products is very low. Although adverse effects were rarely reported, the groups' experience was that any undesirable effects are likely to be trivial. However, the balance of effects could not be ascertained as either favouring the intervention or the comparison. Resource use was thought to be similar to standard of care but no formal cost-effectiveness data was found. Although thought to be feasible, and acceptable to patients and with equity unaffected it was felt that in the absence of certainty of benefit we cannot recommend the use of any of these products for promoting wound healing in diabetes-related foot ulcers.

COLLAGEN OR ALGINATE

Recommendation 8: Do not use collagen or alginate dressings for the purpose of wound healing of diabetes-related foot ulcers (Strong; Low)

Rationale: We found twelve RCTs (29, 44-54) of collagen or alginate (or both) as an intervention to enhance wound healing and which fulfilled our inclusion criteria. All were at moderate or high risk of bias and most were non-blinded. Four studies compared collagen only with moist wound therapy (45, 47, 48, 52), one study (46) used collagen-alginate, one used a calcium alginate. (51), one compared a collagen/oxidised regenerated cellulose/silver treatment with foam (29), one the same collagen/oxidised regenerated cellulose but without silver (54), one compared collagen with negative pressure wound therapy(50), one compared collagen with gauze or hydrocolloid dressings (49) and another two (51, 53) alginate alone as the intervention. Of the twelve studies, nine of them (29, 45-47, 49, 51-54) did not report a difference in wound healing or reduction in ulcer area at the end of study duration. Thus any reported positive outcomes should be treated with caution.

The group agreed that in view of the known low incidence of undesirable effects, it is possible that the balance of effects favours the intervention, although the certainty of this was very low. The cost of these interventions was thought to be moderate, although no formal cost effectiveness studies were found and so the certainty of this was low. Equity, acceptability and feasibility were agreed to be unlikely to be affected. Nevertheless given the uncertainty of benefit and possible cost implications, we do not recommend the use of any of these products for promoting wound healing in diabetes-related foot ulcers.

SUCROSE OCTASULFATE

Recommendation 9: Consider the use of the sucrose-octasulfate impregnated dressing as an adjunctive treatment, in addition to the best standard of care, in non-infected, neuro-ischaemic diabetes-related foot ulcers which have had insufficient change in ulcer area with best standard of care including appropriate offloading for at least 2 weeks (Conditional; Moderate).

Rationale: We found one large double blind multinational RCT (55) assessed to be at low risk of bias investigating the use of sucrose-octasulfate impregnated dressings in non-infected neuro-ischaemic foot ulcers which were deemed hard to heal at the end of a 2 weeks run-in period. There was a significant improvement in complete wound healing at week 20, a significantly faster estimated time to heal and increased percentage area reduction compared to the placebo dressing; and we considered this evidence to be of high certainty. We therefore concluded that, in neuro-ischaemic foot ulcers where there has been insufficient change in ulcer area with best standard of care including appropriate offloading, there is sufficient evidence to consider the use the sucrose-octasulfate impregnated dressing. We found few data on harms and concluded that the balance of risks and benefits were in favour of the intervention. Resource use was considered to be low/moderate and we are aware that there is cost-effectiveness data from modelling studies now available for various Western health-care systems which are supportive (56-59). Equity was not thought to be reduced with this intervention and it was felt to be feasible and acceptable to patients in all health care settings. However, the optimal timing of initiating treatment remains to be established. Furthermore, it is recognised that this is the only study of this intervention, and so despite the quality of the data in this one study, the evidence was considered to be moderate and the strength of the recommendation limited to conditional.

TOPICAL PHENYTOIN

Recommendation 10: Do not use topical phenytoin for the purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: Despite there being 12 RCTs (60-71) investigating the use of topical phenytoin for wound healing of diabetes-related foot ulcers, with some benefit of its use on time to healing and reduction in ulcer area, the evidence to support any benefit was of low certainty, as all were at moderate to high risk of bias and most were unblinded. Although the intervention is not likely to be expensive, and equity and feasibility is unlikely to be unaffected, the certainty of the evidence is such that we cannot recommend this intervention.

TOPICAL HERBAL OR TRADITIONAL MEDICINAL PREPARATIONS

Recommendation 11: Do not use any dressing based or topical applications impregnated with herbal remedies for the sole purpose of wound healing in diabetes-related foot ulcers (Strong; Low)

Rationale: We found nine RCTs which reported on the use of topical herbal or traditional medicinal preparations which fulfilled our inclusion criteria (72-80). Of seven studies reporting on complete wound healing (72-77, 79), all were at moderate or high risk of bias, and any positive effects on wound healing should be interpreted cautiously. Further, reduction in ulcer area was reported in six studies (72, 74, 75, 77, 79, 80) of which only two (72, 77) found an apparent improvement in comparison to the control. Again, these were at high risk of bias. No differences in amputation rates (74) or mortality (78) were reported. No studies reported on quality of life, new infection, resource utilisation or maintenance of function.

Overall, we found nine studies assessing the impact of traditional or herbal based remedies, although all were rated at high risk of bias. Despite some of the studies reporting positive effects on wound healing including reduction in ulcer area, the low confidence in the results and the fact that no two studies evaluated the same product, meant the balance of effects could not be ascertained as either favouring the intervention or the comparison. Furthermore, there was significant heterogeneity in the ulcer type and patients recruited, adherence to standard of care was unclear in many studies, and no cost-effectiveness data was found. Therefore, on balance, given the poor quality of evidence, presently we do not recommend the use of any of these products for the sole purpose of promoting wound healing in difficult to heal diabetes-related foot ulcers.

INTERVENTION: OXYGEN AND OTHER GASES

Clinical question 3: In people with diabetes-related foot ulcers, is hyperbaric oxygen, topical oxygen or the use of other gases compared to standard of care more effective for achieving wound healing?

Oxygen is a critical element in key processes of wound healing including angiogenesis, collagen deposition, and epithelialisation. Hyperbaric oxygen therapy involves breathing 100% oxygen at a pressurised atmosphere of 2ATA or above (i.e twice the atmospheric pressure exerted at sea level), which increases the partial pressure of oxygen in hypoxic or ischemic tissues. This has been proposed as a key mechanism for improving wound healing in diabetes-related foot ulcers with ischaemia or hypoxia. Previous guidelines (6) have conditionally recommended the use of hyperbaric oxygen therapy as an adjunctive treatment on the basis of several RCTs. For this guideline, we included 18 RCTs on hyperbaric oxygen (81-98) with no new studies published in the last four years.

Topical oxygen is a relatively new(er) therapy, and this involves the administration of oxygen topically over tissue by continuous diffusion or pressurised systems using mechanical devices (99). Whilst there was insufficient evidence to recommend its use for healing diabetes-related foot ulcers in 2019 (6), the evidence on topical oxygen has substantially expanded in the last four years with several new RCTs (100-103) with a total of ten included in the systematic review for these guidelines (100-109).

We found additionally one study on nitric oxide (110), three on ozone therapy (111-113), two on cold atmospheric plasma (114, 115) and one on carbon dioxide (116). With all of these studies being either at high risk of bias and/or with lack of demonstrable effect, these were grouped together as "other gases".

Recommendation 12: Consider the use of hyperbaric oxygen as an adjunct therapy in neuro-ischemic or ischemic diabetes-related foot ulcers where standard of care alone has failed and where resources already exist to support this intervention. (Conditional; Low)

Rationale: Of the 18 studies on the evaluation of the use of hyperbaric oxygen as an adjunct therapy to improve diabetes-related foot ulcer healing, only three were double-blinded RCTs (87, 89, 91). One of these showed no difference in the critical outcome of wound healing (87) with both the others showing improved wound healing (89, 91). Overall, the evidence is conflicting, but the studies with lowest risk of bias suggest that there may be some benefit for its use in improving absolute wound healing and reduction in ulcer area. Good evidence of benefit in preventing amputation is, however, lacking. Different time points (ranging between 30 days and 12 months), degree of ischaemia and definitions of healing make comparisons between studies difficult.

Overall, the evidence at low risk of bias behind the use of hyperbaric oxygen therapy was limited. The majority of studies were at high risk of bias although there was one good quality study showing evidence of benefit on the critical outcomes of healing and time to healing. Overall the certainty of evidence was low and although there were moderate desirable effects with benefit in improving absolute wound healing and reduction in ulcer area, evidence of amputation reduction was not found. People with diabetes require assessment for suitability for hyperbaric oxygen therapy; and those with general frailty and comorbid conditions may have to be excluded from this treatment modality due to increased risks of adverse events. Amongst those assessed as suitable, however, reported undesirable effects were small. Overall, the group felt the balance of effects will likely favour the use of hyperbaric oxygen over standard of care alone. However, hyperbaric oxygen therapy requires large costs and although several poor quality in-trial studies have demonstrated cost savings with its use, these fail to account for costs of construction of hyperbaric oxygen units. Nonetheless, where there are already established hyperbaric oxygen units used for treating other medical conditions, there may be cost effectiveness justifying the use of this intervention if desirable effects of improved wound healing are achieved. Although time consuming, hyperbaric oxygen was thought to be acceptable to most patients and clinicians. Overall, because hyperbaric oxygen is only limited to individuals assessed as being suitable, who live in close proximity to established hyperbaric units, and are able to commit to weeks of intense treatment, we acknowledge that this conditional recommendation is likely to reduce equity.

Our ratings are consistent with findings from previous guidelines; and with no new good quality evidence published in the last four years, we continue to conditionally recommend the use of hyperbaric oxygen as an adjunct therapy where standard of care alone has failed although we recognise that the groups most likely to benefit still requires evaluation.

TOPICAL OXYGEN

Recommendation 13: Consider the use of topical oxygen as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention. (Conditional; Low)

Rationale: We found three double-blinded RCTs (100, 104, 105) and seven non-blinded studies(101-103, 106-109) for the use of topical oxygen. Of the double-blinded studies, one was terminated early and had uneven baseline characteristics between control and intervention group (100). Two double-blinded trials were at low risk of bias, but only one had statistically significant results for complete wound healing in favour of topical oxygen at 12 weeks (104) with the other showing no difference between topical oxygen and standard of care (105). There was no benefit of topical oxygen on amputation, probably due to short duration of follow-up in most trials. We found no data on resource use, and few data on adverse events.

The evidence behind the use of topical oxygen in diabetes-related foot ulcers was of low certainty, with overall desirable effects rated as moderate with benefit on achieving absolute wound healing and reduction in ulcer area, but no evidence for reduction in amputation up to 12 weeks. Undesirable effects were poorly reported in the studies available to us, but assumed to be trivial based on expert opinion. Overall, the group felt that the balance of effects would favour the use of topical oxygen, but the certainty of evidence is rated as low across the different devices delivering topical oxygen, and at present it is difficult to say which devices, if any, are superior. There was also a lack of cost effectiveness or published data on resource use, but expert opinion agreed upon moderate costs, with therapy requiring multiple units of single-use topical oxygen delivery devices. Unlike hyperbaric oxygen, topical oxygen therapy can be administered in patients' homes, and is likely to be feasible and acceptable to patients and clinicians alike but due to the moderate costs for mainly single-use devices, it was felt that equity may be reduced. Overall, despite the balance of effects being in favour of the intervention, a conditional recommendation only for topical oxygen was made because of the costs involved and their effect on equity.

OTHER GASES

Recommendation 14: Do not use other gases (e.g. cold atmospheric plasma, ozone, nitric oxide, CO2) in comparison to standard of care for wound healing in people with diabetes-related foot ulcers. (Strong; Low)

Rationale: The evidence to support the use of other gases such as nitric oxide, ozone, carbon dioxide and cold atmospheric plasma is poor, with no studies assessed to be at low risk of bias (110-116) . Overall, the desirable and undesirable effects were both rated to be trivial, although the latter was an assumption with lack of data on adverse events reported in trials. Due to high risk of bias, the certainty of evidence is rated as very low, and the balance of effects was felt unlikely to favour the use of other gases over standard of care. Expert opinion rated the costs of therapy as moderate, again with lack of cost effectiveness data from trials. Thus, the use of other gases is probably not as cost-effective when compared to standard of care. Due to limited availability and information about use, storage and administration of these gases, these therapies are unlikely to be acceptable or feasible for wide use. Thus, we cannot recommend the use of these interventions to support wound healing of diabetes-related foot ulcers.

INTERVENTION: PHYSICAL ALTERATION OF WOUND BED

Clinical question 4: In people with diabetes-related foot ulceration, is the use of interventions which physically alter the wound bed compared to standard of care more effective for wound healing?

We found a number of studies relating to the use of "physical wound bed alteration therapies" including; heat application, therapeutic ultrasound, compression, electrical or electromagnetic stimulation (ES/EM), light and laser treatment, Extracorporeal Shock Wave Therapy (ESWT), ischaemic preconditioning, therapeutic magnetic resonance and connective tissue manipulation.

As there were few studies on each of these interventions individually, and those that we did identify were either at high risk or moderate risk of bias and/or showed no benefit, we have taken this group all together in making a recommendation.

Recommendation 15: Do not use any interventions reported in the field of physical therapies for wound healing in the management of diabetes-related foot ulcers. (Strong; Low)

Rationale: The evidence to support the use of heat application for diabetes-related foot ulcer management is weak, depending on only three small, non-blinded RCTs (117-119) all at high risk of bias and in one of which (117) the incidence of healing in the comparator group seemed to be much lower than expected for the type of ulcers included. We found just two studies of therapeutic ultrasound (120, 121), only one of which was methodologically sound(120), although healing rates were again lower than expected in the control arm.

Three studies (122-124) evaluated compression on some of our outcomes of importance. All three were at moderate or high risk of bias.

We identified six studies investigating the use electrical or electromagnetic stimulation on some of our outcomes of importance (125-130).

Eight studies were found on the use of light and laser therapy (131-138). Only three of these (131-133) reported complete healing or time to healing, the remainder reporting only area reduction. Results were conflicting, possibly contributed by the heterogeneity of treatment protocols

We identified four studies of extra corporeal shock wave therapy (139-142). Of our outcomes of importance only complete healing (139-141), time to healing (139, 141) and percentage area reduction of the ulcer (142) were reported.

The evidence available from the single study (143) of ischaemic preconditioning identified does not support its use of due to its high risk of bias.

We identified only one study identified of therapeutic magnetic resonance (144), which was at moderate risk of bias, and did not show any differences in outcome between the two groups.

We found only one study of connective tissue manipulation (145), reporting only percentage area reduction, and no benefit was shown in the use of the intervention.

The analysis of the studies dealing with different physical therapies proposed for diabetes-related foot ulcer management provided limited evidence to suggest that these therapies might be beneficial in improving outcomes in diabetes-related foot ulcers. While a small number of studies were at low risk of bias, none of these indicated any effect. Overall, the desirable effects of physical therapies on wound healing were considered small, and in most cases no significant differences emerged when compared to standard of care. As the studies focussed on a number of interventions and as the results were not strong, it was decided to consider them as part of the whole group of "physical therapies", rather than analysing them separately. It was also noted that undesirable effects were rarely reported, and no severe adverse events were described. It was considered, therefore, that the balance of effects would not favour either the intervention or usual care, but that this was based on low certainty evidence. In addition, it was considered that most, if not all, of the treatments might be associated with appreciable extra costs and resources. Although formal cost-effectiveness studies were not found, it was felt that cost-effectiveness would be unlikely given the small size of effects noted. It was also noted that some treatments might have reduced acceptability and equity for patients, and hence feasibility. For these reasons, we do not currently recommend the use of any of the physical therapies described either as first-line or as adjuvant therapies for diabetes-related foot ulcer management.

INTERVENTION: SKIN SUBSTITUTES

Clinical question 5: In people with diabetes-related foot ulcers, are skin substitutes more effective for wound healing compared to best standard of care?

Skin substitutes are a grouping of wound care products that include cellular, acellular, and autologous skin graft subgroups. These products are applied to non-healing wounds to supply structural and/or biological support to the site via this externally derived product. They are generally secured with suture, adhesive strips, and/or a secondary dressing. This heterogenous group of products are generally used to artificially deliver wound healing stimulation and seek to mimic the composition and function of human skin.

We found 28 RCTs across the wider category of skin substitutes. This body of research has greatly expanded over the last decade and now contains a significant number of enrolled people with diabetes-related foot ulcers, but presents a very complex review challenge given the non-uniformity of products, significant drop out rates, inconsistent blinding, and analysis that was often per protocol and not intention to treat. A helpful way to categorize and compare skin substitutes is to divide them into groups based on cellular (those products that contain cells) and acellular (those products that do not contain cells). An example of a cellular skin substitute would be a product containing human cells such as fibroblasts or keratinocytes. Some examples of acellular skin substitutes would be products such as human acellular dermal matrix and bovine collagen dermal matrix where the cells have been removed and the support structure or matrix is left in place. For the systematic review (7), we found 10 RCTs (146-155) on celular products, 13 RCTs (150, 156-167) on acellular products, and 5 RCTs (168-172) on autologous skin graft products.

CELLULAR SKIN SUBSTITUTES

Recommendation 16: We suggest not using cellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

Rationale: Although evidence from 10 RCTs (146-155) suggest that Cellular Skin Substitutes may improve the healing and reduce the time to healing in patients with diabetes-related foot ulcers when provided in addition to standard of care, all studies were at high risk of bias due to non-blinding, had high dropout rates and per-protocol analyses. Moreover, there is insufficient evidence to establish which particular cellular skin substitutes may be more effective. There is, additionally, limited evidence to indicate that cellular skin substitutes are associated with a reduction in amputation rates. Minimal undesirable effects were reported with its use, and whilst the overall balance of effects are likely to favour the intervention, cellular skin substitutes are likely to require moderate costs/resources. Despite the certainty of evidence of resources being low with lack of formal cost effectiveness data, the moderate resources required meant that the group decided that cost effectiveness would not favours cellular skin substitutes over standard of care. This raises concerns for equity, and whilst likely acceptable for general use, feasibility is low due to the expertise and costs required in using these products.

ACELLULAR SKIN SUBSTITUTES

Recommendation 17: We suggest not using acellular skin substitute products as a routine adjunct therapy to standard of care for wound healing in patients with diabetes-related foot ulcers. (Conditional; Low)

Rationale: Based on the review of the 13 RCTs (150, 156-167) found on acellular skin substitutes we concluded that these interventions may improve the incidence of healing and reduce the time to healing in patients with diabetes-related foot ulcers, when provided in addition to standard of care. However, all of the studies were considered at high risk of bias with the majority having no blinding as part of the protocol and only three (158, 160, 166) being blinded for outcome assessment. Thus any positive effects should be considered with caution. In addition, evidence to establish which, if any, particular acellular skin substitutes are superior is lacking, and there was insufficient evidence on cost effectiveness of this modality. There is limited evidence to indicate that acellular skin substitutes are associated with a reduction in amputation rates, with only two studies, and conflicting results reporting on this outcome (156, 159). Moreover, the lack of negative studies may suggest a degree of publication bias, and most studies were industry-sponsored. Thus, while there is some evidence that the balance of effects probably favours the intervention, the certainty of the evidence is low. Limited resource utilisation data were found, indicating moderate costs in a single heath care setting, but it was agreed that these products do come with a significant cost and that this raises concern for equity and availability, although limited data is available on cost effectiveness. The groups agreed that the products would be acceptable for general use, but feasibility is probably low due to expertise and costs required.

AUTOLOGOUS SKIN GRAFT SKIN SUBSTITUTES

Recommendation 18: Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in patients with diabetes-related foot ulcers. (Strong; Low)

Rationale: We identified just five RCTs (168-172) with publication dates ranging from 2003 to 2021. All were at high risk of bias and thus the positive outcomes of two of them should be treated with caution. There is insufficient evidence to establish their effectiveness or cost utility. Overall, we considered the balance of effects is not likely to favour autologous skin substitutes over standard of care. Although backed by limited evidence, the resources required come at moderate costs and thus cost effectiveness does not favour autologous skin substitutes over standard of care. Concerns are raised for equity and availability along with the additional challenge of autologous harvest from the patient. Whilst acceptable for general use, feasibility is probably low due to expertise and costs required.

INTERVENTION: AUTOLOGOUS PRODUCTS

Clinical question 6: In people with diabetes-related foot ulcers, is the use of autologous and other cellular products including growth factors and placental-derived products more effective for wound healing compared to standard of care?

One possible treatment option for nonhealing ulcers is the use of interventions which either promote the release of cytokines and growth factors involved in tissue repair, angiogenesis, and inflammation or directly donate these factors to the ulcer bed.

Thus the use of autologous cells including autologous platelets, cells which are fundamental to the co-ordination of normal wound healing has been investigated in a few trials. Most cells including adipocytes derived stem cells, and fibroblasts require relatively invasive methods to extract the relevant cells from donor sites. Although only requiring venepuncture, the difficulty of the volume of blood required to produce sufficient platelets has hampered their wider use, although the use of the leucocyte fibrin and platelet patch has largely overcome this.

Individual growth factors applied directly to the wound including platelet derived growth factors (although this is only one of the many types of cytokines released by platelets) have also been trialled, although researchers have noted that individual growth factors alone may not be sufficient to ensure the whole wound healing cascade of cytokines is enhanced.

Human placental membranes contain a combination of growth factors, collagen-rich extracellular matrix, and cells, including mesenchymal stem cells, neonatal fibroblasts, and epithelial cells, that provide mechanisms for coordinated wound healing. Several products derived from different components of the placenta and umbilical cord have been developed. Cryopreserved preparations contain living cells and growth factors, whereas dehydrated products, which are easier to store and handle, contain growth factors but no living cells.

We divided this group of interventions into autologous cells, human/recombinant growth factors, and human placental-derived products.

Of the autologous cells, there were a number of studies utilising platelets in various formulations, but with the exception of the autologous leucocyte, fibrin and platelet patch, the evidence to support the use of any other formulation of platelets or other autologous cells as detailed in our systematic review (7) was limited. For this reason we have considered this intervention separately but grouped platelets together as the evidence to support any particular formulation of this intervention was less certain.

Similarly we have considered other autologous cells, growth factors and placental derived products as separate groups of interventions.

AUTOLOGOUS PLATELETS – WITH EXCEPTION OF THE AUTOLOGOUS LEUCOCYTE AND PLATELET PATCH

Recommendation 19: With the exception of the autologous leucocyte, platelet and fibrin patch we suggest not using autologous platelets therapy (including blood bank derived platelets) as an adjunct therapy to standard of care. (Conditional; Low)

Rationale: We included 15 RCTs (173-187) on the use of platelet products for the management of diabetes-related foot ulcers. The majority of studies investigated the use of platelet gel, with the inherent problem of requiring moderate amounts of autologous venous blood to generate the product.

Of the studies looking at complete wound healing all were at risk of bias with only one of a platelet gel being outcome blinded (174), however the positive outcome in this study was of low certainty with per protocol analysis only. The problem of autologous blood volumes was overcome in one study using a blood bank of platelets (179) but the apparent superior outcome of healing was marred by non-blinded outcomes' assessment and was considered at high risk of bias. A number of these studies also assessed percentage wound area reduction as well as absolute wound healing, but all were at high risk of bias or did not report a difference between groups. Only one study reported an apparent benefit in terms of amputation but the evidence was of low certainty (176). The only study reporting resource use (182) was limited by including hospitalised patients only.

The different timescales to the outcomes chosen made comparison of different interventions difficult to establish.

Although there were 15 included RCTs, the studies were at high risk of bias overall, with only one being

outcome blinded and one with patient- but not outcome-blind. Those at the lowest risk of bias demonstrated the lowest improvement in healing outcomes casting doubt on the size of the effect seen in the majority of the studies. On this basis we evaluated the size of the potential positive effect as small although the certainty of this was very low. Few studies published adverse effects but expert opinion suggested that undesirable effects would be small. Overall it was felt that it would be difficult to be certain that in clinical practice a positive effect on healing would be seen consistently above what would

be expected with good standard of care. The costs of these interventions was thought to be moderately high, although no formal cost effectiveness analyses were found. Thus, it was felt that the use of these interventions would decrease equity given the costs involved, and the need for venous samples to be taken for the autologous platelet gel products, and hence feasibility would be reduced in some lower income countries. Where resources existed in health care systems their use might, however be feasible and acceptable to patients.

Overall weighing up the lack of certainty around the effectiveness of these interventions, the resource use and possible lack of feasibility in most health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

LEUCOCYTE, FIBRIN AND PLATELET PATCH

Recommendation 20: Consider the use of autologous leucocyte, platelet and fibrin patch for diabetes-related foot ulcers as an adjunctive therapy to standard of care, where best standard of care alone has been ineffective, and where the resources and expertise exist for the regular venepuncture required. (Conditional; Moderate)

Rationale: One high quality multicentre outcome blinded RCT (188) at low risk of bias was identified which showed significant improvements in healing, time to healing and wound area reduction at 20 and 26 weeks after weekly treatment with the intervention in patients with hard to heal ulcers, when used in addition to best standard of care. Participants in the intervention arm had weekly visits for venesection to produce the patch. No differences were seen in the outcomes of new infection, major or minor amputations or mortality. Although 18-36 mL of venous blood was required weekly to create the patch at the bedside, no increase in the incidence of new anaemia was found and there were no other additional reported undesirable effects. For these reasons it was felt that there was a favourable balance of effects in favour of the intervention but the findings of a single study suggested that the certainty of this was moderate at best. We found no formal published cost effectiveness data even though it was recognised that the weekly venepuncture would incur costs and that in some health care systems the expertise for this may not be readily available. If confirmed, these could have a negative impact on equity and feasibility in some health care systems. However, where such a resource exists, it was felt that the use of this intervention would be acceptable to patients. Hence we concluded that the use of autologous leucocytes, platelets, and fibrin patches could be conditionally recommended for hard to heal ulcers in addition to best standard of care where the best standard of care including offloading (where appropriate) had not healed the ulcer. Nevertheless, we recognise that this may not be feasible where expertise and resources for regular venepuncture are not available.

OTHER CELL THERAPIES

This group of interventions included other cell therapies for the promotion of healing of diabetes-related foot ulcers including adipocytes (189-193), fibroblasts (194), keratinocytes(195, 196), bone marrow derived stem cells (197), allogeneic bone marrow mesenchymal stromal cells (allohBM MSC)

and cultured allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) (198).

Recommendation 21: We suggest not using other cell therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)

Rationale: In total, 10 studies were identified. These included studies investigating autologous adipocytes (189-193), fibroblasts (194), keratinocytes (195, 196), bone marrow derived stem cells (197), allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) and allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) (198)

Of the adipocyte or adipocyte stem cell studies which reported complete healing only two were outcome-blinded. There was heterogeneity of outcomes with some studies showing no improvement in healing, and those reporting positive benefit being at high risk of bias. Similarly the single studies of autologous fibroblast or keratinocytes were assessed at being high risk of bias, neither being blinded. The single study of the use of periwound autologous bone marrow stem cells in patients with critical limb ischaemia was outcome blind but there was a high loss to follow-up with a per-protocol analysis only presented. A second study of allogeneic bone marrow mesenchymal stromal cells (allohBM MSC) and allogeneic bone marrow mesenchymal stromal cells derivatives (cultured allohBM MSCs) was at high risk of bias and consequently no clear conclusions could be drawn.

Only one study at moderate risk of bias (197) reported major amputation at 12 weeks noting no difference between the groups. Only one described resource utilisation (192) but this was, however, not a full health economic analysis and the trial was considered at high risk of bias.

Overall, the evidence to support improved wound healing, wound area reduction or time to healing for the use of cultured keratinocytes, fibroblasts, adipocytes, either as fat grafting or following lipo-aspirates and bone marrow derived cells is currently poor, with most studies being at moderate to high risk of bias.

The available evidence as described suggested moderate beneficial effects on healing although the confidence in this was low. Few studies published adverse effects or serious adverse effects but expert opinion suggested that undesirable effects could be present. The one study which published quality of life suggested that there was little improvement. Overall it was felt that the balance of effects may favour the intervention but this was based on limited studies with high risk of bias. The resource use involved in these interventions was thought to be high as they required access to cell culture and the ability to harvest the cells from patients. Thus, this would decrease equity and feasibility, particularly in health care systems in low income countries.

Overall, weighing up the lack of certainty around the effectiveness of these interventions and the costs and possible lack of feasibility in some health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

GROWTH FACTORS

Within this category we included: Platelet derived growth factor (PDGF), granulocyte stimulating factor (GCSF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and studies of combined growth factors.

Recommendation 22: We suggest not using growth factor therapy as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers. (Conditional; Low)

Rationale: We identified seven studies (199-205) investigating the use of PDGF. Only two of the studies were double blind (200) only one of which was considered to be at low risk of bias and this, like one of the other large studies (202), showed no difference in healing between the two groups. An earlier large trial did show a difference in healing and time to healing (204) but was at moderate risk of bias thus reducing confidence in the result. The other studies reporting a positive outcome for those treated with the intervention, were considered at high risk of bias, thus any positive results should be treated with caution.

None of the studies reported on the outcomes of sustained healing, amputation, resource utilisation, maintenance of function or mortality and, therefore, the evidence to support the use of PDGF was poor with the majority of studies being assessed as being at high risk of bias.

Three studies were identified investigating the use of GCSF (206-208). None of the studies showed benefit in terms of wound healing, amputation or any other of our outcomes of importance, however the studies identified were mainly aimed at the treatment of infection.

We identified four studies investigating the use of EGF (209-212) which reported wound healing of diabetes-related foot ulcers at 6 and 12 weeks. With the exception of one study (210), which investigated topical EGFR spray, all were at high risk of bias. The single low risk of bias study reported improved healing at 12 weeks, although the effect size was only moderate.

Two studies investigating FGF (213, 214) also reported healing in double blinded RCTs. The small size of one study and the high risk of bias in the other mean that the positive results reported should be treated with caution

A single study (215) investigated a combination of growth factors (EGF, & FGF) but was judged to be at high risk of bias. It also showed no difference in time to healing between the four groups.

No studies of any GFs reporting on the outcomes of sustained healing, amputation, quality of life, new infection, resource utilisation or mortality.

Few studies of any of the growth factors published adverse effects but expert opinion suggested that these would be small. Overall it was felt that the balance of effects was therefore not in favour of the intervention for PDGF or GCSF and possibly in favour for EGF although this was based on very low certainty evidence. Resource use was thought to be moderate for all growth factors although formal cost effectiveness data was not found. Thus, although feasible, equity would likely to be reduced especially in lower income countries where resource use may be limited.

On balance, it was felt that the lack of certainty of effectiveness of these interventions and the costs and possible lack of feasibility in some health care systems we felt we could not recommend these interventions as an adjunctive therapy to good standard of care.

PLACENTAL DERIVED PRODUCTS

Recommendation 23: Consider the use of placental derived products as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed. (Conditional; Low)

Rationale: We identified ten studies of placental derived products (153, 203, 216-223). Of these, one described the use of dehydrated amnion/chorion graft (221), seven used dehydrated human amniotic membrane (dHAM) (153, 203, 216, 218, 219, 222, 223), one the use of cryopreserved placental membrane (217), one the use of dehydrated human umbilical cord (220)

All of the studies described absolute wound healing at times points between 4 and 20 weeks, however only three studies were assessed at being at low risk of bias (219, 220, 223), and only one (223), a small pilot/feasibility study was double blinded. All suggested improved healing and time to healing. Reports of percentage area reduction in five studies (203, 216, 217, 221, 223) suggested improvements in favour of the intervention, although two of these studies were at high risk of bias and so the positive results should be treated with caution. New infection was reported to be similar in one study (219), although no studies reported any effect on amputation.

Two papers reported the cost of the intervention per healed ulcer (219, 220). In neither case was there any assessment of the cost of the control interventions; however the mean cost per healed ulcer was over $2000 for the dHAM, and over $3000 for the dehydrated umbilical cord product. Cost effectiveness data was only published in one post hoc analysis of a study otherwise judged at high risk of bias (224).

There were no studies reporting quality of life or maintenance of function.

Although most of the studies were considered at high risk of bias, and none of the definitive studies were patient or care giver blind, those at low risk of bias suggest that the use of placental derived products (and particularly of amniotic membrane) are associated with improved absolute healing at times up to 20 week, and reduced time to healing. We found no evidence to suggest that there was an influence on new infections, and the short term nature of the majority of studies and the lack of inclusion of patients with significant PAD means that we have no evidence of improvement in incidence of amputation. No formal cost effectiveness data were found but the resource use data suggest the interventions may be less expensive for some providers compared to other skin substitutes.

Overall the group felt that the balance of effects was in favour of the intervention although the certainty of the evidence was low. Although formal cost effectiveness data was not available and resource use was noted to be lower than skin substitutes in one study, it was recognised that there would be moderate costs involved in their use. Thus it was felt that equity may be reduced in some health care

systems particularly those of lower countries. However, where resources existed it was felt that, apart from cryopreserved products which would need storage and defrosting time, acceptability and feasibility would not be reduced in most settings.

INTERVENTION: PHARMACOLOGICAL INTERVENTIONS

Clinical question 7: In people with diabetes-related foot ulcers, is the use of pharmacological interventions more effective for wound healing compared to best standard of care?

This intervention is the systemic administration of naturally occurring or pharmacological agents prescribed to the person with diabetes-related foot ulcers in an attempt to improve wound healing outcomes. These agents may consist of 'over-the-counter' (e.g., vitamins and minerals), or physician only prescribed agents, including traditional Chinese herbal medicines. We included 18 full papers describing randomised trials of pharmacological interventions promoting wound healing.

AGENTS PROMOTING PERFUSION AND ANGIOGENESIS

Recommendation 24: Do not use pharmacological agents promoting perfusion and angiogenesis to improve wound healing outcomes over standard of care. (Strong; Low).

Rationale: We found nine studies (225-233) of agents promoting perfusion and angiogenesis. The studies comparing the use of pentoxyfilline (225), resveratrol (226), low-dose erythropoietin (EPO) (227), subcutaneous injection dalteparin (228), insulin plus sulodexide to insulin plus placebo (229), a two-herb traditional chinese medicine formula (232) and an intravenous native herbal extract, angipars (230) contained too few patients to be certain of the results, and only the latter performed an intention-to-treat analysis. As such, any apparent improvement in healing should be treated with caution. One study (231) investigating injections of a DNA derivative, polydeoxyribonucleotide, although double blinded was considered to be at moderate risk of bias. A second study of polydeoxyribonucleotide was too small to show any difference between the two groups (233). Overall, the evidence suggests that certain pharmacological interventions that promote perfusion and angiogenesis may improve wound healing but the quality of evidence is low and findings should be interpreted with caution.

Of the studies identified, none provided cost effectiveness data.

Overall, the studies showed only small beneficial effects on wound healing, with trivial undesirable effects even though the level of certainty was very low. Overall, therefore, it was felt that the balance of effects suggested little difference between intervention or control. It is also likely that the intervention has a resource implication of moderate costs but with a lack of published data there was low certainty of the required resources. Due to the additional resources required to provide agents promoting perfusion and angiogenesis, equity is probably reduced, particularly in lower income regions, even though the intervention is probably acceptable to patients and would be feasible. Due to limited evidence, we cannot recommend agents promoting perfusion and angiogenesis over standard of care.

AGENTS THAT SUPPLEMENT VITAMINS AND TRACE ELEMENTS

Recommendation 25: Do not use pharmacological agents that supplement vitamins and trace elements to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified four studies using systemic supplementation of vitamins and trace elements (234-237), all at moderate or high risk of bias. The interventions investigated were daily doses of Vitamins E and C (with platelet-rich plasma-fibrin glue) (237), oral weekly doses Vitamin D (234), a daily probiotic (235), and oral omega-3 fatty acids (236). Although the latter two studies were double blinded the outcome measure of absolute reductions in ulcer length and width, and the lack of detail of baseline ulcer characteristics and offloading means that the positive results reported should be treated with caution. We found no studies of these interventions reporting on outcomes of complete wound healing, time to healing, sustained healing, amputation, quality of life, maintenance of function and ability to perform activities of daily living, new infection, resource utilization and mortality. The available evidence suggests that certain pharmacological interventions, that is, probiotic or omega-3 fatty acids supplementation, may promote reduction in ulcer area with no overall difference in complete healing; however, the quality of evidence is low and findings should be interpreted with caution.

The studies were at moderate or high risk of bias with no cost effectiveness data. The studies showed small desirable effects in regards to wound healing outcomes with trivial undesirable effects, but this was considered to be of low certainty of evidence. Overall, therefore the balance of effects was thought to favour neither the intervention nor control. It is likely that the intervention has a resource implication of moderate costs however the certainty of this was as no formal evaluation was found. From the limited data it is uncertain as to whether the costs incurred would be offset by the small desirable effects. Due to the additional resources required to provide the vitamin and trace element supplementation equity is probably reduced, particularly in lower income regions, however the intervention is probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend agents that supplement vitamins and trace elements over standard of care.

AGENTS THAT STIMULATE RED CELL PRODUCTION OR PROTEIN SUPPLEMENTATION

Recommendation 26: Do not use pharmacological agents that stimulate red cell production or protein supplementation to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified one study of an agent that stimulates red cell production or protein supplementation that matched our prespecified inclusion criteria (238). This study was considered at moderate risk of bias. There were no differences in wound healing outcomes when the whole group was considered, although there were small desirable effects on wound healing limited to those with a low albumin, with trivial undesirable effects. Overall, the balance of effects was felt to favour neither the intervention nor the control. It is likely that the intervention has a resource implication of moderate costs with low certainty of evidence of the required resources. From the limited data it is uncertain as to whether the costs incurred would be offset by the small desirable effects in those with low albumin.

Due to the additional resources required to provide the protein supplementation equity is probably reduced, however the intervention is probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend agents that stimulate red cell production or protein supplementation over standard of care.

OTHER PHARMACOLOGICAL AGENTS

Recommendation 27: Do not use other pharmacological agents to improve wound healing outcomes over standard of care. (Strong; Low)

Rationale: We identified four studies of other pharmacological agents (239-242), all at moderate or high risk of bias. One study (240), suggested that time to healing was lower with the use of fluconazole in wounds with invasive fungal infections. However, the certainty of these results was considered to be very low. The other study of a Chinese Herb preparation (239) showed no difference in wound healing outcomes when compared to standard of care. One study designed to stimulate the release of bone marrow stem cells, which although at low risk of bias, was not powered to show a difference in healing (242). The final study showed no difference in ulcer area reduction with use of nanocurcumin supplements compared to placebo (241).

Overall, the balance of effects was not thought to favour either the interventions or control. It is likely that the interventions have a resource implication of moderate costs with low certainty of evidence of the required resources. From the limited data it is uncertain as to whether the costs incurred are offset by the small desirable effects. Due to the additional resources required to provide other pharmacological agents equity is probably reduced; however, the interventions are probably acceptable to patients and feasible. Due to limited evidence, we cannot recommend other pharmacological agents over standard of care.

INTERVENTION: NEGATIVE PRESSURE WOUND THERAPY (NPWT)

Clinical question 8: In people with diabetes-related foot ulcers, is the use of negative pressure wound therapy more effective for wound healing when compared to standard of care?

Negative Pressure Wound Therapy (NPWT) involves the controlled application of sub-atmospheric pressure to a wound using a sealed wound dressing connected to a vacuum pump. The sub-atmospheric pressure may be applied continuously or intermittently. The mechanism of action for NPWT has been described to include macro- and micro- deformation of wound tissue, drainage of extracellular inflammatory fluids, and stabilization of the wound environment (243).

Recommendation 28: Consider the use of NPWT as an adjunct therapy to standard of care for the healing of postsurgical diabetes-related foot wounds. (Conditional; Low)

Recommendation 28a: Do not use NPWT as an adjunct therapy to standard of care for the healing of non-surgically related diabetes foot ulcers. (Strong; Low)

Rationale: We identified 19 studies which fulfilled our inclusion criteria (50, 152, 244-260). All studies were thought to be at moderate to high risk of bias.

Of all the studies only three (244, 250, 256) were undertaken in non-surgical wounds, two of which were in a mixed population comprising post-surgical and non-surgical wounds (244, 256). The one study in entirely non-surgical wounds was at high risk of bias, and reported per protocol analyses only, hence the positive benefits reported should be treated with caution (250). The first study in a mixed population (256) although at risk of bias, had blinded outcomes, but reported no difference in healing or time to healing between the two groups. The latter was a nonblinded study at high risk of bias (244). Hence, any evidence to support the use of NPWT in non-surgical wounds is of low certainty.

The remaining studies investigated the use of NPWT in post operative wounds alone. Two studies thought to be of moderate risk of bias reported positive benefit after partial foot amputation (257) and beneficial effects in terms of healing (255), although these outcomes were not assessed blind. Another study at moderate risk of bias reported no difference in healing after soft tissue incision and drainage (258).

Amputation was reported as an outcome in nine studies (244, 246, 247, 249, 254-258). Those at the lowest risk of bias noted no difference in amputation; however the studies were of relatively short duration. Only one study at high risk of bias (244) noted any improvement in quality of life, although this should be treated with caution. New infection was reported in 5 studies with no difference between the groups, although all were at moderate or high risk of bias (244, 245, 255, 257, 258).

Three studies documented resource utilization as an outcome (259, 261, 262). The first two were post hoc analyses of previously reported studies (255, 257) and one only reported resource use (259). All three reported either lower resource use or better cost effectiveness than the comparator although the certainty was thought to be low because of the use of post hoc analyses. We identified no studies which documented death/ mortality as an outcome. NPWT may thus reduce the time to healing in postsurgical wounds when provided in addition to standard of care. For chronic ulcers, there is insufficient evidence to establish whether NPWT reduces time to healing when provided in addition to standard of care.

Thus, overall, the evidence behind the use of NPWT was of low certainty. There were moderate desirable effects that NPWT may reduce the time to healing in postsurgical wounds, but not in chronic wounds, when provided in addition to standard of care. Our conclusions are consistent with the findings from previous guidelines, as no new good quality evidence has been published in the last four years. In regions where NPWT is a widely available and affordable modality, undesirable effects are considered small and it is therefore likely that the use of NPWT will be favoured as an addition to high standard of care. NPWT may require moderate to high costs, and in areas where NPWT is widely available there may be cost effectiveness justifying its use. This is of low certainty though. NPWT was generally considered acceptable to most patients and clinicians. We acknowledge that this recommendation may

reduce equity when considering the limited access to and financial burden of starting NPWT in regions where this modality is not already widely available.

EDUCATION AND LIFESTYLE PROGRAMMES

Clinical question 9: In people with diabetes-related foot ulcers, are education and lifestyle programmes compared to standard of care more effective for wound healing?

Recommendation 29: We do not recommend any specific educational and lifestyle support programmes over standard of care to improve healing of diabetes-related foot ulcers. (Strong; Low)

Rationale: We found one RCT of educational and lifestyle support programmes that met our predefined inclusion criteria but was judged to be at high risk of bias (263). The evidence from this one study showed small desirable effects in regards to reduction in wound area. The certainty of the evidence is therefore low. The educational and lifestyle support programme would have incurred moderate costs but there was very low evidence of the resources required. From the limited data it is uncertain as to whether the costs incurred are offset by the small desirable effects. Due to the additional resources required to deliver the educational and lifestyle programme equity is probably reduced even though the programme is likely acceptable to patients and feasible to deliver. Due to an absence of evidence we cannot recommend any specific educational and lifestyle support programmes over current standards of care, which should include ongoing advice on foot health. Further high quality evidence for the impact of educational and lifestyle programmes are needed.

FURTHER CONSIDERATIONS

This document represents the update of our 2019 recommendations on interventions designed to support healing of foot ulcers in people with diabetes (6). However, we have not simply updated the systematic review done in 2019 but completely re-reviewed the published literature, as our clinical questions and outcomes have changed after consultation with external experts and patients. We have, additionally, considered only randomised controlled trials for inclusion in our current systematic review (7). Thus some interventions previously supported have not been recommended in these guidelines, particularly where more recent studies have not shown the positive results seen in earlier controlled but non-randomised studies. Furthermore we have used the full GRADE approach (8) for the evidence analysis and development of the recommendations, and this has led to a change in the certainty of evidence for several interventions.

The group decided to not undertake any meta-analyses, because for most groups of interventions it was considered that heterogeneity of patients characteristics, follow-up and clinical settings would be high. However where high quality meta-analyses were found we took them into consideration in our discussions.

With this process we have developed 29 recommendations based on our systematic review (7). The systematic review described a number of different interventions which the expert clinical group divided into nine different overarching groups of interventions as described above. Given the change in the number of articles retrieved for some interventions and the lack of any new data from others we have regrouped some of the intervention categories compared to our last guideline. In particular, surgical debridement of the wound has been regrouped with other debridement interventions, skin substitutes and placental derived products were grouped together, albeit with separate recommendations, and we looked for the first time at educational and behavioural interventions which reported any of our outcomes of importance.

It is of note that since the last review, there has been a significant increase in research activity in this field with over 400 articles retrieved describing RCTs of our chosen interventions compared with just 284 controlled (but not necessarily randomised) studies from our previous systematic review (264). However, despite the number of RCTs being published, many are at high risk of bias and for many commonly used wound healing interventions there is a complete lack of RCTs at low risk of bias to guide health care practitioners as to the relevance of their use. In addition, it is still the case that many of the studies included types of ulcers that should heal with good standard of care alone (1) and that good standard of care was either not well described or not well implemented in many cases. It is also the case that in many health care systems people with diabetes and ulcers of the feet are increasingly frail and may have multiple co-morbidities (265), a patient cohort which is frequently excluded from clinical trials, and hence, for whom, even more uncertainty about treatment choices remains.

Due to the limitations in the available evidence we were only able to conditionally recommend the use of six interventions or types of intervention. In some cases we were unable to make a decision on a particular intervention within a groups of interventions, either because comparative data were not available, or because the patient cohorts differed, or because we had little information on resource use for the majority of the interventions. Indeed we were disappointed to see so few studies which looked within trial at the resource use of interventions, and so much of the information was based on post hoc modelling. It was also disappointing that it is still the case that the majority of trials are done outside countries or regions where health care resource is lacking, and as such it was difficult for the group to draw conclusions as to the feasibility and equity for many interventions. Thus, their applicability outside these settings, in particular, where there are limitations of human and financial resource, and where climate, humidity and other environmental issues may impact on ulcer healing remains unknown.

FUTURE RESEARCH AGENDA

Whilst writing this guideline based on our systematic review we were encouraged to see that the numbers of randomised controlled trials had increased since we last reviewed this group of interventions. Nevertheless the quality of the trials remains poor, the majority being at moderate or high risk of bias, with outcomes poorly described, lack of blinding or even any attempt to blind outcome assessors and frequently with sample sizes which were either not pre-defined or which were too small to any lead to confidence in any positive results. We have repeatedly called for researchers and journal editors to be aware of the IWGDF/EWMA standards of reporting of trials of this type (5) and make no apology for repeating this advice here.

Equally many of the studies reported included ulcers which, according to international and national audits should have healed anyway should best standard of care have been instituted early as described in the IWGDF practical guidelines (1). That few studies adequately described best standard of care, including relevant offloading means that we can have little confidence of the ability of some interventions to provide not just effective, but cost effective improvements in outcome.

Information on undesirable effects (such as adverse events, quality of life and costs), equity, acceptability, and feasibility is critical in clinical decision for any intervention. Using the GRADE methodology in these 2023 guidelines (8) we have paid more attention to the these outcomes than previous versions of these guidelines. Few studies however reported these outcomes. As above, we urge future researchers to ensure all outcomes whether positive or negative are reported.

Costs and particularly cost-effectiveness have also received little attention in many studies. Whilst accepting that cost effectiveness in particular varies between health care systems and providers, the fact that costs are rarely reported is disappointing given the cost pressures on health care systems, throughout the world.

Inconsistency in timeframes for measuring critical outcomes also limited ability to perform meaningful comparisons between studies. A significant number of studies reported very short follow-up periods whereas yet others reported outcomes over timeframes as long as 12 months. Consensus on a minimum or recommended timeframe for outcome collection across wound healing or indeed other diabetes-related foot ulcer intervention studies will reduce heterogeneity between studies and may lead to better quality meta-analyses in the future.

Finally we are aware that wound healing is a cascade of physiological processes and that wound healing interventions may not be appropriate in all phases of the wound healing cycle. Thus more innovative approaches to trial design may be needed to ensure that a wound healing protocol is relevant to all stages of the process and that outcomes relevant to this are developed, agreed and objectively measured.

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GUIDELINE WORKING GROUP CONFLICT OF INTEREST POLICY

The IWGDF is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major conflict of interest (COI) members of the guideline were not allowed to serve as an officer, board member, trustee, owner or employee of a company directly or indirectly involved in the topic of this guideline. At each working group meeting members were asked to report on any new conflicts of interest in writing, and any conflicts were declared on a written COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownership of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents etc. These incomes could either be personal or obtained by an institution with which the member had a relationship.

Working group members were additionally requested to declare COI and refrain from the risk of bias scoring process or voting process for particular interventions if they had a professional working relationship with any of the co-authors on a particular paper.

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Full conflict of interest statements of all authors can be found online at *www.iwgdfguidelines.org*.

AUTHOR CONTRIBUTIONS

The working group was chaired by FG (on behalf of the IWGDF). PC acted as scientific secretary. All members of the guideline were involved in summarising available evidence in the supporting systematic reviews which are published separately (7) and in writing this guideline. All members were assigned to individual sections of the guideline, and all authors reviewed and discussed during group meetings the evidence obtained, the evidence to decision making items according to GRADE and each recommendation (further details are available in the Methods section). All authors reviewed and agreed with the final document before external review and subsequent submission for endorsement. The list of authors and their contributions to the guideline is listed at the end of this document. All members of the working group undertook Level 1 GRADE training and both FG and PC additionally undertook Level 2 Guideline Methodology training (McMaster University).

REFERENCES

(1) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease. Diab Metab Res Rev. 2023;e3657.

(2) Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. 2014;37(3):651-8.

(3) Greenidge AR, Quimby KR, Rose AMC, Speede A, Hambleton IR, Anderson SG, et al. Direct healthcare services cost of non-healing diabetic foot wounds in an African origin population in Barbados. Diabetic medicine : a journal of the British Diabetic Association. 2022;39(6):e14773.

(4) Jeffcoate W, Kerr M. The costs of foot disease in diabetes in resource poor countries. Diabetic medicine : a journal of the British Diabetic Association. 2022;39(9):e14900.

(5) Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. The lancet Diabetes & endocrinology. 2016;4(9):781-8.

(6) Rayman G, Vas P, Dhatariya K, Driver V, Hartemann A, Londahl M, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes/metabolism research and reviews. 2020;36 Suppl 1:e3283.

(7) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diab Metab Res Rev. 2023;in press.

(8) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. Bmj. 2016;353:i2089.

(9) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(10) Bus SA, Van Netten JJ, Hinchliffe RJ, Apelqvist J, Lipsky BA, Schaper NC. Standards for the development and methodology of the 2019 International Working Group on the Diabetic Foot guidelines. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3267.

(11) van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, et al. Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3268.

(12) Bus SA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Guidelines on offloading foot ulcers in persons with diabetes – IWGDF 2023 update. Diab Metab Res Rev. 2023;e3647.

(13) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023; in press.

(14) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(15) Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2019;366:l4898.

(16) Jimenez JC, Agnew PS, Mayer P, Clements JR, Caporusso JM, Lange DL, et al. Enzymatic Debridement of Chronic Nonischemic Diabetic Foot Ulcers: Results of a Randomized, Controlled Trial. Wounds-a Compendium of Clinical Research and Practice. 2017;29(5):133-9.

(17) Motley TA, Caporusso JM, Lange DL, Eichelkraut RA, Cargill DI, Dickerson JE. Clinical Outcomes for Diabetic Foot Ulcers Treated with Clostridial Collagenase Ointment or with a Product Containing Silver. Advances in wound care. 2018;7(10):339-48.

(18) Tallis A, Motley TA, Wunderlich RP, Dickerson JE, Waycaster C, Slade HB, et al. Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. Clinical therapeutics. 2013;35(11):1805-20.

(19) Galperin RC, Lange DL, Ramsay SJ, Shi L, Weedon KA, Hudson NM, et al. Anti-inflammatory Effects of Clostridial Collagenase Results from In Vitro and Clinical Studies. Journal of the American Podiatric Medical Association. 2015;105(6):509-19.

(20) Lantis Ii JC, Gordon I. Clostridial Collagenase for the Management of Diabetic Foot Ulcers: Results of Four Randomized Controlled Trials. Wounds : a compendium of clinical research and practice. 2017;29(10):297-305.

(21) Lazaro-Martinez JL, Alvaro-Afonso FJ, Sevillano-Fernandez D, Garcia-alvarez Y, Sanz-Corbalan I, Garcia-Morales E. Cellular proliferation, dermal repair, and microbiological effectiveness of ultrasound-assisted wound debridement (UAW) versus standard wound treatment in complicated diabetic foot ulcers (DFU): An open-label randomized controlled trial. Journal of Clinical Medicine. 2020;9(12):1-13.

(22) Amini S, ShojaeeFard A, Annabestani Z, Hammami MR, Shaiganmehr Z, Larijani B, et al. Low-Frequency Ultrasound Debridement in Patients with Diabetic Foot Ulcers and Osteomyelitis. Wounds-a Compendium of Clinical Research and Practice. 2013;25(7):193-8.

(23) Michailidis L, Bergin SM, Haines TP, Williams CM. Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial. BMC research notes. 2018;11(1):732.

(24) Piaggesi A, Schipani E, Campi F, Romanelli M, Baccetti F, Arvia C, et al. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabetic medicine : a journal of the British Diabetic Association. 1998;15(5):412-7.

(25) Nube VL, White JM, Brewer K, Veldhoen D, Meler C, Frank G, et al. A Randomized Trial Comparing Weekly With Every Second Week Sharp Debridement in People With Diabetes-Related Foot Ulcers Shows Similar Healing Outcomes: potential Benefit to Resource Utilization. Diabetes care. 2021.

(26) Nube VL, Alison JA, Twigg SM. Frequency of sharp wound debridement in the management of diabetes-related foot ulcers: exploring current practice. Journal of foot and ankle research. 2021;14(1):52.

(27) Jude EB, Apelqvist J, Spraul M, Martini J. Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabetic medicine : a journal of the British Diabetic Association. 2007;24(3):280-8.

(28) Tsang KK, Kwong E-Y, To T-S, Chung J-Y, Wong T-S. A Pilot Randomized, Controlled Study of Nanocrystalline Silver, Manuka Honey, and Conventional Dressing in Healing Diabetic Foot Ulcer. Evidence-based complementary and alternative medicine. 2017;2017(no pagination).

(29) Gottrup F, Cullen BM, Karlsmark T, Bischoff-Mikkelsen M, Nisbet L, Gibson MC. Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2013;21(2):216-25.

(30) Belcaro G, Cesarone MR, Errichi BM, Ricci A, Dugall M, Pellegrini L, et al. Venous and diabetic ulcerations: management with topical multivalent silver oxide ointment. Panminerva medica. 2010;52(2 Suppl 1):37-42.

(31) Gwak HC, Han SH, Lee J, Park S, Sung KS, Kim HJ, et al. Efficacy of a povidone-iodine foam dressing (Betafoam) on diabetic foot ulcer. International wound journal. 2020;17(1):91-9.

(32) Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health technology assessment (Winchester, England). 2009;13(54):1-86, iii-iv.

(33) Apelqvist J, Ragnarson Tennvall G. Cavity foot ulcers in diabetic patients: a comparative study of cadexomer iodine ointment and standard treatment. An economic analysis alongside a clinical trial. Acta dermato-venereologica. 1996;76(3):231-5.

(34) Bal A, Jain SK, Jagannath, Mohapatra KC, Rao S, Deshpande N, et al. Efficacy and Safety of Topical Solution of Diperoxochloric Acid for Neuropathic Diabetic Foot Ulcer: Results from a Phase 3, Multicentre, Randomized, Active-controlled, Parallel-group Study. The international journal of lower extremity wounds. 2022:15347346221076625.

(35) Varga M, Sixta B, Bem R, Matia I, Jirkovska A, Adamec M. Application of gentamicin-collagen sponge shortened wound healing time after minor amputations in diabetic patients - A prospective, randomised trial. Archives of Medical Science. 2014;10(2):283-7.

(36) Uckay I, Kressmann B, Di Tommaso S, Portela M, Alwan H, Vuagnat H, et al. A randomized controlled trial of the safety and efficacy of a topical gentamicin-collagen sponge in diabetic patients with a mild foot ulcer infection. SAGE Open Medicine. 2018;6(no pagination).

(37) Yahia EA, El-Sharkawey AE, Bayoumi MM. Quantitative evaluation of diabetic foot wound healing using hydrogel composite nanosilver (agnps) - based dressing vs. traditional dressing: A prospective randomized control study. Pakistan Journal of Medical and Health Sciences. 2021;15(6):2043-7.

(38) Iacopi E, Abbruzzese L, Goretti C, Riitano N, Piaggesi A. The Use of a Novel Super-Oxidized Solution on Top of Standard Treatment in the Home Care Management of Postsurgical Lesions of the Diabetic Foot Reduces Reinfections and Shortens Healing Time. The international journal of lower extremity wounds. 2018;17(4):268-74.

(39) Imran M, Hussain MB, Baig M. A Randomized, Controlled Clinical Trial of Honey-Impregnated Dressing for Treating Diabetic Foot Ulcer. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2015;25(10):721-5.

(40) Siavash M, Shokri S, Haghighi S, Shahtalebi MA, Farajzadehgan Z. The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal. 2015;12(2):137-42.

(41) Yakoot M, Abdelatif M, Helmy S. Efficacy of a new local limb salvage treatment for limb-threatening diabetic foot wounds - a randomized controlled study. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019;12:1659-65.

(42) Afkhamizadeh M, Aboutorabi R, Ravari H, Fathi Najafi M, Ataei Azimi S, Javadian Langaroodi A, et al. Topical propolis improves wound healing in patients with diabetic foot ulcer: a randomized controlled trial. Natural product research. 2018;32(17):2096-9.

(43) Mujica V, Orrego R, Fuentealba R, Leiva E, Zúñiga-Hernández J. Propolis as an Adjuvant in the Healing of Human Diabetic Foot Wounds Receiving Care in the Diagnostic and Treatment Centre from the Regional Hospital of Talca. Journal of diabetes research. 2019;2019:2507578.

(44) Djavid GE, Tabaie SM, Tajali SB, Totounchi M, Farhoud A, Fateh M, et al. Application of a collagen matrix dressing on a neuropathic diabetic foot ulcer: a randomised control trial. Journal of wound care. 2020;29(Sup3):S13-s8.

(45) Blume P, Driver VR, Tallis AJ, Kirsner RS, Kroeker R, Payne WG, et al. Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2011;19(3):302-8.

(46) Donaghue VM, Chrzan JS, Rosenblum BI, Giurini JM, Habershaw GM, Veves A. Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers. Advances in wound care : the journal for prevention and healing. 1998;11(3):114-9.

(47) Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Archives of surgery (Chicago, Ill : 1960). 2002;137(7):822-7.

(48) Park KH, Kwon JB, Park JH, Shin JC, Han SH, Lee JW. Collagen dressing in the treatment of diabetic foot ulcer: A prospective, randomized, placebo-controlled, single-center study. Diabetes research and clinical practice. 2019;156:107861.

(49) Stupin VA, Silina EV, Gorskij VA, Gorjunov SV, Zhidkih SY, Komarov AN, et al. [Efficacy and safety of collagen biomaterial local application in complex treatment of the diabetic foot syndrome (final results of the multicenter randomised study)]. Khirurgiia. 2018(6):91-100.

(50) Zaitseva EL, Tokmakova AY, Shestakova MV, Galstyan GR, Doronina LP. [The Study of Influence of Different Methods of Local Treatment on Wound Healing in Patients with Diabetic Foot Ulcers]. Vestnik Rossiiskoi akademii meditsinskikh nauk. 2016;71(6):466-71.

(51) Lalau JD, Bresson R, Charpentier P, Coliche V, Erlher S, Ha Van G, et al. Efficacy and tolerance of calcium alginate versus vaseline gauze dressings in the treatment of diabetic foot lesions. Diabetes & metabolism. 2002;28(3):223-9.

(52) Tiwari S. Study to Assess the Efficacy of Collagen Dressing in Diabetic Foot Ulcer Patients. European Journal of Molecular and Clinical Medicine. 2022;9(3):10929-35.

(53) Chitrambalam TG, Christopher PJ, Sundaraj J, Paladugu R, Selvamuthukumaran S. Comparison of Efficacy of Alginate Filler Dressings with Conventional Saline Dressings for Cavity Wounds in Diabetic Foot Ulcer- A Prospective Cohort Study. Journal of Clinical and Diagnostic Research. 2020;14(11):PC1-PC4.

(54) Motzkau M, Tautenhahn J, Lehnert H, Lobmann R. Expression of matrix-metalloproteases in the fluid of chronic diabetic foot wounds treated with a protease absorbent dressing. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2011;119(5):286-90.

(55) Edmonds M, Lázaro-Martínez JL, Alfayate-García JM, Martini J, Petit JM, Rayman G, et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. The lancet Diabetes & endocrinology. 2018;6(3):186-96.

(56) Maunoury F, Oury A, Fortin S, Thomassin L, Bohbot S, Explorer S. Cost-effectiveness of TLC-NOSF dressings versus neutral dressings for the treatment of diabetic foot ulcers in France. PLoS One. 2021;16(1):e0245652.

(57) National Institute for Health and Care Excellence. UrgoStart for treating diabetic foot ulcers and leg ulcers. Medical technologies guidance [MTG42] Published: 31 January 2019. *www.nice.org.uk/guidance/mtg42*. Accessed 28/02/2023.

(58) Wen J, Jin X, Al Sayah F, Johnson JA, Paulden M, Ohinmaa A. Economic Evaluation of Sucrose Octasulfate Dressing for Treatment of Diabetic Foot Ulcers in Patients with Type 2 Diabetes. Can J Diabetes. 2022;46(2):126-33.

(59) Lobmann R, Augustin M, Lawall H, Tigges W, Potempa C, Thiem H, et al. Cost-effectiveness of TLC-sucrose octasulfate versus control dressings in the treatment of diabetic foot ulcers. Journal of wound care. 2019;28(12):808-16.

(60) Ahmed A, Ahmed MI. A comparison of efficacy of topical use of phenytoin and vaseline gauze dressing with vaseline gauze dressing alone in healing of diabetic foot ulcers. J Postgrad Med Inst. 2014;28(3):297-302.

(61) Hajong R, Naku N, Hajong D, Anand M, Singh KL, Majumdar N. Effect of topical phenytoin on wound healing. IOSR Journal of Dental and Medical Sciences. 2016;15(9):161-4.

(62) Jayalal JA, Kumar SJ, Thambithurai DD, Kadar JMA. Efficiency of topical phenytoin on healing in diabetic foot ulcer: a randomized control trial. International Journal of Scientific Study. 2015;3(3):84-9.

(63) Kalyani R, Rajachidambaram K. Effect of local insulin vs topical phenytoin in diabetic foot ulcer. Neuroquantology. 2022;20(17):1870-2.

(64) Motawea A, El-Gawad H, El-Gawad AH, Borg T, Motawea M, Tharshoby M. The impact of topical phenytoin loaded nanostructured lipid carriers in diabetic foot ulceration. The Foot. 2019.

(65) Nagaraj J, Subbiah V. The efficacy of local insulin vs topical phenytoin or normal saline in diabetic foot ulcer management: a prospective comparative study. Cureus. 2022;14(10).

(66) Prasad S, Prakash A, Patel S, Lunawat A, Mahore D. A comparative analysis of the efficacy of topical phenytoin with conventional wound dressing in healing of diabetic foot ulcers. International Surgery Journal. 2017;4(4):1389-93.

(67) Soundarapandiyan R, Srikanth R, Udhayasankar V. Role of topical phenytoin in diabetic foot ulcer care - a randomized control trial. J Evolution Med Dent Sci. 2017;6(4):264-8.

(68) Sudhir S, Ganashree MH, Naik D, Dilip DK. To compare the efficacy of topical phenytoin over conventional wound care (5% povidone-iodine) in diabetic ulcer. International Journal of Surgery Science. 2020;4(1):122-8.

(69) Pai MR, Sitaraman N, Kotian MS. Topical phenytoin in diabetic ulcers: a double blind controlled trial. Indian journal of medical sciences. 2001;55(11):593-9.

(70) Patil V, Patil R, Kariholu PL, Patil LS, Shahapur P. Topical phenytoin application in grade i and ii diabetic foot ulcers:A prospective study. Journal of Clinical and Diagnostic Research. 2013;7(10):2238-40.

(71) Shaw J, Hughes CM, Lagan KM, Stevenson MR, Irwin CR, Bell PM. The effect of topical phenytoin on healing in diabetic foot ulcers: a randomized controlled trial. Diabetic medicine : a journal of the British Diabetic Association. 2011;28(10):1154-7.

(72) Fallah Huseini H, Yaghoobi M, Fallahi F, Boroumand F, Ezzati MH, Tabatabaei SM, et al. Topical Administration of Teucrium polium on Diabetic Foot Ulcers Accelerates Healing: A Placebo-Controlled Randomized Clinical Study. International Journal of Lower Extremity Wounds. 2021.

(73) Li FL, Deng H, Wang HW, Xu R, Chen J, Wang YF, et al. Effects of external application of chinese medicine on diabetic ulcers and the expressions of beta-catenin, c-myc and K6. Chinese Journal of Integrative Medicine. 2011;17(4):261-6.

(74) Li S, Zhao J, Liu J, Xiang F, Lu D, Liu B, et al. Prospective randomized controlled study of a Chinese herbal medicine compound Tangzu Yuyang Ointment for chronic diabetic foot ulcers: a preliminary report. Journal of ethnopharmacology. 2011;133(2):543-50.

(75) Tonaco LAB, Gomes FL, Velasquez-Melendez G, Lopes MTP, Salas CE. The Proteolytic Fraction from Latex of Vasconcellea cundinamarcensis (P1G10) Enhances Wound Healing of Diabetic Foot Ulcers: A Double-Blind Randomized Pilot Study. Advances in therapy. 2018;35(4):494-502.

(76) Jacobs AM, Tomczak R. Evaluation of Bensal HP for the treatment of diabetic foot ulcers. Advances in skin & wound care. 2008;21(10):461-5.

(77) Aybar JNA, Mayor SO, Olea L, Garcia JJ, Nisoria S, Kolling Y, et al. Topical Administration of Lactiplantibacillus plantarum Accelerates the Healing of Chronic Diabetic Foot Ulcers through Modifications of Infection, Angiogenesis, Macrophage Phenotype and Neutrophil Response. Microorganisms. 2022;10(3):14.

(78) Viswanathan V, Kesavan R, Kavitha KV, Kumpatla S. A pilot study on the effects of a polyherbal formulation cream on diabetic foot ulcers. The Indian journal of medical research. 2011;134(2):168-73.

(79) Chokpaisarn J, Chusri S, Voravuthikunchai SP. Clinical randomized trial of topical Quercus infectoria ethanolic extract for the treatment of chronic diabetic ulcers. Journal of herbal medicine. 2019.

(80) Verdu-Soriano J, de Cristino-Espinar M, Luna-Morales S, Dios-Guerra C, Caballero-Villarraso J, Moreno-Moreno P, et al. Superiority of a Novel Multifunctional Amorphous Hydrogel Containing Olea europaea Leaf Extract (EHO-85) for the Treatment of Skin Ulcers: A Randomized, Active-Controlled Clinical Trial. Journal of Clinical Medicine. 2022;11(5):19.

(81) Chen CY, Wu RW, Hsu MC, Hsieh CJ, Chou MC. Adjunctive Hyperbaric Oxygen Therapy for Healing of Chronic Diabetic Foot Ulcers: A Randomized Controlled Trial. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society. 2017;44(6):536-45.

(82) Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2008;47(6):515-9.

(83) Nik Hisamuddin NAR, Wan Mohd Zahiruddin WN, Mohd Yazid B, Rahmah S. Use of hyperbaric oxygen therapy (HBOT) in chronic diabetic wound - A randomised trial. The Medical journal of Malaysia. 2019;74(5):418-24.

(84) Semadi NI. The role of VEGF and TNF-alpha on epithelialization of diabetic foot ulcers after hyperbaric oxygen therapy. Open Access Macedonian Journal of Medical Sciences. 2019;7(19):3177-83.

(85) Salama SE, Eldeeb AE, Elbarbary AH, Abdelghany SE. Adjuvant Hyperbaric Oxygen Therapy Enhances Healing of Nonischemic Diabetic Foot Ulcers Compared With Standard Wound Care Alone. The international journal of lower extremity wounds. 2019;18(1):75-80.

(86) Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes care. 2003;26(8):2378-82.

(87) Fedorko L, Bowen JM, Jones W, Oreopoulos G, Goeree R, Hopkins RB, et al. Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial. Diabetes care. 2016;39(3):392-9.

(88) Santema KTB, Stoekenbroek RM, Koelemay MJW, Reekers JA, Van Dortmont LMC, Oomen A, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: Results of the DAMO2CLES multicenter randomized clinical trial. Diabetes care. 2018;41(1):112-9.

(89) Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes care. 2010;33(5):998-1003.

(90) Londahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. Diabetic medicine. 2011;28(2):186-90.

(91) Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2003;25(6):513-8.

(92) Li G, Hopkins RB, Levine MAH, Jin X, Bowen JM, Thabane L, et al. Relationship between hyperbaric oxygen therapy and quality of life in participants with chronic diabetic foot ulcers: data from a randomized controlled trial. Acta diabetologica. 2017;54(9):823-31.

(93) Li N, Meng XE, Guo DZ, Fan DF, Pan SY. Wound healing process and related laboratory indexes in patients with type 2 diabetes mellitus after hyperbaric oxygen intervention. Biomedical Research (India). 2017;28(20):8838-43.

(94) Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. Ostomy/wound management. 2013;59(3):18-24.

(95) Dhamodharan U, Karan A, Sireesh D, Vaishnavi A, Somasundar A, Rajesh K, et al. Tissue-specific role of Nrf2 in the treatment of diabetic foot ulcers during hyperbaric oxygen therapy. Free radical biology & medicine. 2019;138:53-62.

(96) Perren S, Gatt A, Papanas N, Formosa C. Hyperbaric oxygen therapy in ischaemic foot ulcers in type 2 diabetes: A clinical trial. Open Cardiovascular Medicine Journal. 2018;12(1):80-5.

(97) Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. Journal of postgraduate medicine. 1992;38(3):112-4, 1.

(98) Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. Diabetes care. 1996;19(12):1338-43.

(99) Frykberg RG. Topical Wound Oxygen Therapy in the Treatment of Chronic Diabetic Foot Ulcers. Medicina. 2021;57(9):917.

(100) Frykberg RG, Franks PJ, Edmonds M, Brantley JN, Téot L, Wild T, et al. A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen (TWO2) Therapy in the Treatment of Chronic Diabetic Foot Ulcers: The TWO2 Study. Diabetes care. 2020;43(3):616-24.

(101) Serena TE, Bullock NM, Cole W, Lantis J, Li L, Moore S, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. Journal of wound care. 2021;30(Sup5):S7-s14.

(102) Wang S, Pan LF, Gao L, Qin XY, Wang JN. Randomized research on the mechanism of local oxygen therapy promoting wound healing of diabetic foot based on RNA-seq technology. Annals of palliative medicine. 2021;10(2):973-83.

(103) He S, Liang C, Yi C, Wu M. Therapeutic effect of continuous diffusion of oxygen therapy combined with traditional moist wound dressing therapy in the treatment of diabetic foot ulcers. Diabetes research and clinical practice. 2021;174:108743.

(104) Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. Journal of wound care. 2018;27(Sup9):S30-s45.

(105) Driver VR, Reyzelman A, Kawalec J, French M. A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers. Ostomy/wound management. 2017;63(4):12-28.

(106) Yu J, Lu S, McLaren AM, Perry JA, Cross KM. Topical oxygen therapy results in complete wound healing in diabetic foot ulcers. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2016;24(6):1066-72.

(107) Anirudh V, Kamath DY, Ghosh S, Bhuvana KB, Sharma S, Maruthy K, et al. Topical Controlled Warm Oxygen Therapy Delivered Through a Novel Device (KADAM (TM)) to Treat Diabetic Foot Ulcers: A Randomized Controlled, Open, Pilot Trial. Indian Journal of Surgery.

(108) Leslie CA, Sapico FL, Ginunas VJ, Adkins RH. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes care. 1988;11(2):111-5.

(109) Zhang J, Guan M, Xie C, Luo X, Zhang Q, Xue Y. Increased growth factors play a role in wound healing promoted by noninvasive oxygen-ozone therapy in diabetic patients with foot ulcers. Oxidative medicine and cellular longevity. 2014;2014:273475.

(110) Edmonds ME, Bodansky HJ, Boulton AJM, Chadwick PJ, Dang CN, D'Costa R, et al. Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes-ProNOx1 study. Wound repair and regeneration. 2018;26(2):228-37.

(111) Wainstein J, Feldbrin Z, Boaz M, Harman-Boehm I. Efficacy of ozone-oxygen therapy for the treatment of diabetic foot ulcers. Diabetes technology & therapeutics. 2011;13(12):1255-60.

(112) Izadi M, Kheirjou R, Mohammadpour R, Aliyoldashi MH, Moghadam SJ, Khorvash F, et al. Efficacy of comprehensive ozone therapy in diabetic foot ulcer healing. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2019;13(1):822-5.

(113) Martinez-Sanchez G, Al-Dalain SM, Menendez S, Re L, Giuliani A, Candelario-Jalil E, et al. Therapeutic efficacy of ozone in patients with diabetic foot. European journal of pharmacology. 2005;523(1-3):151-61.

(114) Mirpour S, Fathollah S, Mansouri P, Larijani B, Ghoranneviss M, Mohajeri Tehrani M, et al. Cold atmospheric plasma as an effective method to treat diabetic foot ulcers: A randomized clinical trial. Scientific reports. 2020;10(1):10440.

(115) Stratmann B, Costea TC, Nolte C, Hiller J, Schmidt J, Reindel J, et al. Effect of Cold Atmospheric Plasma Therapy vs Standard Therapy Placebo on Wound Healing in Patients With Diabetic Foot Ulcers: A Randomized Clinical Trial. JAMA network open. 2020;3(7):e2010411.

(116) Macura M, Ban Frangez H, Cankar K, Finžgar M, Frangez I. The effect of transcutaneous application of gaseous CO(2) on diabetic chronic wound healing-A double-blind randomized clinical trial. International wound journal. 2020;17(6):1607-14.

(117) Alvarez O, Patel M, Rogers R, Booker J. Effect of non-contact normothermic wound therapy on the healing of diabetic neuropathic foot ulcers. Journal of tissue viability. 2006;16(1):8-11.

(118) McCulloch J, Knight CA. Noncontact normothermic wound therapy and offloading in the treatment of neuropathic foot ulcers in patients with diabetes. Ostomy/wound management. 2002;48(3):38-44.

(119) Petrofsky JS, Lawson D, Berk L, Suh H. Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30 min three times per week. Journal of diabetes. 2010;2(1):41-6.

(120) Rastogi A, Bhansali A, Ramachandran S. Efficacy and Safety of Low-Frequency, Noncontact Airborne Ultrasound Therapy (Glybetac) For Neuropathic Diabetic Foot Ulcers: A Randomized, Double-Blind, Sham-Control Study. The international journal of lower extremity wounds. 2019;18(1):81-8.

(121) Ennis WJ, Foremann P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. Ostomy/wound management. 2005;51(8):24-39.

(122) Armstrong DG, Nguyen HC. Oedema reduction by mechanical compression improved the healing of foot infection in patients with diabetes mellitus. Evidence-Based Medicine. 2001;6(4):122.

(123) Mars M, Desai Y, Gregory MA. Compressed air massage hastens healing of the diabetic foot. Diabetes technology & therapeutics. 2008;10(1):39-45.

(124) Akbari A, Moodi H, Ghiasi F, Sagheb HM, Rashidi H. Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of rehabilitation research and development. 2007;44(5):631-6.

(125) Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. Archives of physical medicine and rehabilitation. 2001;82(6):721-5.

(126) Baker LL, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes care. 1997;20(3):405-12.

(127) Asadi MR, Torkaman G, Hedayati M, Mohajeri-Tehrani MR, Ahmadi M, Gohardani RF. Angiogenic effects of low-intensity cathodal direct current on ischemic diabetic foot ulcers: A randomized controlled trial. Diabetes research and clinical practice. 2017;127:147-55.

(128) Mohajeri-Tehrani MR, Nasiripoor F, Torkaman G, Hedayati M, Annabestani Z, Asadi MR. Effect of low-intensity direct current on expression of vascular endothelial growth factor and nitric oxide in diabetic foot ulcers. Journal of rehabilitation research and development. 2014;51(5):815-24.

(129) Zulbaran-Rojas A, Park C, El-Refaei N, Lepow B, Najafi B. Home-Based Electrical Stimulation to Accelerate Wound Healing-A Double-Blinded Randomized Control Trial. Journal of Diabetes Science and Technology. 2021.

(130) Kwan R-C, Wong WC, Yip SL, Chan KL, Zheng YP, Cheing G-Y. Pulsed electromagnetic field therapy promotes healing and microcirculation of chronic diabetic foot ulcers: a pilot study. Advances in skin & wound care. 2015;28(5):212-9.

(131) Haze A, Gavish L, Elishoov O, Shorka D, Tsohar T, Gellman YN, et al. Treatment of diabetic foot ulcers in a frail population with severe co-morbidities using at-home photobiomodulation laser therapy: a double-blind, randomized, sham-controlled pilot clinical study. Lasers in Medical Science. 2021.

(132) Kaviani A, Djavid GE, Ataie-Fashtami L, Fateh M, Ghodsi M, Salami M, et al. A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. Photomedicine and laser surgery. 2011;29(2):109-14.

(133) Landau Z, Migdal M, Lipovsky A, Lubart R. Visible light-induced healing of diabetic or venous foot ulcers: a placebo-controlled double-blind study. Photomedicine and laser surgery. 2011;29(6):399-404.

(134) Wadee AN, Aref MHF, Nassar AA, Aboughaleb IH, Fahmy SM. The influence of low- intensity laser irradiation versus hyperbaric oxygen therapy on transcutaneous oxygen tension in chronic diabetic foot ulcers: a controlled randomized trial. Journal of Diabetes and Metabolic Disorders. 2021;20(2):1489-97.

(135) Srilestari A, Nareswari I, Simadibrata C, Tarigan TJE. Effectiveness of combined laser-puncture and conventional wound care to accelerate diabetic foot ulcer healing. Medical Journal of Indonesia. 2017;26(1):26-34.

(136) Mathur RK, Sahu K, Saraf S, Patheja P, Khan F, Gupta PK. Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers. Lasers in medical science. 2017;32(2):275-82.

(137) Kajagar BM, Godhi AS, Pandit A, Khatri S. Efficacy of Low Level Laser Therapy on Wound Healing in Patients with Chronic Diabetic Foot Ulcers-A Randomised Control Trial. Indian Journal of Surgery. 2012;74(5):359-63.

(138) de Alencar Fonseca Santos J, Campelo MBD, de Oliveira RA, Nicolau RA, Rezende VEA, Arisawa E. Effects of Low-Power Light Therapy on the Tissue Repair Process of Chronic Wounds in Diabetic Feet. Photomedicine and laser surgery. 2018;36(6):298-304.

(139) Moretti B, Notarnicola A, Maggio G, Moretti L, Pascone M, Tafuri S, et al. The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC musculoskeletal disorders. 2009;10:54.

(140) Snyder R, Galiano R, Mayer P, Rogers LC, Alvarez O. Diabetic foot ulcer treatment with focused shockwave therapy: two multicentre, prospective, controlled, double-blinded, randomised phase III clinical trials. Journal of wound care. 2018;27(12):822-36.

(141) Omar MT, Alghadir A, Al-Wahhabi KK, Al-Askar AB. Efficacy of shock wave therapy on chronic diabetic foot ulcer: a single-blinded randomized controlled clinical trial. Diabetes research and clinical practice. 2014;106(3):548-54.

(142) Jeppesen SM, Yderstraede KB, Rasmussen BS, Hanna M, Lund L. Extracorporeal shockwave therapy in the treatment of chronic diabetic foot ulcers: a prospective randomised trial. Journal of wound care. 2016;25(11):641-9.

(143) Shaked G, Czeiger D, Abu Arar A, Katz T, Harman-Boehm I, Sebbag G. Intermittent cycles of remote ischemic preconditioning augment diabetic foot ulcer healing. Wound Repair and Regeneration. 2015;23(2):191-6.

(144) Piaggesi A, Sambataro M, Nicoletti C, Goretti C, Lacopi E, Coppelli A. Safety and effectiveness of therapeutic magnetic resonance in diabetic foot ulcers: a prospective randomised controlled trial. Journal of wound care. 2016;25(12):704-11.

(145) Joseph LH, Paungmali A, Dixon J, Holey L, Naicker AS, Htwe O. Therapeutic effects of connective tissue manipulation on wound healing and bacterial colonization count among patients with diabetic foot ulcer. Journal of Bodywork and Movement Therapies. 2016;20(3):650-6.

(146) Edmonds M. Apligraf in the treatment of neuropathic diabetic foot ulcers. The international journal of lower extremity wounds. 2009;8(1):11-8.

(147) Gentzkow GD, Iwasaki SD, Hershon KS, Mengel M, Prendergast JJ, Ricotta JJ, et al. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes care. 1996;19(4):350-4.

(148) Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2002;41(5):291-9.

(149) Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: Results of a prospective randomized trial. Diabetes care. 2003;26(6):1701-5.

(150) Tchanque-Fossuo CN, Dahle SE, Lev-Tov H, West KIM, Li CS, Rocke DM, et al. Cellular versus acellular matrix devices in the treatment of diabetic foot ulcers: Interim results of a comparative efficacy randomized controlled trial. Journal of tissue engineering and regenerative medicine. 2019;13(8):1430-7.

(151) Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes care. 2001;24(2):290-5.

(152) Binienko MA, Kotslova AA, Davydenko VV, Vlasov TD. APPLICATION OF GRAFTSKIN TO ACCELERATE HEALING OF ULCERS IN DIABETIC FOOT SYNDROME. Vestnik khirurgii imeni I I Grekova. 2016;175(5):63-8.

(153) Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. International wound journal. 2015;12(6):724-32.

(154) Lipkin S, Chaikof E, Isseroff Z, Silverstein P. Effectiveness of bilayered cellular matrix in healing of neuropathic diabetic foot ulcers: results of a multicenter pilot trial. Wounds: a compendium of clinical research & practice. 2003;15(7):230-6.

(155) Gould LJ, Orgill DP, Armstrong DG, Galiano RD, Glat PM, Zelen CM, et al. Improved healing of chronic diabetic foot wounds in a prospective randomised controlled multi-centre clinical trial with a microvascular tissue allograft. Int Wound J. 2022;19(4):811-25.

(156) Campitiello F, Mancone M, Della Corte A, Guerniero R, Canonico S. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. Updates in surgery. 2017;69(4):523-9.

(157) Driver VR, Lavery LA, Reyzelman AM, Dutra TG, Dove CR, Kotsis SV, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2015;23(6):891-900.

(158) Zelen CM, Orgill DP, Serena TE, Galiano RE, Carter MJ, DiDomenico LA, et al. An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: A prospective, randomised, controlled, multicentre follow-up trial. International wound journal. 2018;15(5):731-9.

(159) Lantis JC, Snyder R, Reyzelman AM, Van Gils CC, Sigal F, Vayser D, et al. Fetal bovine acellular dermal matrix for the closure of diabetic foot ulcers: a prospective randomised controlled trial. Journal of wound care. 2021;30(Sup7):S18-s27.

(160) Lullove EJ, Liden B, Winters C, McEneaney P, Raphael A, Lantis Ii JC. A Multicenter, Blinded, Randomized Controlled Clinical Trial Evaluating the Effect of Omega-3-Rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers. Wounds : a compendium of clinical research and practice. 2021;33(7):169-77.

(161) Cetinkalp S, Gokce EH, Simsir I, Tuncay Tanriverdi S, Dogan F, Biray Avci C, et al. Comparative Evaluation of Clinical Efficacy and Safety of Collagen Laminin-Based Dermal Matrix Combined With Resveratrol Microparticles (Dermalix) and Standard Wound Care for Diabetic Foot Ulcers. International Journal of Lower Extremity Wounds. 2021;20(3):217-26.

(162) Cazzell S, Vayser D, Pham H, Walters J, Reyzelman A, Samsell B, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2017;25(3):483-97.

(163) Reyzelman A, Crews RT, Moore JC, Moore L, Mukker JS, Offutt S, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. International wound journal. 2009;6(3):196-208.

(164) Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal. 2006;3(3):181-7.

(165) Hahn HM, Lee DH, Lee IJ. Ready-to-Use Micronized Human Acellular Dermal Matrix to Accelerate Wound Healing in Diabetic Foot Ulcers: A Prospective Randomized Pilot Study. Advances in skin & wound care. 2021;34(5):1-6.

(166) Armstrong DG, Orgill DP, Galiano RD, Glat PM, Kaufman JP, Carter MJ, et al. Use of a purified reconstituted bilayer matrix in the management of chronic diabetic foot ulcers improves patient outcomes vs standard of care: Results of a prospective randomised controlled multi-centre clinical trial. Int Wound J. 2022;19(5):1197-209.

(167) Montanaro M, Meloni M, Anemona L, Giurato L, Scimeca M, Izzo V, et al. Macrophage Activation and M2 Polarization in Wound Bed of Diabetic Patients Treated by Dermal/Epidermal Substitute Nevelia. International Journal of Lower Extremity Wounds. 2020.

(168) Armstrong DG, Orgill DP, Galiano R, Glat PM, Didomenico L, Reyzelman A, et al. A multicentre, randomised controlled clinical trial evaluating the effects of a novel autologous, heterogeneous skin construct in the treatment of Wagner one diabetic foot ulcers: Interim analysis. Int Wound J. 2022;19(1):64-75.

(169) Caravaggi C, De Giglio R, Pritelli C, Sommaria M, Dalla Noce S, Faglia E, et al. HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. Diabetes care. 2003;26(10):2853-9.

(170) Uccioli L, Giurato L, Ruotolo V, Ciavarella A, Grimaldi MS, Piaggesi A, et al. Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. International journal of lower extremity wounds. 2011;10(2):80-5.

(171) Manning L, Ferreira IB, Gittings P, Hiew J, Ryan E, Baba M, et al. Wound healing with "spray-on" autologous skin grafting (ReCell) compared with standard care in patients with large diabetes-related foot wounds: an open-label randomised controlled trial. International Wound Journal. 2021.

(172) Armstrong DG, Galiano RD, Orgill DP, Glat PM, Carter MJ, Di Domenico LA, et al. Multi-centre prospective randomised controlled clinical trial to evaluate a bioactive split thickness skin allograft vs standard of care in the treatment of diabetic foot ulcers. Int Wound J. 2022;19(4):932-44.

(173) Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-Rich Plasma for the Treatment of Clean Diabetic Foot Ulcers. Annals of vascular surgery. 2017;38:206-11.

(174) Driver VR, Hanft J, Fylling CP, Beriou JM. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy/wound management. 2006;52(6):68-70, 2, 4 passim.

(175) Elsaid A, El-Said M, Emile S, Youssef M, Khafagy W, Elshobaky A. Randomized Controlled Trial on Autologous Platelet-Rich Plasma Versus Saline Dressing in Treatment of Non-healing Diabetic Foot Ulcers. World journal of surgery. 2020;44(4):1294-301.

(176) Gude W, Hagan D, Abood F, Clausen P. Aurix Gel Is an Effective Intervention for Chronic Diabetic Foot Ulcers: A Pragmatic Randomized Controlled Trial. Advances in skin & wound care. 2019;32(9):416-26.

(177) Gupta A, Channaveera C, Sethi S, Ranga S, Anand V. Efficacy of Intralesional Platelet-Rich Plasma in Diabetic Foot Ulcer. Journal of the American Podiatric Medical Association. 2021;111(3).

(178) Li L, Chen D, Wang C, Yuan N, Wang Y, He L, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: A prospective, randomized clinical trial. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2015;23(4):495-505.

(179) Jeong SH, Han SK, Kim WK. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. Plastic and reconstructive surgery. 2010;125(3):944-52.

(180) Singh SP, Kumar V, Pandey A, Pandey P, Gupta V, Verma R. Role of platelet-rich plasma in healing diabetic foot ulcers: a prospective study. Journal of wound care. 2018;27(9):550-6.

(181) Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. Diabetes care. 1992;15(11):1598-604.

(182) Xie J, Fang Y, Zhao Y, Cao D, Lv Y. Autologous Platelet-Rich Gel for the Treatment of Diabetic Sinus Tract Wounds: A Clinical Study. The Journal of surgical research. 2020;247:271-9.

(183) Alamdari NM, Sha A, Mirmohseni A, Besharat S. Evaluation of the efficacy of platelet-rich plasma on healing of clean diabetic foot ulcers: A randomized clinical trial in Tehran, Iran. Diabetes & Metabolic Syndrome-Clinical Research & Reviews. 2021;15(2):621-6.

(184) Yang L, Gao L, Lv Y, Wang JN. Autologous platelet-rich gel for lower-extremity ischemic ulcers in patients with type 2 diabetes. International Journal of Clinical and Experimental Medicine. 2017;10(9):13796-801.

(185) Hosseini SE, Molavi B, Goodarzi A, Alizadeh A, Yousefzadeh A, Sodeifi N, et al. The efficacy of platelet gel derived from umbilical cord blood on diabetic foot ulcers: A double-blind randomized clinical trial. Wound Medicine. 2020;28 (no pagination)(100178).

(186) Volpe P, Marcuccio D, Stilo G, Alberti A, Foti G, Volpe A, et al. Efficacy of cord blood platelet gel application for enhancing diabetic foot ulcer healing after lower limb revascularization. Seminars in vascular surgery. 2017;30(4):106-12.

(187) Orban YA, Soliman MAE, Hegab YH, Alkilany MM. Autologous Platelet-rich Plasma vs Conventional Dressing in the Management of Chronic Diabetic Foot Ulcers. Wounds-a Compendium of Clinical Research and Practice. 2022;34(2):36-42.

(188) Game F, Jeffcoate W, Tarnow L, Jacobsen JL, Whitham DJ, Harrison EF, et al. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The lancet Diabetes & endocrinology. 2018;6(11):870-8.

(189) Han SK, Kim HR, Kim WK. The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2010;18(4):342-8.

(190) Lonardi R, Leone N, Gennai S, Borsari GT, Covic T, Silingardi R. Autologous micro-fragmented adipose tissue for the treatment of diabetic foot minor amputations: a randomized controlled single-center clinical trial (MiFrAADiF). Stem cell research & therapy. 2019;10.

(191) Moon KC, Suh HS, Kim KB, Han SK, Young KW, Lee JW, et al. Potential of Allogeneic Adipose-Derived Stem Cell-Hydrogel Complex for Treating Diabetic Foot Ulcers. Diabetes. 2019;68(4):837-46.

(192) Smith OJ, Leigh R, Kanapathy M, Macneal P, Jell G, Hachach-Haram N, et al. Fat grafting and platelet-rich plasma for the treatment of diabetic foot ulcers: A feasibility-randomised controlled trial. International wound journal. 2020;17(6):1578-94.

(193) Kesavan R, Sheela Sasikumar C, Narayanamurthy VB, Rajagopalan A, Kim J. Management of Diabetic Foot Ulcer with MA-ECM (Minimally Manipulated Autologous Extracellular Matrix) Using 3D Bioprinting Technology - An Innovative Approach. International Journal of Lower Extremity Wounds. 2021.

(194) You HJ, Han SK, Rhie JW. Randomised controlled clinical trial for autologous fibroblast-hyaluronic acid complex in treating diabetic foot ulcers. Journal of wound care. 2014;23(11):521-2, 4, 6-30.

(195) You HJ, Han SK, Lee JW, Chang H. Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes--a pilot study. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2012;20(4):491-9.

(196) Bayram Y, Deveci M, Imirzalioglu N, Soysal Y, Sengezer M. The cell based dressing with living allogenic keratinocytes in the treatment of foot ulcers: a case study. British journal of plastic surgery. 2005;58(7):988-96.

(197) Dubsky M, Husakova J, Bem R, Jirkovska A, Nemcova A, Fejfarova V, et al. Comparison of the impact of autologous cell therapy and conservative standard treatment on tissue oxygen supply and course of the diabetic foot in patients with chronic limb-threatening ischaemia: A randomized controlled trial. Frontiers in Endocrinology. 2022;13:10.

(198) Arango-Rodríguez ML, Solarte-David VA, Becerra-Bayona SM, Callegari E, Paez MD, Sossa CL, et al. Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial. Cytotherapy. 2022;24(10):1035-48.

(199) Landsman A, Agnew P, Parish L, Joseph R, Galiano RD. Diabetic foot ulcers treated with becaplermin and TheraGauze, a moisture-controlling smart dressing: a randomized, multicenter, prospective analysis. Journal of the American Podiatric Medical Association. 2010;100(3):155-60.

(200) Ma C, Hernandez MA, Kirkpatrick VE, Liang LJ, Nouvong AL, Gordon, II. Topical platelet-derived growth factor vs placebo therapy of diabetic foot ulcers offloaded with windowed casts: a randomized, controlled trial. Wounds : a compendium of clinical research and practice. 2015;27(4):83-91.

(201) Samuel A, Mahajan A, Mam MK, Prakash JS. Platelet derived growth factor in diabetic lower extremity ulcer: A randomized, double blind, placebo controlled study in Indian condition. International Journal of Pharmaceutical Sciences and Research. 2016;7(9):3887-92.

(202) Smiell JM, Wieman TJ, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 1999;7(5):335-46.

(203) Tofigh AM, Tajik M. Comparing the standard surgical dressing with dehydrated amnion and platelet-derived growth factor dressings in the healing rate of diabetic foot ulcer: A randomized clinical trial. Diabetes Research and Clinical Practice. 2022;185:6.

(204) Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes care. 1998;21(5):822-7.

(205) Bhansali A, Venkatesh S, Dutta P, Dhillon MS, Das S, Agrawal A. Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast? Diabetes research and clinical practice. 2009;83(1):e13-6.

(206) Gough A, Clapperton M, Rolando N, Foster AV, Philpott-Howard J, Edmonds ME. Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet (London, England). 1997;350(9081):855-9.

(207) de Lalla F, Pellizzer G, Strazzabosco M, Martini Z, Du Jardin G, Lora L, et al. Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. Antimicrobial agents and chemotherapy. 2001;45(4):1094-8.

(208) Kästenbauer T, Hörnlein B, Sokol G, Irsigler K. Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. Diabetologia. 2003;46(1):27-30.

(209) Gomez-Villa R, Aguilar-Rebolledo F, Lozano-Platonoff A, Teran-Soto JM, Fabian-Victoriano MR, Kresch-Tronik NS, et al. Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: a randomized double-blinded controlled trial. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2014;22(4):497-503.

(210) Park KH, Han SH, Hong JP, Han SK, Lee DH, Kim BS, et al. Topical epidermal growth factor spray for the treatment of chronic diabetic foot ulcers: A phase III multicenter, double-blind, randomized, placebo-controlled trial. Diabetes research and clinical practice. 2018;142:335-44.

(211) Tsang MW, Wong WK, Hung CS, Lai KM, Tang W, Cheung EY, et al. Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes care. 2003;26(6):1856-61.

(212) Hanft JR, Pollak RA, Barbul A, van Gils C, Kwon PS, Gray SM, et al. Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. Journal of wound care. 2008;17(1):30-2, 4-7.

(213) Richard JL, Parer-Richard C, Daures JP, Clouet S, Vannereau D, Bringer J, et al. Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled study. Diabetes care. 1995;18(1):64-9.

(214) Uchi H, Igarashi A, Urabe K, Koga T, Nakayama J, Kawamori R, et al. Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. European Journal of Dermatology. 2009;19(5):461-8.

(215) Xu J, Min D, Guo G, Liao X, Fu Z. Experimental study of epidermal growth factor and acidic fibroblast growth factor in the treatment of diabetic foot wounds. Experimental and Therapeutic Medicine. 2018;15(6):5365-70.

(216) Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. International wound journal. 2013;10(5):502-7.

(217) Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, et al. The efficacy and safety of Grafix(®) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal. 2014;11(5):554-60.

(218) Snyder RJ, Shimozaki K, Tallis A, Kerzner M, Reyzelman A, Lintzeris D, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds : a compendium of clinical research and practice. 2016;28(3):70-7.

(219) Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: a prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. International wound journal. 2018.

(220) Tettelbach W, Cazzell S, Sigal F, Caporusso JM, Agnew PS, Hanft J, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. International wound journal. 2018.

(221) DiDomenico LA, Orgill DP, Galiano RD, Serena TE, Carter MJ, Kaufman JP, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. International wound journal. 2018;15(6):950-7.

(222) Thompson P, Hanson DS, Langemo D, Anderson J. Comparing Human Amniotic Allograft and Standard Wound Care When Using Total Contact Casting in the Treatment of Patients with Diabetic Foot Ulcers. Advances in skin & wound care. 2019;32(6):272-7.

(223) Game F, Gray K, Davis D, Sherman R, Chokkalingam K, Connan Z, et al. The effectiveness of a new dried human amnion derived membrane in addition to standard care in treating diabetic foot ulcers: A patient and assessor blind, randomised controlled pilot study. International wound journal. 2021;18(5):692-700.

(224) Zelen CM, Serena TE, Gould L, Le L, Carter MJ, Keller J, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. International wound journal. 2016;13(2):272-82.

(225) Al-Nimer M, Ratha R, Mahwi T. Pentoxifylline improves the quality of life in type-2 diabetes foot syndrome. Pakistan journal of medical sciences. 2019;35(5):1370-5.

(226) Bashmakov YK, Assaad-Khalil SH, Abou Seif M, Udumyan R, Megallaa M, Rohoma KH, et al. Resveratrol promotes foot ulcer size reduction in type 2 diabetes patients. ISRN Endocrinology. 2014;2014 (no pagination)(816307).

(227) Chatzikyrkou C, Bahlmann FH, Sushakova N, Scurt FG, Menne J, Nawroth P, et al. Low-dose erythropoietin promotes wound-healing of ulcers in diabetics: Evidence from a phase-IIa clinical study. Diabetes and Metabolism. 2016;42(6):466-70.

(228) Kalani M, Apelqvist J, Blombäck M, Brismar K, Eliasson B, Eriksson JW, et al. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes care. 2003;26(9):2575-80.

(229) Koblik T, Sieradzki J, Sendur R, Biernat J, Czarnobilski K, Gryz E, et al. The effect of insulin and sulodexide (Vessel Due F) on diabetic foot syndrome: pilot study in elderly patients. Journal of diabetes and its complications. 2001;15(2):69-74.

(230) Larijani B, Heshmat R, Bahrami A, Delshad H, Ranjbar Omrani G, Mohammad K, et al. Effects of intravenous Semelil (ANGIPARS™) on diabetic foot ulcers healing: a multicenter clinical trial. Daru. 2008;16(SUPPL. 1):35-40.

(231) Squadrito F, Bitto A, Altavilla D, Arcoraci V, De Caridi G, De Feo ME, et al. The effect of PDRN, an adenosine receptor A2A agonist, on the healing of chronic diabetic foot ulcers: results of a clinical trial. Journal of clinical endocrinology and metabolism. 2014;99(5):E746-E53.

(232) Ko CH, Yi S, Ozaki R, Cochrane H, Chung H, Lau W, et al. Healing effect of a two-herb recipe (NF3) on foot ulcers in Chinese patients with diabetes: a randomized double-blind placebo-controlled study. Journal of diabetes. 2014;6(4):323-34.

(233) Kim S, Kim J, Choi J, Jeong W, Kwon S. Polydeoxyribonucleotide improves peripheral tissue oxygenation and accelerates angiogenesis in diabetic foot ulcers. Archives of Plastic Surgery. 2017;44(6):482-9.

(234) Kamble A, Ambad RS, Padamwar M, Kakade A, Yeola M. To study the effect of oral vitamin d supplements on wound healing in patient with diabetic foot ulcer and its effect on lipid metabolism. International Journal of Research in Pharmaceutical Sciences. 2020;11(2):2701-6.

(235) Mohseni S, Bayani M, Bahmani F, Tajabadi-Ebrahimi M, Bayani MA, Jafari P, et al. The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. Diabetes/metabolism research and reviews. 2018;34(3).

(236) Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Journal of diabetes and its complications. 2017;31(9):1394-400.

(237) Yarahmadi A, Saeed Modaghegh MH, Mostafavi-Pour Z, Azarpira N, Mousavian A, Bonakdaran S, et al. The effect of platelet-rich plasma-fibrin glue dressing in combination with oral vitamin E and C for treatment of non-healing diabetic foot ulcers: a randomized, double-blind, parallel-group, clinical trial. Expert opinion on biological therapy. 2021;21(5):687-96.

(238) Armstrong DG, Hanft JR, Driver VR, Smith AP, Lazaro-Martinez JL, Reyzelman AM, et al. Effect of oral nutritional supplementation on wound healing in diabetic foot ulcers: a prospective randomized controlled trial. Diabetic medicine. 2014;31(9):1069-77.

(239) Wong LY, Leung PC, Wong WN, Wong WC, Lau TW, Cheng KF. Clinical research on diabetic foot ulcers: Demonstration of a comprehensive methodology. Journal of Complementary and Integrative Medicine. 2010;7(1) (no pagination)(54).

(240) Chellan G, Neethu K, Varma AK, Mangalanandan TS, Shashikala S, Dinesh KR, et al. Targeted treatment of invasive fungal infections accelerates healing of foot wounds in patients with Type 2 diabetes. Diabetic medicine. 2012;29(9):e255-62.

(241) Mokhtari M, Razzaghi R, Momen-Heravi M. The effects of curcumin intake on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Phytotherapy research : PTR. 2021;35(4):2099-107.

(242) Bonora BM, Cappellari R, Mazzucato M, Rigato M, Grasso M, Menegolo M, et al. Stem cell mobilization with plerixafor and healing of diabetic ischemic wounds: A phase IIa, randomized, double-blind, placebo-controlled trial. Stem cells translational medicine. 2020;9(9):965-73.

(243) Normandin S, Safran T, Winocour S, Chu CK, Vorstenbosch J, Murphy AM, et al. Negative Pressure Wound Therapy: Mechanism of Action and Clinical Applications. Semin Plast Surg. 2021;35(3):164-70.

(244) Malekpour Alamdari N, Mehraneroodi B, Gholizadeh B, Zeinalpour A, Safe P, Besharat S. The efficacy of negative pressure wound therapy compared with conventional dressing in treating infected diabetic foot ulcers: a randomized controlled trial. International Journal of Diabetes in Developing Countries. 2021.

(245) Campitiello F, Mancone M, Corte AD, Guerniero R, Canonico S. Expanded negative pressure wound therapy in healing diabetic foot ulcers: a prospective randomised study. Journal of wound care. 2021;30(2):121-9.

(246) Chiang N, Rodda OA, Sleigh J, Vasudevan T. Effects of topical negative pressure therapy on tissue oxygenation and wound healing in vascular foot wounds. Journal of vascular surgery. 2017;66(2):564-71.

(247) Hu X, Ni Y, Lian W, Kang L, Jiang J, Li M. Combination of negative pressure wound therapy using vacuum-assisted closure and ozone water flushing for treatment of diabetic foot ulcers. International Journal of Diabetes in Developing Countries. 2020;40(2):290-5.

(248) Karatepe O, Eken I, Acet E, Unal O, Mert M, Koc B, et al. Vacuum assisted closure improves the quality of life in patients with diabetic foot. Acta chirurgica Belgica. 2011;111(5):298-302.

(249) Lone AM, Zaroo MI, Laway BA, Pala NA, Bashir SA, Rasool A. Vacuum-assisted closure versus conventional dressings in the management of diabetic foot ulcers: A prospective case-control study. Diabetic Foot and Ankle. 2014;5(1) (no pagination)(23345).

(250) Maranna H, Lal P, Mishra A, Bains L, Sawant G, Bhatia R, et al. Negative pressure wound therapy in grade 1 and 2 diabetic foot ulcers: A randomized controlled study. Diabetes & metabolic syndrome. 2021;15(1):365-71.

(251) McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. Ostomy/wound management. 2000;46(8):28-32, 4.

(252) Nain PS, Uppal SK, Garg R, Bajaj K, Garg S. Role of negative pressure wound therapy in healing of diabetic foot ulcers. Journal of Surgical Technique and Case Report. 2011;3(1):17-22.

(253) Sajid MT, Mustafa Q, Shaheen N, Hussain SM, Shukr I, Ahmed M. Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure with Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2015;25(11):789-93.

(254) Zhang X, Wan L, Yang R, Jin P, Xia W, Ye Y, et al. Expression of connective tissue growth factor and periostin of wound tissue in patients with diabetes who had vacuum sealing drainage. International journal of clinical and experimental medicine. 2017;10(8):12942-50.

(255) Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes care. 2008;31(4):631-6.

(256) Seidel D, Storck M, Lawall H, Wozniak G, Mauckner P, Hochlenert D, et al. Negative pressure wound therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice: results of the German DiaFu-RCT. BMJ open. 2020;10(3):e026345.

(257) Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet (London, England). 2005;366(9498):1704-10.

(258) Lavery LA, Davis KE, La Fontaine J, Farrar JD, Bhavan K, Oz OK, et al. Does negative pressure wound therapy with irrigation improve clinical outcomes? A randomized clinical trial in patients with diabetic foot infections. American journal of surgery. 2020;220(4):1076-82.

(259) Vaidhya N, Panchal A, Anchalia MM. A New Cost-effective Method of NPWT in Diabetic Foot Wound. Indian Journal of Surgery. 2015;77:S525-S9.

(260) Lavery LA, La Fontaine J, Thakral G, Kim PJ, Bhavan K, Davis KE. Randomized clinical trial to compare negative-pressure wound therapy approaches with low and high pressure, silicone-coated dressing, and polyurethane foam dressing. Plastic and reconstructive surgery. 2014;133(3):722-6.

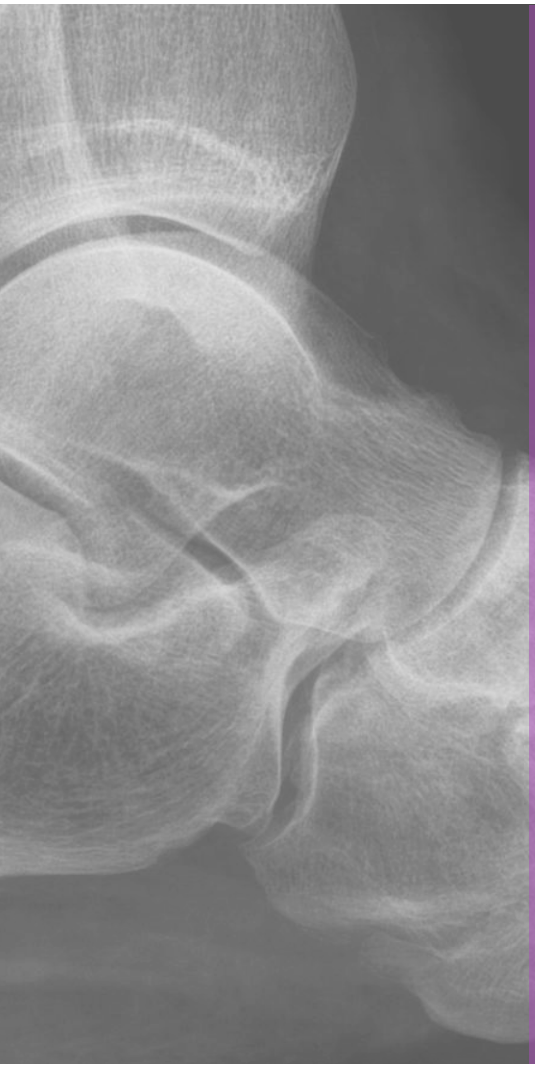
(261) Apelqvist J, Armstrong DG, Lavery LA, Boulton AJ. Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. American journal of surgery. 2008;195(6):782-8.

(262) Driver VR, Blume PA. Evaluation of wound care and health-care use costs in patients with diabetic foot ulcers treated with negative pressure wound therapy versus advanced moist wound therapy. Journal of the American Podiatric Medical Association. 2014;104(2):147-53.

(263) Subrata SA, Phuphaibul R, Grey M, Siripitayakunkit A, Piaseu N. Improving clinical outcomes of diabetic foot ulcers by the 3-month self- and family management support programs in Indonesia: A randomized controlled trial study. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2020;14(5):857-63.

(264) Vas P, Rayman G, Dhatariya K, Driver V, Hartemann A, Londahl M, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3284.

(265) Yelland AC, Meace C, Knighton P, Holman N, Wild SH, Michalowski J, et al. Impact of case-mix adjustment on observed variation in the healing of diabetic foot ulcers at 12 weeks using data from the National Diabetes Foot Care Audit of England and Wales: A cohort study. Diabetic medicine : a journal of the British Diabetic Association. 2023;40(1):e14959.



Guidelines on the diagnosis and treatment of active Charcot neuro-osteoarthropathy in persons with diabetes mellitus

Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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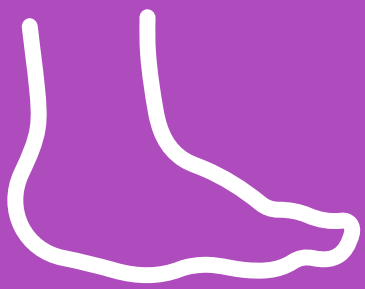

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ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This is the first guideline on the diagnosis and treatment of active Charcot Neuro-osteoarthropathy in persons with diabetes published by the IWGDF. We followed the GRADE Methodology to devise clinical questions in the PACO (Population, Assessment, Comparison, Outcome) and PICO (Population, Intervention, Comparison, Outcome) format, conducted a systematic review of the medical literature, and developed recommendations with rationale. The recommendations are based on the evidence from our systematic review, expert opinion when evidence was not available, and also taking into account weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to an intervention. We here present the 2023 Guidelines on the diagnosis and treatment of active Charcot Neuro-osteoarthropathy in persons with diabetes mellitus and also suggest key future topics of research.

ABBREVIATIONS

AFO: Ankle Foot Orthosis

CNO: Charcot neuro-osteoarthropathy

CROW: Charcot Restraining Orthotic Walker

CT: Computed Tomography

IWGDF: International Working Group on the Diabetic Foot

MRI: Magnetic Resonance Imaging

PTH: Parathyroid hormone

LIST OF RECOMMENDATIONS

DIAGNOSIS

1. Always consider active Charcot neuro-osteoarthropathy in a person with diabetes mellitus, neuropathy and intact skin when there are clinical findings of an increase in temperature, oedema, and/or redness of the foot, compared to the contralateral foot. Best Practice Statement.
2. Consider using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected Charcot neuro-osteoarthropathy with intact skin, using a standardised approach to the measurement of temperatures to allow for more accurate comparison over time. (GRADE recommendation: Conditional; Certainty of the evidence: Low)
3. When using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin, consider calculating temperature difference between both legs, using the highest temperature on the affected foot or ankle in comparison with the same anatomic point on the contralateral extremity. (Conditional; Low)
4. In a person with diabetes mellitus with bilateral active Charcot neuro-osteoarthropathy (CNO) and intact skin or with unilateral CNO and intact skin in the absence of the contralateral limb, ascending temperature gradients (toe-knee) may be useful for comparison over time. Best Practice Statement.
5. Initiate knee high immobilization/offloading promptly while further diagnostic studies are performed to confirm or rule out active Charcot neuro-osteoarthropathy (CNO) when active CNO is suspected in a person with diabetes mellitus and intact skin. (Strong; Low)
6. Perform plain X-ray of the foot and ankle in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. Ideally, bilateral plain X-rays should be performed, if possible, for comparison purposes. Best Practice Statement.
7. Perform X-rays that include the anteroposterior (AP), medial oblique, and lateral projections in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. The ankle and foot views should include the AP, mortise, and lateral projections. Ideally, standing (also known as "weight- bearing") radiographs should be performed. If a patient is not able to bear weight on their feet, non-weight-bearing radiographs are an alternative, but may not demonstrate malalignments that are more apparent in the standing position. Best Practice Statement.
8. Perform Magnetic Resonance Imaging in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with normal appearance of the plain X-rays to diagnose or exclude the disease and its activity. (Strong; Moderate)
9. If Magnetic Resonance Imaging is unavailable or is contraindicated in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy, consider a nuclear imaging scan (scintigraphy), CT (computed tomography) scan, or SPECT-CT (Single Photon Emission Computed Tomography) to support the diagnosis of active Charcot neuro-osteoarthropathy. (Conditional; Low)

10. We suggest not using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count, alkaline phosphatase, or other blood tests in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin to diagnose or exclude the disease. (Conditional; Low)

IDENTIFICATION OF REMISSION

11. Consider measurement of skin temperature of the affected and unaffected limb with serial examinations to monitor disease activity in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin. (Conditional; Low)
12. We suggest not using soft tissue oedema alone to determine when active Charcot neuro-osteoarthropathy is in remission. (Conditional; Low)
13. We suggest that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that active Charcot neuro-osteoarthropathy is in remission. (Conditional; Low)
14. We suggest that frequency of appointments for assessing disease activity in active Charcot neuro-osteoarthropathy should depend on specific factors such as fluctuation in oedema volume, co-morbidities, the risks associated with treatment and recovery, access to assistance with home treatment needs, and a person's progress and recovery. (Conditional; Low)

TREATMENT

15. Use a non-removable knee-high device to immobilise and offload the foot to promote remission of the disease, and prevention or progression of deformity in a person with active Charcot neuro-osteoarthropathy and intact skin. (Strong; Low)
16. Consider using a total contact cast in the treatment of active Charcot neuro-osteoarthropathy with intact skin in a person with diabetes mellitus. A knee-high walker rendered non-removable can be considered as a second choice in order to immobilise and offload the foot. (Conditional; Low)
17. A removable knee-high device worn at all times can be considered as the third treatment choice in a person with diabetes mellitus, active Charcot neuro-osteoarthropathy and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated. (Conditional; Low)
18. We suggest not to use a below the ankle offloading device (e.g. surgical shoe, postoperative sandal, custom moulded shoe, or slipper cast) in the treatment of active Charcot neuro-osteoarthropathy and intact skin, given the inadequate immobilisation of the diseased bone and joints, and limited off-loading capacity. (Conditional; Low)
19. Treatment with a knee-high offloading device should be considered as soon as possible once the diagnosis of active Charcot neuro-osteoarthropathy is considered. (Strong; Low)
20. In a person with active Charcot neuro-osteoarthropathy who is being treated with a knee-high device, we suggest using assistive devices to reduce weight-bearing on the affected limb. (Conditional; Low)

21. Do not use alendronate, pamidronate, zoledronate, calcitonin, PTH, or methylprednisolone as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin. (Strong; Moderate)
22. We suggest not to use denosumab as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin. (Conditional; Low)
23. We suggest to evaluate the need for vitamin D and calcium supplementation in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin during the phase of fracture healing, in doses according to (inter)national guidelines on supplementation in persons at risk for vitamin D deficiency and/or those with insufficient calcium intake. (Conditional; Low)
24. In a person with active Charcot neuro-osteoarthropathy and intact skin, and with instability of foot and ankle joints, and/or deformity with a high-risk of developing ulcer in the offloading device, or pain that cannot be sufficiently stabilized in a total contact cast or a non-removable knee-high device, we suggest that surgical intervention should be considered. (Conditional; Low)

PREVENTION OF RE-ACTIVATION

25. Footwear and/or orthoses that best accommodate and support the shape of the foot/feet and ankle to help prevent re-activation of Charcot neuro-osteoarthropathy (CNO) are recommended in a person with diabetes mellitus, intact skin, treated for active CNO with an off-loading device and who is now in remission. (Strong; Moderate)
26. When deformity and/or joint instability is present, in order to optimise plantar pressure distribution, below the knee customized devices should be used for additional protection in a person with diabetes mellitus, intact skin, treated for active Charcot neuro-osteoarthropathy who is now in remission. (Strong; Moderate)

INTRODUCTION

According to current insights, Charcot neuro-osteoarthropathy (CNO) is viewed as an inflammatory process in persons with peripheral polyneuropathy which results in injury to bones, joints, and soft tissues. Most commonly, CNO occurs in people with diabetes mellitus and involves the foot and ankle although it can occur in anyone with peripheral neuropathy. The soft tissue and osseous injury in individuals with neuropathy may result in distortion of the architecture of the foot and ankle and long-term deformity because of fractures, dislocations, and fracture-dislocations. The true incidence and prevalence of CNO in diabetes mellitus are unknown, largely because the absence of pain from peripheral neuropathy often impacts the timing of presentation to healthcare providers. Previous studies of several populations have reported prevalence rates ranging from 0.04% of patients with diabetes mellitus at seven foot care specialist centres in England (1), to 0.3% of patients with diabetes mellitus at a regional referral center in Ireland (2), to 0.53% of all people with diabetes mellitus in a national registry study in Denmark (3). The International Diabetes Foundation has estimated that 537 million adults worldwide were living with diabetes in 2021. Using a prevalence of 0.3%, this estimates that approximately 1.6 million people worldwide are living with CNO, with an annual incidence of 160,000 new cases per year (4). To put this in a global perspective, in 2020, the estimated number of new cases of melanoma per year (320,000) were only twice that of CNO, and the new cases of Hodgkin's lymphoma (83,000) were half of CNO (5).

Numerous studies have found that patient-reported health related quality of life is negatively impacted by CNO (6-9). Furthermore, after resolution of the inflammatory phase CNO can result in permanent deformity of the foot and/or ankle. Bone and joint deformities, as a consequence of active CNO, predispose to ulceration and infection, both of which significantly increase the risk of major lower extremity amputation. Studies have identified a six to 12 times increased risk of major amputation in individuals with a foot ulcer that is the consequence of a CNO deformity as compared to those without an ulcer (10, 11). A major amputation can have a profound impact on the individual, their families and society. In many cases, people who have undergone major amputation can no longer work, and this has financial consequences for the individual and their families (12). In addition to the impact on quality of life, a recent study collected data from studies published following 2007 and calculated a pooled mean five-year mortality of 29% in patients with CNO (13).

Improved understanding of the pathophysiology of CNO has occurred over the past two decades. It is assumed that some form of trauma, either perceived or not perceived (14), provokes an acute inflammatory response in the foot and/or ankle of persons with peripheral neuropathy. Disproportionate release of proinflammatory and anti-inflammatory cytokines results in activation of nuclear factor-κB (NF-κB) via the receptor activator of nuclear factor-κβ ligand-(RANK-L) pathway, which stimulates osteoclastogenesis (15, 16). In the inflamed foot, there is targeted recruitment, proliferation and differentiation of osteoclastic precursors into highly aggressive osteoclasts with enhanced resorbing activity in response to RANKL and TNF-α (17, 18). This inflammatory process, in combination with the mechanical forces applied during ambulation on a neuropathic foot, can lead to disruption or weakening of ligaments, joint dislocations and/or fractures of the foot/ankle. Another important component of the pathophysiology of active CNO involves the potential role of genetics.

Genes of the OPG/RANKL/RANK axis and their single nucleotide polymorphisms are possibly additional risk factors for the development of CNO (19-21).

At the current time there are uncertainties about diagnostic criteria, optimal treatment methods, pharmacologic intervention, monitoring, and identification of remission of CNO. The aim of this new guideline of the International Working Group on the Diabetic Foot (IWGDF) on CNO is to provide evidence-based recommendations on the diagnosis and management of active CNO of the foot with intact skin in persons with diabetes mellitus. This guideline also includes a rationale of how we came to each recommendation based on our systematic review of the literature which is published in parallel (22), together with a consideration of the benefits and harm, patients' values and preferences, and the costs related to each intervention. We also propose an agenda for future research. This guideline on CNO is part of the IWGDF guidelines on the prevention and management of diabetic foot disease (23-29).

TARGET POPULATION AND TARGET AUDIENCE

The primary target population of this guideline is persons with diabetes mellitus and active CNO, with intact skin. The primary target audience of this guideline are all health care professionals who are involved in the diagnosis and treatment of persons with CNO and diabetes mellitus.

BACKGROUND: DEFINITIONS AND TERMINOLOGY

The following section is a background summary on the definitions of the disease and the terminology used for the purposes of this guideline. Due to insufficient high-quality evidence this section on definitions is primarily based on expert opinion.

Charcot neuro-osteoarthropathy: CNO is an inflammatory process in persons with diabetes mellitus and neuropathy which results in injury to bones, joints, and soft tissues.

Active Charcot neuro-osteoarthropathy: Active CNO is the presence of a red, warm, swollen foot with osseous abnormalities on imaging in a person with diabetes mellitus and neuropathy. During the course of the disease, as long as there are signs of inflammation in the affected foot, the CNO is presumed to be "active."

Charcot neuro-osteoarthropathy in clinical remission: The absence of clinical signs of inflammation, with or without deformity, and radiographic consolidation of fractures, if present, on plain X-ray. Remission is synonymous with the "inactive" stage of CNO.

Re-activation of Charcot neuro-osteoarthropathy: A repeat "episode"/ return of symptoms in the ipsilateral foot after resolution of the original active CNO event. If active CNO develops in the contralateral foot, that should be considered a "new" CNO event and not re-activation.

Stage 0 active CNO: A person with diabetes mellitus and neuropathy who presents with clinical signs of active CNO and normal plain X-rays. In this stage, plain X-rays are considered normal but demonstrable osseous abnormalities will be present on Magnetic Resonance Imaging (MRI) (30, 31).

Offloading: The relief of mechanical stress (pressure) from the bones and joints of the affected foot during standing or walking. For purposes of this guideline, offloading should not be interpreted as complete non-weightbearing.

The recommendations in this guideline are focused on the individual with active CNO and intact skin. During the course of the disease, as long as there are signs of inflammation in the affected foot, the CNO is presumed to be "active". As will be further discussed in this document, there is no "gold standard" test to diagnose active CNO. Therefore both clinical signs of inflammation as well as signs of bone or joint injury/abnormalities on imaging studies such as plain X-ray or MRI have to be present in order to make a definitive diagnosis. Remission is synonymous with the inactive stage of CNO. As discussed below, it usually takes several months of offloading/immobilization before the clinical signs of active CNO have resolved and the fractures have healed. If at that stage offloading therapy is stopped and the patient starts walking in inappropriate footwear, there is a chance of reactivation of the disease process with risk of development of new fractures or worsening of an existing deformity. For this reason, we choose the terminology 'in remission' instead of 'healed'.

METHODS

For these guidelines, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology was followed. The GRADE System is structured by the development of clinical questions in the PACO (Population, Assessment, Comparison, Outcome) and PICO (Population, Intervention, Comparison, Outcome) format, systematic review, and assessment of the available evidence. After assessment of the evidence, recommendations are developed with their supporting rationale (32, 33). In specific situations when reviewers were authors of papers under consideration, the authors recused themselves to reduce the risk of bias in assessments and selection of articles.

To begin this process, an international, multidisciplinary working group of experts in this field (the authors of this guideline) was installed by the IWGDF Editorial Board. The working group developed the clinical questions to be investigated after consultation with external experts from diverse geographic locations as well as a patient representative. Critically important outcomes for clinical questions focused on intervention were formulated and voted upon by the working group members as deemed necessary. Subsequently, PACOs and PICOs were created which were reviewed by the IWGDF Editorial Board.

Next, a systematic review of the literature was performed to address the clinical questions. The systematic review for this guideline is published as a separate document (22). Studies that reported on CNO patients with a foot ulcer were excluded as this may affect diagnosis and treatment, unless the data of patients without an ulcer were reported separately or when this was unlikely to influence the outcomes. For each clinical question the certainty of evidence was graded and then rated as "high," "moderate," or "low" (34).

Finally, recommendations were formulated to address each clinical question based on the evidence from the systematic review. Using the GRADE system, rationale was provided for how we determined each recommendation. The rationale was based on the evidence from the systematic review (22) and expert opinion when evidence was not available. The strength of each recommendation was graded as "strong" or "conditional". "Best Practice Statements" were developed when the certainty of the desirable effects of an intervention clearly outweighed its undesirable effects in the situations where the available evidence was indirect (35). The recommendations and corresponding rationales were reviewed by the same international external experts and IWGDF Editorial Board who initially reviewed the PACOs and PICOs. A summary of judgements table was created for each intervention recommendation based on the GRADE approach (34) (See Appendix 1). The framework for each judgement table included a column for criteria, judgments, and impact of the intervention. For a more detailed description of the methodology and writing of these guidelines, please refer to the IWGDF Guidelines development and methodology document (36).

CONFLICT OF INTEREST STATEMENT

The Charcot guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and these can be found at *www.iwgdfguidelines.org*. No company was involved in the development or review of the guideline. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting in-person.

RECOMMENDATIONS

In this guideline, the recommendations for the diagnosis and treatment of active CNO in persons with diabetes mellitus and intact skin are discussed based on the following categories: Diagnosis, Identification of Remission, Treatment, and Prevention of Re-Activation. First, we formulated clinical questions and subsequently using the PACO and PICO format a systematic review of the literature was performed based on these clinical questions (22). We identified a total of 37 studies; 14 studies relevant to Diagnosis, 18 for Treatment and 5 studies for Identification of Remission. We did not identify studies that met inclusion criteria for Prevention of Re-activation. After completion of the systematic review, evidence statements were developed based on the available literature (22). We subsequently formulated the following 26 recommendations.

DIAGNOSIS

Clinical Question: In a person with diabetes mellitus and intact skin, in whom active Charcot neuro-osteoarthropathy (CNO) is considered, what is the accuracy of clinical findings to diagnose active CNO?

Recommendation 1: Always consider active Charcot neuro-osteoarthropathy in a person with diabetes mellitus, neuropathy and intact skin when there are clinical findings of an increase in temperature, oedema, and/or redness of the foot, compared to the contralateral foot. Best Practice Statement.

Recommendation 2: Consider using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected Charcot neuro-osteoarthropathy with intact skin, using a standardised approach to the measurement of temperatures to allow for more accurate comparison over time. (Conditional; Low)

Recommendation 3: When using infrared thermometry to measure skin temperature of the feet in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin, consider calculating temperature difference between both legs, using the highest temperature on the affected foot or ankle in comparison with the same anatomic point on the contralateral extremity. (Conditional; Low)

Recommendation 4: In a person with diabetes mellitus with bilateral active Charcot neuro-osteoarthropathy (CNO) and intact skin or with unilateral CNO and intact skin in the absence of the contralateral limb, ascending temperature gradients (toe-knee) may be useful for comparison over time. Best Practice Statement

Recommendation 5: Initiate knee high immobilization/offloading promptly while further diagnostic studies are performed to confirm or rule out active Charcot neuro-osteoarthropathy (CNO), when active CNO is suspected in a person with diabetes mellitus and intact skin. (Strong; Low)

Rationale: Active CNO should always be suspected when a person with diabetes and neuropathy presents with a unilateral red, warm, swollen foot, intact skin, and no history of ulceration. CNO left untreated presents a high risk of developing bone fractures, dislocations, deformity, ulceration, infection

and even amputation with major lifelong consequences (37, 38). Clinical signs of inflammation, such as hyperemia, increased foot skin temperature and oedema should be present when the diagnosis of active CNO is considered, after exclusion of other diagnoses such as infection, gout, and deep venous thrombosis. Pain may be absent or relatively mild due to sensory neuropathy (39). However, there are some individuals who present with more severe pain despite having peripheral neuropathy. Based on these arguments the Guideline committee formulated a Best Practice Statement, i.e. that the disease should always be suspected in a hot swollen foot in a person with diabetes mellitus due to the severe consequences that may develop if this disease is left untreated such as fracture, dislocation, development of deformity, ulceration, infection and loss of limb.

In healthy individuals there is a symmetry in skin foot temperature, but in the presence of inflammation this symmetry is lost and the temperature difference between both feet can be a more reliable measure than an isolated, unilateral measure (40). In one retrospective study in people with active CNO, the site of maximum skin temperature difference between the affected and unaffected foot correlated to the radiographic imaging at diagnosis in 92% of cases (and during follow-up in 72% of cases) (35). When local radionucleotide uptake was measured with quantitative bone scans in individuals with active CNO, the difference in local skin temperature correlated with this uptake (41). This suggests that skin temperature can be viewed as a proxy measure of the underlying active disease process in those with CNO (41). Initially this temperature difference was assessed by palpation, but in recent decades several studies reported the use of handheld dermal infrared thermometry devices to diagnose CNO. Our systematic review could not identify studies demonstrating the diagnostic accuracy of such measurement when using radiological imaging and/or scintigraphy as a comparator in persons with active CNO (22). We identified one retrospective case series of patients with diabetes that compared foot skin temperature measurements using dermal infrared thermometry in patients with active CNO and patients with asymptomatic sensory neuropathy (42).

An increase in skin temperature of 2° Celsius or 4° Fahrenheit (which is actually 2.2° Celsius) of the involved foot compared to the same location on the uninvolved foot has been used as a diagnostic threshold for active CNO in several publications (43). Our systematic review could not identify studies demonstrating the diagnostic accuracy of such measurement when using imaging as a comparator for the diagnosis of active CNO, however, there is evidence in regard to elevated temperature as a sensitive indicator of inflammation in diabetic feet and a precursor to ulceration (22). In the absence of other signs and symptoms of inflammation (i.e. redness and swelling), an isolated increase in foot temperature may not always be indicative of active CNO and should be interpreted in the context of other clinical findings (44, 45). Although an essential part of the diagnostic evaluation, isolated elevation of foot skin temperature is not sufficient to diagnose or rule out active CNO. Consequently, unilateral asymmetric temperature elevation is sensitive but not specific in diagnosis active CNO.

There is no evidence to define which method/protocol for infrared skin temperature measurement is most accurate to diagnose active CNO and where, i.e. on which anatomical locations, these measurements should be performed. A recent cohort study of 32 people with active CNO reported good intra- and inter-rater reliability of skin foot temperatures measured by infrared thermometry, but did not address uncertainties around the diagnostic accuracy of this technique (46). There is uncertainty about the accuracy of existing thermometers (47) and if contact or non-contact thermometry devices

should be preferred (48). There is limited information on normative values of skin temperature in the neuropathic foot, and whether current thermometry devices are valid for these temperature ranges (45), and factors such as the influence of ambient temperature and the acclimatization time that is needed after the footwear and socks are removed. The presence of concomitant ulceration and/or infection can also limit the usefulness of foot temperature to monitor CNO (35). The use of the uninvolved foot as a comparator can probably overcome some, but not all, of these problems, because the contralateral foot can be affected by diseases that influence skin temperature. The presence of bilateral active CNO disease will reduce the reliability of the temperature difference.

Despite the uncertainties, infrared thermometry currently seems to be preferable to assess foot skin temperature in order to calculate the temperature difference between both feet as this is objective and measurable (49). In the presence of bilateral foot disease or in the absence of the contra-lateral limb (i.e., amputation), calculating such a temperature difference is not feasible or possible. In these circumstances the increase in temperature due to the inflammatory process can probably be detected by comparing the distal temperature in the foot to the more proximal temperature in the lower and upper leg. We could not identify any studies that evaluated ascending temperature gradients in our systematic review. As detecting a locally elevated temperature is an important component in diagnosis and follow up, the Working Group suggests to measure ascending temperature gradients (toe-knee in the aforementioned circumstances. All members of the Working Group use this approach when bilateral measurements are not possible, but studies supporting this approach are lacking and therefore we made this a Best Practice Statement. Infrared thermometry is a relatively simple, inexpensive, and objective method to monitor changes over time, as discussed in the section Identification of Remission. To allow for more accurate comparison between visits we advise a standardized approach regarding acclimatization period, number and location of skin sites to be tested, and with which temperature measurement technique should be used. Finally, in the absence of access to quantitative tools that assess foot temperature, clinicians should rely on using hand palpation to assess temperature difference. The benefits of assessing temperature, either with handheld thermometry devices or by palpation, are not associated with any risk of harm to the patient. We recognize that equity and feasibility can be impacted because not everyone treating patients with CNO will have access to a handheld device. Health equity, as it relates to this guideline, is when everyone has a fair and equal opportunity to attain their highest level of health despite their social, economic, cultural or geographic differences. Finally, we recognize that selection bias may be present in the studies which report on the efficacy of temperature assessment of handheld thermometry devices due to the variability of the studies.

Knee high immobilization/offloading should be initiated immediately when active CNO is suspected in a person with diabetes mellitus and intact skin. Early detection, immobilisation and reduced weight-bearing on the diseased foot has been shown to minimize development of deformity (37, 38). Evidence for this recommendation is low but withholding offloading therapy in a person with a suspected serious disease puts this person unnecessarily at risk for the dire consequences of untreated disease which is why we graded this as "Strong". Knee high immobilization should be employed immediately while further diagnostic testing is performed to confirm or rule out presence of the disease.

In summary, active CNO can be diagnosed when there are clinical signs of inflammation in combination with abnormalities on imaging. If such imaging is not immediately available, immediate

immobilization/offloading with a below knee-high offloading device should be initiated while awaiting further diagnostic testing (discussed in the next section of this guideline) in order to prevent further progression of the disease. Offloading will be discussed in more detail in the "Treatment" section of this guideline. Thorough clinical examination, high index of suspicion, imaging, and prompt offloading are paramount to recognizing and treating active CNO.

Clinical Question: Which imaging modalities have sufficient accuracy to render the diagnosis of active Charcot neuro-osteoarthropathy (CNO) more likely in a person with diabetes mellitus and intact skin in whom the diagnosis of active CNO is considered?

Recommendation 6: Perform plain X-ray of the foot and ankle in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. Ideally, bilateral plain X-rays should be performed, if possible, for comparison purposes. Best Practice Statement.

Recommendation 7: Perform X-rays that include the anteroposterior (AP), medial oblique, and lateral projections in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy. The ankle and foot views should include the AP, mortise, and lateral projections. Ideally, standing (also known as "weight- bearing") radiographs should be performed. If a patient is not able to bear weight on their feet, non-weight-bearing radiographs are an alternative, but may not demonstrate malalignments that are more apparent in the standing position. Best Practice Statement.

Recommendation 8: Perform Magnetic Resonance Imaging in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with normal appearance of the plain X-rays to diagnose or exclude the disease and its activity. (Strong; Moderate)

Recommendation 9: If Magnetic Resonance Imaging is unavailable or is contraindicated in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy, consider a nuclear imaging scan (scintigraphy), CT (computed tomography) scan, or SPECT-CT (Single Photon Emission Computed Tomography) to support the diagnosis of active Charcot neuro-osteoarthropathy. (Conditional; Low)

Rationale: In a person with suspected active CNO, plain X-rays of the foot and ankle should be obtained in order to diagnose the disease as involvement of bones and/or joints play a central role. Weight- bearing radiographs are preferred, as they may detect dynamic abnormalities, such as joint mal-alignment, joint subluxation, and/or fracture displacement that may not be apparent on non-weight-bearing radiographs (50). The three standard foot views (antero-posterior (AP), medial oblique, and lateral) and three standard ankle views (AP, mortise and lateral) provide sufficient radiographic evaluation of the osseous anatomy. For an accurate diagnosis, all potentially involved bone and joint structures should be adequately visualized using such a standardized approach. Based on these arguments, we made the two Best Practice Statements as formulated above. We do acknowledge that weight-bearing radiographs are sometimes not feasible due to limited mobility of the person involved or when the risk of further displacement of joints and/or bones is probably excessive. In such circumstances, non-weight bearing plain X-rays can be obtained. Table 1 describes the typical imaging abnormalities that can be observed in active CNO on plain X-ray.

Table 1: Findings on Radiographs and MRI

Modality	Active stage of CNO	Remission stage of CNO
Radiographs (XR)		
	• Diffuse soft tissue swelling • Joint effusion (s) • Reduced bone density • Cortical erosions • Fracture (s) • Fracture fragments/ Calcific debris in soft tissues • Radio-opaque foreign body may be seen • Subluxation or dislocation (s) • Disorganization of articulation (s) • Background XR findings of remission stage may be present	• Decreased or resolved soft tissue swelling • Improved/ Restored / Increased bone density • Cortical and subcortical cysts • Osteosclerosis and bony consolidation • Calcific debris in soft tissues • Disorganization of articulation (s) • Radio-opaque foreign body may be seen
CT scan		
	• Above described XR findings are more conspicuous • Joint effusions of small joints better seen • Fluid collection or tenosynovitis may be seen at the areas of bony destruction • Skin ulceration may be present • Plantar muscle fatty atrophy may be seen. • Dual-energy CT shows bone marrow oedema at CNA sites	• Above described XR findings are more conspicuous • Decreased joint effusion, tenosynovitis, or fluid collection • Plantar muscle fatty atrophy may be seen.
MRI		
	• Diffuse soft tissue swelling and fascial oedema • Denervation oedema-like signal on fluid-sensitive imaging sequences (T2W or STIR- short tau inversion recovery) and/or fatty replacement on T1W imaging of foot muscles • Increased signal and/or thickening of the posterior tibial nerve • Joint effusion (s) and tenosynovitis • Increased fatty marrow related to osteopenia • Cortical erosions as loss of T1W signal intensity and bone marrow oedema on fluid-sensitive sequences. Overlying cartilage erosions are common • Multiple (>2) hindfoot bones are typically involved	• Decreased or resolved soft tissue swelling • Decreased bone marrow oedema • Cortical and subcortical cysts • Better defined bony hypointense cortical margins • Calcific debris / chronic fracture fragments / necrotic-sclerotic bones as hypointense signal on all sequences • Disorganization of articulation (s) • Spring ligament / plantar fascial /tibialis posterior tears, etc. • Increased signal and/or thickening of the posterior tibial nerve • Decreased soft tissue and bone perfusion on dynamic contrast enhanced MRI

- Subchondral fracture (as subchondral dark signal in a cloud of oedema on fluid sensitive T2W or STIR sequence) and other cortical fracture (s)
- Fracture fragments
- Subluxation or dislocation (s)
- Disorganization of articulation (s)
- Skin ulcer or devitalized / gangrenous soft tissue better seen as non-enhancing soft tissue on contrast-enhanced MRI
- Increased soft tissue and bone perfusion on dynamic contrast enhanced MRI
- Background MRI findings of remission stage may be present

As has been shown in several studies, patients with suspected active CNO based on the clinical grounds (i.e. warm, swollen foot) can exhibit normal appearing plain X-rays, however with clear abnormalities on more advanced imaging confirming involvement of bones and/or joints of the affected feet(37, 51-53). These patients can subsequently progress to overt fractures (37) and progressive malalignments. Such abnormalities, therefore, are also sufficient to support the diagnosis of active CNO, after exclusion of other causes of acute bone and/or joint injury. MRI is most studied in this domain (37, 51-54), and this advanced imaging technique is not only able to detect bone/ joint abnormalities but also signs of inflammation and/or remission in and around bones and joints with good to excellent sensitivity and specificity in various disease states (55). In our systematic review, MRI demonstrated high sensitivity but unknown specificity for the diagnosis of active CNO in individuals with clinical suspicion, intact skin, and normal radiographs although these studies were from one center only (37, 51-53). Because of lack of data on specificity of MRI to identify active CNO, but high values of specificity reported in other inflammatory conditions to detect inflammation, we rated the certainty of evidence as moderate. Due to the fact that not diagnosing and treating the disease can have deleterious consequences, we made a Strong recommendation to perform MRI in the event of normal plain X-rays and clinical suspicion of active CNO, in order to diagnose or exclude the disease.

There are several clinical scenarios where MRI cannot be performed: it can be contraindicated (for example, a patient with an MRI-unsafe pacemaker or MRI being not available at the medical facility) or too costly for the patient with suspected active CNO and negative X-rays. In these situations, other advanced imaging modalities can be performed as feasible, such as a nuclear imaging scan (scintigraphy) or CT scan to support the diagnosis of active CNO (56-58). In our systematic review, we identified three studies that assessed the findings of nuclear imaging in persons with suspected active CNO and intact skin (56-58). In a retrospective interrupted time-series non-controlled cohort study, 99 mTc-hydroxymethylene diphosphate three-phase bone scintigraphy was performed in 148 patients with suspected active CNO and had a high (89%) sensitivity but limited (58%) specificity (57). A non-controlled study of 18F-FDG PET/CT scanning in 25 patients with suspected active CNO demonstrated increased uptake in all patients with suspected active CNO (58). We recognize the limited specificity

does not confirm the presence or absence of the diagnosis of active CNO, however a negative bone scan, SPECT/CT or negative PET/CT would be strong evidence against the diagnosis of active CNO. The diagnostic accuracy of MRI has not been compared with nuclear medicine scintigraphy. We have chosen MRI as first option after plain X-ray, as this imaging technique provides more information to support or exclude the diagnosis of CNO due to better soft tissue contrast, and probably has, in our opinion, a better specificity.

When MRI is not available or not possible, we recommend other modalities, such as nuclear imaging scan or CT scan for further assessment. Nuclear imaging combined with CT (SPECT-CT) may provide more utility than either nuclear imaging or CT alone due to improved spatial and contrast resolution, although this has not been studied specifically in active CNO in a case-controlled design. If the diagnosis is missed because these alternative investigations are not performed and the active CNO is not treated adequately, there is a substantial chance that the disease will progress, leading to worsening deformity and increased morbidity. When active CNO is considered and the radiographs are normal, immobilization/offloading with preferably, non-removable below knee- high offloading device should be initiated immediately while advanced imaging results are pending. If these investigations cannot be performed, the patient should be treated as having the active disease until all symptoms have disappeared, but such a pragmatic approach may also result in unnecessary treatment and increased financial and non-financial burden in persons not having the disease.

Possible adverse effects of X-rays and CT are increased exposure to ionizing radiation for the individual and the environment. CT scanning involves more exposure than radiographs and increased/repetitive exposure over time can increase the risk for long term health effects. However, extremities are relatively radioresistant (59-61). Weight-bearing CT is also available to detect malalignment of the foot and ankle, although not as readily available as conventional CT. Nuclear imaging utilizing radioactive tracers has minimal risks and these risks would be limited to very rare allergic reactions and radiation exposure risk from small doses of ionizing radiation. The disadvantages of advanced imaging are that they are less readily available, incur higher costs compared to the standard radiographs, and can lead to a substantial financial burden for affected individuals and the health care system. However, advanced imaging including MRI has become more affordable and accessible recently, especially in high income countries, resulting in more accuracy in diagnosing and excluding CNO. Although costs-effectiveness data are lacking, it is therefore recommended that these imaging techniques, in particular MRI as the first step, should be considered when plain radiographs are normal.

Clinical Question: Which blood tests have sufficient accuracy to make the diagnosis of active Charcot neuro-osteoarthropathy more likely in a person with diabetes mellitus and intact skin?

Recommendation 10: We suggest not using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count, alkaline phosphatase, or other blood tests in a person with diabetes mellitus and suspected active Charcot neuro-osteoarthropathy with intact skin to diagnose or exclude the disease. (Conditional; Low)

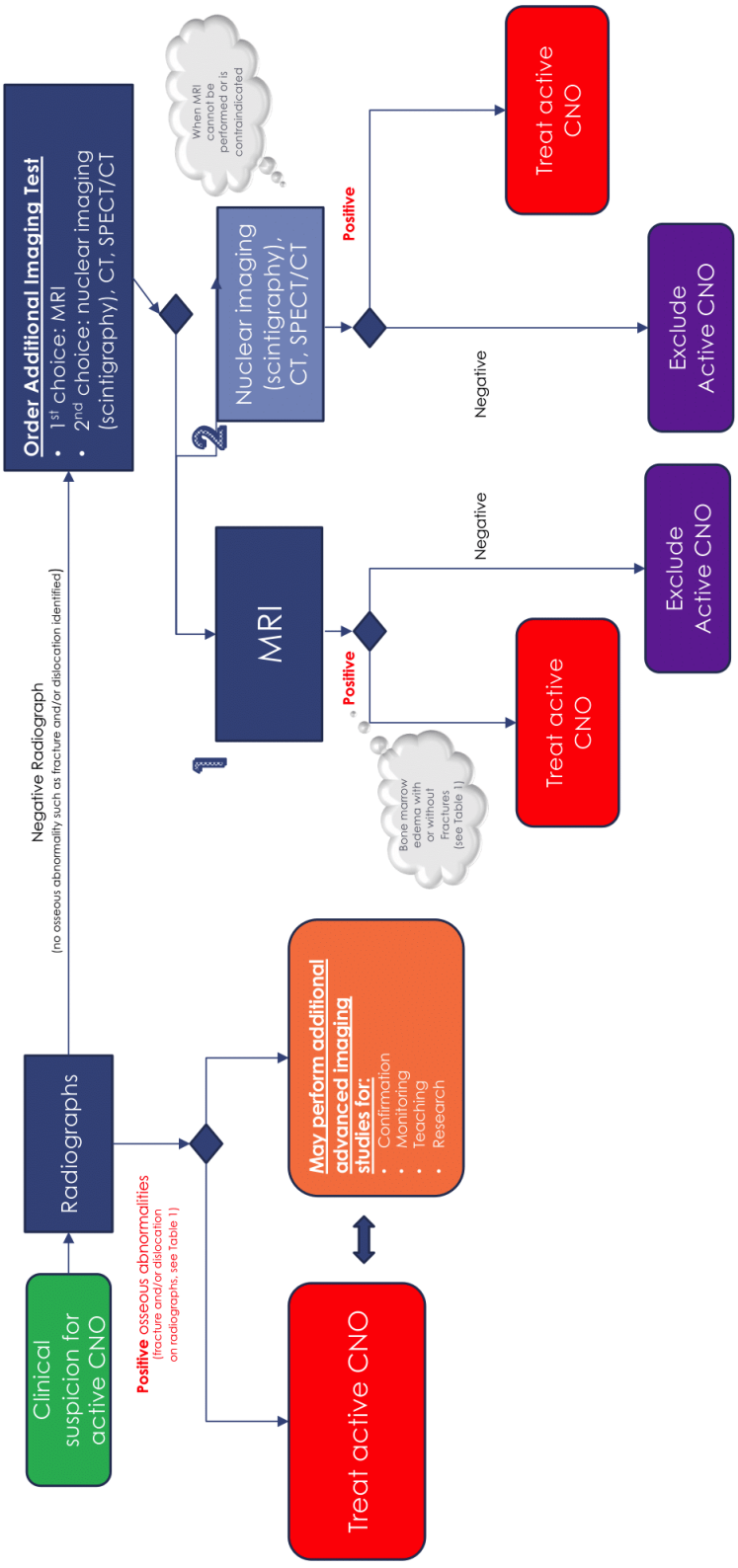
Rationale: Blood tests such as measurements of serum inflammatory markers (CRP, ESR and WBC) or alkaline phosphatase are often obtained in the setting of active CNO. Our systematic review identified five observational studies that measured either CRP, ESR, and/or alkaline phosphatase in patients with

active CNO and intact skin (22). Five of the studies that we identified measured CRP (62-66), three measured ESR (63, 64, 66), three measured white blood cell count (WBC) (63, 65, 66) and three measured alkaline phosphatase (62, 63, 67). All studies were of low quality and at high risk of bias.

In the studies included for review, serum CRP ranged from normal to as high as 324% above the reference range (< 5 mg/l) (62-66). ESR in active CNO patients with intact skin ranged from a mild increase (5%) to as high as 350% above the reference range (<20mm/h) (63, 64, 66). WBC was reported normal (63, 65) in two studies (reference range < 10^9/L) and mildly elevated (10% above reference range) in one study (66). Serum alkaline phosphate was found to be normal in active CNO in two studies (63, 67). Serum bone-specific alkaline phosphatase was 21% higher in patients with active CNO compared to control participants with diabetes mellitus however this elevation was not statistically significant (62).

In conclusion, we did not identify evidence to support the use of CRP, ESR, WBC or alkaline phosphatase in diagnosing active CNO. Our conclusion was based on the wide range of values reported in these studies with high imprecision. The quality of evidence was low and for this reason we graded the recommendation as "conditional". Although the aforementioned systemic inflammatory markers can be elevated in active CNO, probably due to the underlying sterile inflammation in the foot, other diagnoses should also be considered (68). The recommendations on diagnosis of active CNO are summarized in Figure 1.

Figure 1: Flow chart for active CNO diagnosis



IDENTIFICATION OF REMISSION

Clinical Question: Which clinical examinations and imaging techniques can be used to ascertain remission of Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin who has been treated for the disease?

Recommendation 11: Consider measurement of skin temperature of the affected and unaffected limb with serial examinations to monitor disease activity in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin. (Conditional; Low)

Recommendation 12: We suggest not using soft tissue oedema alone to determine when active Charcot neuro-osteoarthropathy is in remission. (Conditional; Low)

Recommendation 13: We suggest that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that active Charcot neuro-osteoarthropathy is in remission. (Conditional; Low)

Recommendation 14: We suggest that frequency of appointments for assessing disease activity in active Charcot neuro-osteoarthropathy should depend on specific factors such as fluctuation in oedema volume, co-morbidities, the risks associated with treatment and recovery, access to assistance with home treatment needs, and a person's progress and recovery. (Conditional; Low)

Rationale: Our systematic review identified five studies that evaluated different types of monitoring techniques to define remission of active CNO (49, 54, 69-71). All were observational studies with high risk of bias. Two studies reported the predictive value of using infrared thermometry to monitor and identify remission based on clinical grounds, following the same protocol but using different thermometry devices (49, 70). In one study, the site of maximum skin temperature difference between the affected and unaffected foot was found to correlate to the radiographic imaging at diagnoses in 92% of cases and during follow-up in 72% of cases (49). Another prospective observational study provided a narrative report showing agreement between a temperature difference (4°F/ 2°C) and radiographic findings for identifying remission in active CNO (70).

There were three studies that evaluated the use of MRI to identify remission in active CNO, and also reported that they assessed skin temperature (54, 69, 71). The first study was an open label cohort study and compared 3-monthly dynamic MRI scans, with gadolinium contrast medium, with the clinical healing defined as the combination of a temperature difference <1°C and difference in the circumference at the midfoot and ankle level <1 cm (as measure of swelling) (69). The authors reported a 90% agreement between clinical and MRI findings. However, in 23% of patients clinical healing (absence of inflammation) preceded MRI healing by 3-6 months. The authors did not analyze the results of skin temperature separately. Unfortunately, the second and third MRI studies could not provide any useful evidence to help answer this clinical question and support subsequent recommendations (54, 71).

We recommend that providers use infrared thermometry to monitor active CNO and identify remission based on the balance of risks and harms, confidence in the results, feasibility, acceptability, and equity. Measurement of temperature is of no harm and no risk to the patient and is a safe, low/no cost

examination tool that is relatively easy to perform. The higher the temperature difference between the affected and unaffected foot the greater the likelihood of ongoing disease activity and conversely, the lower the temperature difference the greater the likelihood that the CNO is going into remission. At this time, there is insufficient evidence to recommend a specific temperature cut-off at which point remission occurs. As such we recommend that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that the active CNO is in remission. Both the provider and patient must recognize that the transition from active CNO to remission may take many months. The advantages of infrared skin temperature measurement over radiological investigations to monitor active CNO are that it is cheaper, quicker, more readily available, non-invasive, and there are no safety considerations. The protocols for temperature measurements in these studies allowed for an acclimatisation period of 15 minutes, which is time consuming.

There is evidence that when the limb with active CNO is offloaded, the amount of leg/foot oedema reduces. In our systematic review we identified two studies which compared objective assessment of soft tissue oedema to radiological findings and in another study soft tissue oedema was assessed subjectively (54, 69, 71) . From these studies it was not possible to identify whether there is a relationship between clinical assessment of oedema and radiological findings to ascertain remission in active CNO. Based on expert opinion, we recommend that subjective or objective assessment of soft tissue oedema may contribute to a complete patient assessment to identify remission in active CNO, and we graded the recommendation as "Conditional". There is no evidence to support a recommendation on a specific protocol for measuring soft tissue oedema in active CNO. However, we would advise that a standardised approach to evaluating soft tissue oedema be used to allow for more accurate comparison over time. It should be noted that the potential limitations of assessing soft tissue oedema are similar to those for temperature measurement, with the presence of bilateral foot disease, absence of contralateral limb or concurrent foot ulceration and/or infection affecting the usability and interpretation of any results. We acknowledge that remission is defined as the absence of clinical signs of inflammation and is based on clinical judgement because we cannot give absolute values to define the absence of inflammation. We recognize that in certain cases mild signs of inflammation such as oedema can persist despite radiographic consolidation.

There is no evidence to support a recommendation on the frequency of infrared thermometry or other clinical measurements to monitor the disease activity of CNO. To reflect clinical practice, we suggest that temperatures are assessed at serial visits, to coincide with appointments for cast change, or to have offloading devices checked. Usually, a shorter period between appointments is necessary in the early phase of the disease as due to reduction of oedema, the offloading device needs to be modified. Weekly clinical evaluations may be required when oedema reduction is rapid and frequent TCC changes are needed. As signs and symptoms stabilize, time between clinical evaluations can be increased up to 3 to 5 weeks. We suggest close monitoring due to the burdensome and costly effects of unnecessary treatment that would result in missing harmful effects (e.g. ulcers) that may occur if an individual in remission is not closely monitored.

We encountered two main difficulties when developing our recommendations. Firstly, the lack of a standardized clinical or radiological definition of remission of the disease, and secondly, there is currently no agreed 'gold standard' test to ascertain remission of active CNO. None of the studies we identified

in our systematic review reported the sensitivity or specificity of using skin foot temperature to identify remission, either in isolation or compared to imaging (22). For these reasons we graded the strength of our recommendations as "Conditional".

Uncertainty remains about the effectiveness of temperature assessment to monitor active CNO, and whether the different devices and protocols used influence time to remission. Different cut-off points have been used, 4◦F (which is 2.2◦C), 2◦C, and 1◦C (49, 70). There is a need for high-quality studies to assess the diagnostic accuracy of temperature assessment to determine remission in CNO. Until a 'gold standard' test for identifying active CNO has been identified and validated we recommend that the findings of temperature measurement, clinical oedema, and imaging should all be considered when concluding that the active CNO is in remission. We acknowledge that occasionally individuals will present in remission who have not had previous treatment.

TREATMENT

Clinical Question: Which type of offloading device should be advised to a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin and should this be accompanied with non-weight bearing advice?

Recommendation 15: Use a non-removable knee-high device to immobilise and offload the foot to promote remission of the disease, and prevention or progression of deformity in a person with active Charcot neuro-osteoarthropathy and intact skin. (Strong; Low)

Recommendation 16: Consider using a total contact cast in the treatment of active Charcot neuro-osteoarthropathy with intact skin in a person with diabetes mellitus. A knee-high walker rendered non-removable can be considered as a second choice in order to immobilise and offload the foot. (Conditional; Low)

Recommendation 17: A removable knee-high device worn at all times can be considered as the third treatment choice in a person with diabetes mellitus, active Charcot neuro-osteoarthropathy and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated. (Conditional; Low)

Recommendation 18: We suggest not to use a below the ankle offloading device (e.g. surgical shoe, postoperative sandal, custom moulded shoe, or slipper cast) in the treatment of active Charcot neuro-osteoarthropathy and intact skin, given the inadequate immobilisation of the diseased bone and joints, and limited off-loading capacity. (Conditional; Low)

Recommendation 19: Treatment with a knee-high offloading device should be considered as soon as possible once the diagnosis of active Charcot neuro-osteoarthropathy is considered. (Strong; Low)

Recommendation 20: In a person with active Charcot neuro-osteoarthropathy who is being treated with a knee-high device, we suggest using assistive devices to reduce weight-bearing on the affected limb. (Conditional; Low)

Rationale: As discussed below, there are several strong arguments that the diseased, inflamed foot in active CNO should be immobilised and offloaded in a knee-high, non-removable, device. It is important to institute immobilisation even in the absence of fractures on plain radiographs, when other imaging techniques (such as MRI) suggest active CNO. This immobilization should be started immediately once the diagnosis of active CNO is considered. Additional evidence provides guidance that a total contact cast (TCC) might be considered as first choice, and a knee-high walker that is made non-removable as second choice. Total contact casts are usually made of plaster of Paris or fibreglass that is in close contact with the entire foot and lower limb. Comparable offloading of the foot can be achieved by a prefabricated knee-high walker that immobilises the foot and can be rendered irremovable by applying a layer of cast or tie wrap around the device (72). Both devices and their insoles should be applied in such a way that they accommodate any foot deformity safely and provide pressure redistribution in order to prevent subsequent ulceration. A removable knee-high device worn at all times with an appropriate foot-device interface to reduce peak pressure (23) can be considered as the as a third treatment choice in a person with diabetes mellitus and active CNO and intact skin of the foot for whom a non-removable knee-high offloading device is contraindicated or not tolerated. A possible benefit of a removable knee-high device is that it can be removed for bathing or examination of the skin. The main disadvantage and concern when using removable knee-high devices is the potential for non-adherence to the offloading/immobilization treatment which may lead to development/progression of deformity and delayed time to remission.

As described in our systematic review, there is limited high quality evidence on which to base our recommendations (22). Our recommendations on offloading active CNO are based on a combination of the direct and indirect evidence from research where available, and expert opinion where no such evidence exists. The potential negative consequences of not initiating offloading as soon as possible once active CNO is suspected include progressive deformity and potential skin ulceration. Therefore, we made the recommendation of offloading once active CNO is suspected a "Strong" recommendation. The rationale behind offloading the foot and leg in active CNO is that increased mechanical stress plays a central role in perpetuating the underlying inflammatory disease process, resulting in progressive bone destruction, development of fracture(s) and joint dislocation. Although individuals with active CNO can present with only one fracture on plain X-ray, more advanced techniques such as MRI, SPECT/CT and PET-CT usually show that multiple bones and joints in the foot and ankle are affected (51, 56, 73). It is for this reason, that immobilisation and offloading of the complete foot and ankle is indicated. Our recommendations are in line with other guidelines on the management of individuals with high-risk non-displaced foot fractures, irrespective of the presence of diabetes in order to optimise fracture healing, prevent malalignment, non-union and progressive dislocation (74-76).

By using a knee-high device, plantar pressure and ground reactive forces are redistributed more proximally serving to offload the inflamed foot (77). Knee high devices immobilise the ankle joint and minimize the deforming effects of the lower limb muscles on the joints in the foot and ankle. There is evidence from clinical and biomedical/laboratory research that immobilisation and offloading usually results in a decrease in the clinical signs of inflammation as well as reduction in circulating pro-inflammatory markers over time (62, 64). Although immobilisation and offloading of the complete foot and ankle are indicated, patients can have difficulties in accepting and using knee-high offloading devices as they can have little or no pain, and such devices can have negative effects on mobility, autonomy,

driving, self-esteem and perception by others (78). Moreover, if not applied correctly in persons with loss of protective sensation, these devices can result in development of skin breakdown anywhere distal to the knee. A new cast associated blister or ulcer was reported in 14% of people with diabetes who were treated with a total contact cast in a recent study (79). The patient should therefore be well informed about the risks of inadequate treatment, its benefits and harms and should be supported in integrating this treatment in their daily life.

In our systematic review, we could not identify intervention studies comparing the efficacy of a non-removable with a removable off-loading device. However, in the nationwide UK survey of 219 people with active CNO, the median time to remission, defined as patient being mobile in (therapeutic) footwear, was three months longer in those treated with a removable device compared to those who had a non-removable device (80). Likewise, studies in patients with diabetes and a neuropathic foot ulcer have shown that despite intensive education, they do not wear removable offloading devices as advised, and this can contribute to delayed ulcer healing (55). Due to the absence of pain, people with active CNO may continue to walk on the diseased foot and they sometimes only seek medical help when their foot becomes so deformed or swollen that it does not fit in the shoe anymore (34). We could not identify studies on patients' preference in active CNO but one study reported that in patients with a diabetic foot ulcer, patients preferred a non-removable device once the benefits were clearly explained (66). People may therefore initially prefer a prefabricated removable device because they can take it off in situations like going to bed, driving a car, or bathing, but they should be informed about the greater expected benefit of a non-removable knee-high device in preventing deformity, shorter treatment period with consequent lower short- and long-term health care costs (55, 61). For these reasons, we graded the strength of the recommendation on the use a non-removable knee-high device, either a TCC or a prefabricated walker made non-removable, as "strong". However, we acknowledge that for this specific disease state evidence based on clinical trials is lacking.

The affected leg can be immobilised and offloaded either by a TCC or by a prefabricated knee-high walker (23). The majority of studies we included in our systematic review used TCCs as the preferred method of offloading (22). We could not find any studies that addressed our clinical question and compared treatment with TCC to prefabricated knee-high walkers on the outcome of active CNO. As discussed earlier the aim of treatment is primarily to immobilise the joints in the foot and secondly, to offload the foot by redistributing plantar pressure from ground reactive forces. It is this requirement for immobilisation that has led to the recommendation based on the expert opinion of the group that TCCs might be preferable to prefabricated walkers. The advantage of the TCC is that there is probably better immobilisation of the ankle. For instance in patients with severe ankle sprain a TCC had better overall results than an prefabricated walker (81). In addition, a TCC is applied to fit the person's limb, and each TCC is customised to accommodate deformity or significant oedema. The disadvantage of a TCC is that is needs renewal at each visit (unless it is made removable but that can result in less optimal immobilisation), is associated with higher costs, and requires expertise and therefore has a greater negative impact on equity. It is likely that patients value both TCC and knee-high walkers as equally unpleasant interventions, although we could not identify in our systematic review studies on the impact of quality of life of the different treatment modalities. In summary, there is some indirect evidence supporting the use of TCC as first choice in the treatment of active CNO and a non-removable walker as second choice. In particular when costs or equity play an important role or specific expertise is lacking

walkers, made non-removable, can be preferable, but future studies are needed in this area. Therefore, we graded the strength of our recommendation as "conditional".

Treatment with a non-removable knee-high off-loading device should be started immediately when active CNO is suspected, and continued unless an alternative diagnosis is made, in order to prevent the development of deformity (82). The importance of early immobilisation and reduced weight-bearing on the diseased foot is highlighted by two studies of Chantelau and co-workers. In these retrospective observational studies with a high risk of bias, these authors reported that patients diagnosed with Charcot stage 0 who were treated early (i.e. those without fracture on plain X-ray before TCC treatment) rarely developed a subsequent deformity in marked contrast to those diagnosed and treated in stage 1 (i.e. those with a fracture on plain X-ray) (37). In the second study, the time of unrestrained weight-bearing as well as the weight- bearing intensity before treatment was initiated was associated with development of deformity in patients with active CNO (83). Although evidence based on clinical trials is lacking and we have no information on aspects such as cost-effectiveness and equity, the guideline committee concluded that immobilisation of the affected leg should be started at the moment active CNO is considered, given the potentially devastating consequences of untreated CNO.

Persons with active CNO should be informed that it can take many months before the disease goes into remission. Our experience suggests that offloading be continued for four to six weeks after the clinical signs of active CNO have resolved and the patient is diagnosed as in remission. Long-term treatment with a non-removable knee-high device is associated with the risk of complications and adverse effects. Only a few studies identified in our systematic review reported such events. The most important complications being development of foot ulcers that sometimes resulted in amputation in two studies (84, 85), skin lesions from injury during removal of the cast, and pain (86). Other possible adverse effects include muscle weakness and atrophy, falls and musculoskeletal knee or hip complaints because of the acquired limb-length discrepancy when wearing the device, as described in our ulcer offloading guideline (72). One may consider a shoe raise for the contralateral limb to minimize this acquired limb-length discrepancy. The long-term loss of mobility can have major negative consequences on people's psychological health, physical health and socio-economic well-being due to the increased risk of social isolation and loss of work. Furthermore, loss of mobility can have negative effects on glucose control and other cardiovascular risk factors (87).

We suggest not to use below the ankle devices in the management of active CNO. We could not identify studies that evaluated the therapeutic value of below the ankle devices to treat active CNO and made therefore a "conditional" recommendation. However, there is indirect evidence from studies in people with diabetes related foot ulceration that ankle high devices do not immobilise and offload the foot as effectively as knee-high devices (72).

To achieve reduced weight- bearing we suggest using assistive devices to reduce: 1) pressure on the affected limb, 2) risk of falls, 3) time to remission, and 4) the risk of musculoskeletal injury and pain in the affected or contralateral limb. The recommendation on the use of, preferably bilateral, crutches in addition to treatment with a knee-high device is based on one retrospective study in which patients were instructed in partial weightbearing of the casted extremity by using bilateral axillary crutches or walker (88). Seventy-two percent of the patients did not adhere to these instructions as judged by their

treating orthopaedic surgeon and in these patients the average time to healing was 34 days longer compared to those who did comply (88). Secondly, continued walking on the extremity in a knee-high device can result in musculoskeletal complications and pain in the contralateral extremity, as described above. The balance of effects regarding weight-bearing status probably favours reduced weight- bearing compared to unrestricted or non-weight-bearing, however, the quality of evidence is very low. Based on these arguments we suggest to consider partial weight- bearing with the use of crutches, walkers, rolling crutch walkers or other devices, and this choice should be adapted to the patient's living conditions, mobility and motivation of the patient.

Although our recommendations are in line with other guidelines (39, 82, 89), the evidence from observational studies highlight that implementation of our recommendations may be a challenge as many people seem to receive sub-optimal treatment with potentially poorer outcomes. In the nationwide UK survey from 2005-2007 approximately one third of all patients with active CNO were not treated with a non-removable offloading lower leg device (80). Comparable results were obtained in a 1999 survey conducted under members of the Diabetes Committee of the American Orthopaedic Foot and Ankle Society, as approximately half of the patients with a history of a Charcot foot had initially not been treated with a TCC (90). This variability in treatment is likely to be associated with the absence of treatment guidelines accepted by all the different disciplines involved in treating these patients, the lack of evidence based on clinical trials, lack of knowledge, skills and resources to apply TCCs as well as patient-related factors and reimbursement, and perhaps clinical inertia. The phenomenon of clinical inertia is defined as the failure to start a therapy or its intensification/non-intensification when appropriate, in patients with a disease such as active CNO (91).

Treating patients with active CNO as well as the application and use of TCCs and non-removable knee-high devices require specific training, skills and experience. We suggest that the healthcare professionals treating these patients should have access to high quality training according to national or regional standards. To facilitate implementation, offloading recommendations should be culturally appropriate, account for socioeconomic status, align with a patient's health literacy as well as personal circumstances, and should be part of a shared decision-making process. When these factors are taken into account, this will probably enhance their acceptability and feasibility. It is therefore not possible to provide globally applicable recommendations on the best form of offloading given the diversity of contexts and situations in which people present with active CNO. The financial resources required for total contact casting and knee-high removable offloading device can be challenging to provide for healthcare providers, and for people who are required to self-fund their own healthcare.

Clinical Question: Can medical therapy in a person with diabetes mellitus and active CNO with intact skin result in shorter time to remission and prevent complications?

Recommendation 21: Do not use alendronate, pamidronate, zoledronate, calcitonin, parathyroid hormone, or methylprednisolone as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin. (Strong; Moderate)

Recommendation 22: We suggest not to use denosumab as treatment for active Charcot neuro-osteoarthropathy in a person with diabetes mellitus and intact skin. (Conditional; Low)

Recommendation 23: We suggest to evaluate the need for vitamin D and calcium supplementation in a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin during the phase of fracture healing, in doses according to (inter)national guidelines on supplementation in persons at risk for vitamin D deficiency and/or those with insufficient calcium intake. (Conditional; Low)

Rationale: The pathophysiology of CNO is associated with localised increased bone resorption, osteopenia, and osteoporosis, all of which can lead to bone weakness. Therefore, the use of several pharmacological therapies to treat CNO has focused on restoring the balance between bone formation and resorption. The aim of treatment is to reduce time to remission and/or help to prevent the development or worsening of foot deformities that are already present at the first clinical presentation.

Our systematic review identified eight studies, on several different pharmacological interventions used in the management of active CNO (22). There were seven RCTs and one cohort study. The studies could be subdivided firstly into therapies that potentially inhibit bone resorption in the early inflammatory phase of the disease, bisphosphonates (alendronate, pamidronate, zoledronate), calcitonin and denosumab; secondly into agents that could stimulate bone formation, parathyroid hormone and finally, anti-inflammatory therapies, methylprednisolone. Most studies reported time to remission and the development of foot deformity was an outcome in two of the studies.

Five of the eight included studies investigated the potential beneficial effect of bisphosphonates in the treatment of active CNO, as described in our systematic review (22). These drugs have been used in the treatment of osteoporosis for many years and have a well-known risk profile. Most of the bisphosphonate studies had a high risk of bias with the exception of the high quality RCT, from Jude et al. (92), on the efficacy of intravenous pamidronate versus placebo. None of these studies reported an improvement in time to remission (92-95) and treatment with zoledronate was associated with a longer time to remission (94). Two of these studies reported that treatment with pamidronate or alendronate may be associated with a reduction in pain (92, 95). Several of the aforementioned studies reported improvements in biomarkers of bone resorption and/or bone formation, but the clinical significance of these observations is unclear and could possibly also be related to systemic effects of the drugs.

One RCT of intranasal calcitonin, with a high risk of bias, did not observe any effect on time to remission during six months of follow-up (96). Daily subcutaneous PTH was evaluated in one RCT with a low risk of bias, without any beneficial effect on time to remission, fracture healing or prevention/progression of foot deformity (97). A non-blinded RCT with a high risk of bias, reported that treatment with methylprednisolone was associated with a longer time to remission compared to both zoledronate and placebo treatment (98). Given the lack of evidence for their efficacy, potential side effects, resources required and impact on equity, we recommend not to use alendronate, pamidronate, zoledronate, methylprednisolone, calcitonin or PTH as treatment for active CNO in people with diabetes mellitus.

The final study included in the systematic review was a cohort study at high risk of bias with historical controls, some of whom were treated with bisphosphonates. This study reported that a single injection of denosumab was associated with a faster time to remission, the duration of TCC treatment was approximately 1 ½ month shorter, and time to fracture healing on plain X-ray was shortened by approximately two months with less malalignment (99). The effect on prevention of deformities could

not be assessed due to the low number of events. Given the lack of clinical trials, the costs, and potential adverse effects, there was at the time of writing these guidelines insufficient evidence to suggest the use of denosumab in the treatment of active CNO. We made a "conditional" recommendation not to use this therapy based on the limited quality and inconsistency of the evidence reported and the results of randomised clinical trials need to be awaited.

Vitamin D and calcium play an important role in skeletal health and bone repair, and persons with type 2 diabetes have more frequently low vitamin D levels (100) as also observed in patients with active CNO (101). We could not identify intervention studies on possible beneficial effects of vitamin D and calcium supplementation in active CNO. Also, indirect evidence to support such supplementation is poor as studies in traumatic or fragility fractures are scarce (102). We have therefore no information on the impact of low Vitamin D levels or poor calcium intake on the course of active CNO. However, persons with active CNO can be at risk for low vitamin D levels, due to factors as type 2 diabetes, obesity, renal disease, and their older age. It is likely that key stakeholders would find calcium and vitamin D supplementation acceptable and feasible given their importance in bone healing. Therefore, given their importance for bone repair, the lack of major side effects, and the relative low costs, we suggest for pragmatic reasons to evaluate the need for vitamin D and calcium supplementation in persons with active CNO. When treatment is started, the doses of vitamin D and calcium should be prescribed according to (inter)national guidelines on supplementation in persons with -or at risk for- vitamin D deficiency and/or insufficient calcium intake.

In summary, based on indirect evidence we suggest to consider vitamin D and calcium supplementation during treatment of active CNO. There is no evidence to support the use of any other pharmaceutical interventions, as such treatment will be associated with additional costs and potential harmful effects in this specific patient population. Potential harmful effects include impairment of bone healing and iatrogenic fractures.

Clinical Question: In a person with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin, is reconstructive surgery associated with shorter time to remission, prevention of deformity development, and prevention of deformity progression compared to no surgery?

Recommendation 24: In a person with active Charcot neuro-osteoarthropathy and intact skin, and with instability of foot and ankle joints, and/or deformity with a high-risk of developing ulcer in the offloading device, or pain that cannot be sufficiently stabilized in a Total Contact Cast or a non-removable knee-high device, we suggest that surgical intervention should be considered (Conditional; Low)

Rationale: Historically, surgical reconstruction for active CNO has not been recommended largely due to concerns about performing surgery on an acutely inflamed foot. Our systematic review did not identify any prospective, randomised outcome studies comparing surgical versus non-surgical treatment during active CNO (22). We identified one non-controlled retrospective study that evaluated the outcomes of patients with active CNO and intact skin who underwent primary realignment arthrodesis (103). This study was limited to surgical treatment of only 14 patients with active CNO localized to the tarsometatarsal joints, and these findings cannot be extrapolated to more proximal involvement such as the transverse tarsal joint, the subtalar joint, or the ankle joint.

The indications for surgical intervention during active CNO include deformities that result in impending skin ulceration, severe instability, intractable pain, or the inability to immobilize the foot in a cast or non-removable knee high device (39). As discussed previously, deformity associated with impending ulceration can lead to catastrophic outcomes, increasing the risk of major amputation by a factor of six to 12 fold (10, 11). Our recommendation to perform early surgical intervention during active CNO in specific subgroups is consistent with guidelines on the management of foot and ankle fractures in patients irrespective of diabetes status.

Based on clinical experience, proximal deformities of the hindfoot and ankle can be especially difficult to manage with TCCs or knee-high non-removable devices due to deformity in the coronal plane. Varus and valgus deformities of the ankle and hindfoot are poorly tolerated because of the subcutaneous nature of the medial and lateral malleoli. Consequently, skin breakdown and ulceration at the level of the medial and lateral malleoli can lead to osteomyelitis. A previous consensus statement recommended consideration of primary arthrodesis for active CNO of the ankle with severe deformity (39).

Reconstructive surgery for CNO includes realignment arthrodesis, tendon lengthening, tendon transfer or partial ostectomy of a prominent bone (exostectomy). Surgical intervention in CNO is associated with high complication rates and the risk benefit ratio needs to be considered when intervening surgically. A large database study compared outcomes of ankle fusion in a matched cohort of patients with diabetes and CNO (n= 3815) and patients with diabetes but without CNO (n=3815) (104). Significantly higher rates of amputation, hardware removal, wound dehiscence, acute kidney injury, pneumonia, and surgical site infection, were observed in patients with diabetes and CNO compared patients with diabetes but without CNO. This study was not included in our systematic review as a main limitation of this database study was that the timing of surgery (active or remission stage) could not be determined, but these data highlight the risks of surgery in patients with CNO.

Although CNO reconstruction is associated with high upfront costs, reconstruction early in the disease process is, in our opinion, justified for patients who cannot be managed successfully with total contact casting or non-removable knee-high devices. Because CNO reconstruction is challenging and associated with relatively high complication rates, the goal is to pursue a cost-effective strategy of fixation and bone graft augmentation while still achieving a high rate of favorable outcomes. Our systematic review did not identify any studies which supported a superior or specific method of fixation, for example internal versus external fixation, in treating active CNO with intact skin. The decision to use external or internal fixation is highly dependent on the surgeon's preference and experience.

The goal of surgical reconstruction for the patient with active CNO includes restoring a plantigrade foot that is less prone to ulceration because plantar pressure is redistributed throughout the foot. Complications of surgery include surgical site infection, wound dehiscence, non-union, hardware failure and need for further treatment. The level of evidence regarding surgery in active CNO is low, and the current evidence supports offloading with knee-high devices over surgery in the active CNO in patients with intact skin. Consequently, prior to performing surgery in active CNO, we recommend a period of non-surgical care to include immobilization and oedema reduction to allow the inflammation to decrease prior to surgical intervention. The resources and costs associated with surgical intervention are higher than treating patients with offloading using a knee-high device. A Markov model-based study from

Albright et al. (105) hypothesizes that the most effective strategy for unstable midfoot CNO with intact skin favors surgical reconstruction despite its high upfront costs. To date this strategy has not been validated by any clinical series. As our recommendation is mainly based on indirect evidence and expert opinion, we graded it as "conditional". Given the uncertainties described above, the potential complications of surgery and the higher upfront costs, the potential beneficial effects should be carefully balanced with the risk of harm in an individualized manner. The final choice should be made by a well-informed patient as part of a shared decision-making process and the surgical reconstruction should be performed by a surgeon with sufficient expertise in foot surgery in a high- risk patients with diabetes and CNO.

PREVENTION OF RE-ACTIVATION

Clinical Question: In persons with diabetes mellitus and active Charcot neuro-osteoarthropathy with intact skin who have been treated and are in remission, is therapeutic footwear preferred to conventional footwear to prevent re-activation of the disease?

Recommendation 25: Footwear and/or orthoses that best accommodate and support the shape of the foot/feet and ankle to help prevent re-activation of Charcot neuro-osteoarthropathy (CNO) are recommended in a person with diabetes mellitus, intact skin, treated for active CNO with an off-loading device and who is now in remission. (Strong; Moderate)

Recommendation 26: When deformity and/or joint instability is present, in order to optimise plantar pressure distribution, below the knee customized devices should be used for additional protection in a person with diabetes mellitus, intact skin, treated for active Charcot neuro-osteoarthropathy who is now in remission. (Strong; Moderate)

Rationale: Based on our systematic review we did not identify any evidence that demonstrates that therapeutic footwear is superior to conventional footwear to prevent re-activation of active CNO (22). Despite the paucity of data, our recommendation is to consider footwear that best accommodates and supports the shape of the foot/feet to help prevent re-activation of the active disease in people who are in remission. Being at increased risk for ulceration as a result of CNO related deformity, it is important that the person's footwear fits, protects, and accommodates the shape of their feet; this includes footwear having adequate length, width, and depth. When foot and/or ankle deformity is present, it becomes even more important to alter foot biomechanics and reduce plantar pressure on at-risk locations. This may require custom-made footwear, custom made orthoses or below knee braces. The second part of our recommendation, therefore, is that in people with diabetes mellitus and CNO who have been treated and are in remission is to consider prescription custom made orthotics to (redistribute) decrease plantar pressures. When custom made orthotics are prescribed, extra depth footwear should be used to accommodate the increased thickness of the orthotic.

Despite the lack of evidence, we strongly believe that therapeutic footwear would produce benefits in terms of reducing CNO re-activation and mechanical stress reduction. Our recommendation is consistent with IWGDF guidelines on prevention of foot ulcers (24). The IWGDF Risk Stratification

System identifies persons with loss of protective sensation and foot deformity secondary to CNO at increased risk for ulcerations. Considering the potential benefit of additional ankle stability, we recommend removable knee-high offloading over ankle-high offloading in patients who require long term ankle stability. We favor customized devices such as Charcot Restraint Orthotic Walker (CROW), contoured plastic ankle foot orthosis (AFO), and the double upright metal AFO that is attached to the footwear to provide support.

The primary adverse effect of footwear, orthotics and braces in persons with diabetes-related neuropathy is iatrogenic ulcer formation from ill-fitting shoes or orthotic devices. Because persons with loss of protective sensation cannot adequately judge footwear fit, footwear and braces should be evaluated by appropriately trained professionals. The benefits of prescriptive footwear, orthotics, and braces outweigh the low incidence of ulcer formation, and for further information we refer to the IWGDF guidelines on the prevention of foot ulcers (24).

Although evidence is lacking, we suggest that the affected foot should be gradually transitioned to the advised footwear and that in this phase ambulation should slowly increase. Abrupt re-loading of the foot may reactivate the CNO. In addition, probably due to the inflammatory process and the long-term immobilization, the foot skeleton can become osteoporotic (106, 107). Rapid and accelerated transition into weight-bearing activities with increased loading of the foot may, in our clinical experience, may result in osteoporotic fractures.

FUTURE RESEARCH

As discussed in this guideline and in our systematic review (22) there is an urgent need for further clinical research in active CNO. Our systematic review identified multiple areas where high quality evidence is lacking. Although CNO is considered a "rare disease," the number of actual individuals with this disease is likely higher than we think due to misdiagnosis and lack of awareness.

Based on the findings of our systematic review (22) and subsequent guideline development, we consider the following topics to be key in future research:

Diagnosis and Monitoring: One of the major items that needs to be addressed is the development of well-defined and validated, objective and reproducible criteria to diagnose active CNO, to monitor disease activity, and to determine remission. There are no studies that have demonstrated accuracy of foot skin temperature measurement to diagnose active disease or determine the presence of remission. In particular, the diagnostic accuracy of the ≤2°C foot skin temperature measurement "cutoff", that is frequently used, has not been demonstrated in a clinical study and warrants further research. Also, we do not know which specific infrared thermometry device or protocol provides the most accurate method of measuring foot skin temperature. Future studies assessing the use of at home monitoring with infrared thermometry devices to monitor disease activity would be beneficial. This would allow the patient to liaise with the clinic without the need to attend clinic appointments as frequently and be able to identify changes in their foot condition rapidly and seek advice.

Further studies on the monitoring of disease activity from an imaging standpoint are also needed. Although MRI can detect active CNO with high sensitivity, the abnormalities on MRI can persist after the clinical active CNO symptoms have resolved.

Offloading: Although TCC is accepted as the "gold standard" method by many authors for offloading in patients with active CNO, further studies may help demonstrate which offloading modality is most effective to achieve remission, acceptable to people with CNO given socio-economic factors, and most cost-effective.

Weight-bearing: Studies are needed to determine whether or not weight -bearing in an offloading device can negatively impact time to remission and development/progression of an existing deformity.

Pharmacological treatment: We suggest that the potential efficacy of denosumab and tumor necrosis factor inhibitors could be studied in future RCTs to assess the benefits, risks and cost-effectiveness of these potentially useful treatments.

Surgical intervention: Studies are necessary to determine if early surgical intervention during the active CNO phase can improve outcomes (prevention of deformity, time to remission) compared to standard offloading.

Risk factors/genetics: Further work to identify risk factors associated with the development of active CNO is needed. Not all individuals with DM and neuropathy develop CNO therefore identifying risk factors/genetic markers/ a screening tool to assess the level of risk of the development of active CNO would be of significant importance in regard to prevention of complications related to this disease.

In general, the quality of studies related to diagnosis and intervention in active CNO and the way they were reported was, with few exceptions, low. They were generally underpowered, non-blinded, and did not include relevant clinical outcomes such as prevention of deformity. In order to move the field forward with better quality studies, consensus must be reached on appropriate participant selection/characteristics, how the disease is monitored, how objective endpoints should be defined, which side-effects should be systematically monitored, how standard of care should be implemented in all patients and how long people should be followed up for to monitor for relapse.

CONCLUDING REMARKS

The recommendations for these guidelines have been derived from a systematic review (22) of all relevant publications and where evidence was not available, the recommendations were based on expert opinion and established practice. These recommendations are aimed at health care providers treating persons with diabetes mellitus and active CNO. Early recognition of active CNO of the foot and ankle and prompt implementation of evidence-based treatment can reduce morbidity and increase the likelihood of a satisfactory outcome in individuals with active CNO. Health care professionals working as a part of a multidisciplinary team are ideally positioned to treat this disease. Offloading with a total contact cast or non-removable knee-high device is the most important intervention with the

strongest evidence available for treatment of active CNO. In people with diabetes mellitus and neuropathy who present with clinical signs of acute inflammation (redness, increased skin temperature, and oedema) and normal radiographs, advanced imaging is recommended. Currently MRI is the best advanced imaging modality because it allows assessment of bones, joints, ligaments and tendons. Offloading with a TCC or non-removable knee-high device should be implemented as soon as possible and should not be delayed while waiting for advanced imaging.

Our systematic review (22) has demonstrated that that there is a paucity of contemporary high-quality evidence on the diagnosis, management and prognosis of active CNO. Further research is warranted to address the issues surrounding this complex problem. We encourage our colleagues who care for patients with CNO to consider developing some form of surveillance (e.g., registries and pathways) to monitor and attempt to improve outcomes in patients with CNO. We encourage our research colleagues to consider key controversial areas as a platform to conduct well-designed studies in areas of CNO. Future research should address both non-surgical and surgical management to better inform the diabetes related foot disease community on the most effective treatment for persons with diabetes and CNO. To enable the performance of studies with sufficient quality, the core details required in the planning, the conduct and reporting of studies need to be defined and subsequently implemented in CNO research in order to make relevant progress in the management of active CNO.

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CONFLICT OF INTERESTS

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REFERENCES

(1) Metcalf L, Musgrove M, Bentley J, Berrington R, Bunting D, Mousley M, et al. Prevalence of active Charcot disease in the East Midlands of England. Diabet Med. 2018;35(10):1371-4.

(2) O'Loughlin A, Kellegher E, McCusker C, Canavan R. Diabetic charcot neuroarthropathy: prevalence, demographics and outcome in a regional referral centre. Ir J Med Sci. 2017;186(1):151-6.

(3) Svendsen OL, Rabe OC, Winther-Jensen M, Allin KH. How Common Is the Rare Charcot Foot in Patients With Diabetes? Diabetes Care. 2021;44(4):e62-e3.

(4) International Diabetes Foundation. IDF Diabetes Atlas 10th edition 2021. Brussels, Belgium. Available at: *www.diabetesatlas.org* (accessed August 9,2022).

(5) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

(6) Raspovic KM, Wukich DK. Self-reported quality of life in patients with diabetes: a comparison of patients with and without Charcot neuroarthropathy. Foot Ankle Int. 2014;35(3):195-200.

(7) Hogg FR, Peach G, Price P, Thompson MM, Hinchliffe RJ. Measures of health-related quality of life in diabetes-related foot disease: a systematic review. Diabetologia. 2012;55(3):552-65.

(8) Pakarinen TK, Laine HJ, Maenpaa H, Mattila P, Lahtela J. Long-term outcome and quality of life in patients with Charcot foot. Foot Ankle Surg. 2009;15(4):187-91.

(9) Gooday C, Hardeman W, Game F, Woodburn J, Poland F. A qualitative study to understand people's experiences of living with Charcot neuroarthropathy. Diabet Med. 2022;39(6):e14784.

(10) Sohn MW, Stuck RM, Pinzur M, Lee TA, Budiman-Mak E. Lower-extremity amputation risk after charcot arthropathy and diabetic foot ulcer. Diabetes Care. 2010;33(1):98-100.

(11) Wukich DK, Sadoskas D, Vaudreuil NJ, Fourman M. Comparison of Diabetic Charcot Patients With and Without Foot Wounds. Foot Ankle Int. 2017;38(2):140-8.

(12) Fejfarova V, Jirkovska A, Dragomirecka E, Game F, Bem R, Dubsky M, et al. Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus? J Diabetes Res. 2014;2014:371938.

(13) Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res. 2020;13(1):16.

(14) Jeffcoate W, Game F. The Charcot Foot Reflects a Response to Injury That Is Critically Distorted by Preexisting Nerve Damage: An Imperfect Storm. Diabetes Care. 2022;45(7):1691-7.

(15) Uccioli L, Sinistro A, Almerighi C, Ciaprini C, Cavazza A, Giurato L, et al. Proinflammatory modulation of the surface and cytokine phenotype of monocytes in patients with acute Charcot foot. Diabetes Care. 2010;33(2):350-5.

(16) Mabilleau G, Petrova NL, Edmonds ME, Sabokbar A. Increased osteoclastic activity in acute Charcot's osteoarthropathy: the role of receptor activator of nuclear factor-kappaB ligand. Diabetologia. 2008;51(6):1035-40.

(17) Petrova NL, Petrov PK, Edmonds ME, Shanahan CM. Inhibition of TNF-alpha Reverses the Pathological Resorption Pit Profile of Osteoclasts from Patients with Acute Charcot Osteoarthropathy. J Diabetes Res. 2015;2015:917945.

(18) Petrova NL, Petrov PK, Edmonds ME, Shanahan CM. Novel use of a Dektak 150 surface profiler unmasks differences in resorption pit profiles between control and Charcot patient osteoclasts. Calcif Tissue Int. 2014;94(4):403-11.

(19) Pitocco D, Zelano G, Gioffre G, Di Stasio E, Zaccardi F, Martini F, et al. Association between osteoprotegerin G1181C and T245G polymorphisms and diabetic charcot neuroarthropathy: a case-control study. Diabetes Care. 2009;32(9):1694-7.

(20) Bruhn-Olszewska B, Korzon-Burakowska A, Wegrzyn G, Jakobkiewicz-Banecka J. Prevalence of polymorphisms in OPG, RANKL and RANK as potential markers for Charcot arthropathy development. Sci Rep. 2017;7(1):501.

(21) Korzon-Burakowska A, Jakobkiewicz-Banecka J, Fiedosiuk A, Petrova N, Koblik T, Gabig-Ciminska M, et al. Osteoprotegerin gene polymorphism in diabetic Charcot neuroarthropathy. Diabet Med. 2012;29(6):771-5.

(22) Raspovic KM, Schaper NC, Gooday C, Bal A, Bem R, Chabra A, et al. Diagnosis and Treatment of Active Charcot Neuro-osteoarthropathy in Persons with Diabetes Mellitus: A Systematic Review. Diab Metab Res Rev. 2023;e3653.

(23) Bus SA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3647.

(24) Bus SA, Sacco ICN, Monteiro-Soares M, Raspovic A, Paton J, Rasmussen A, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3651.

(25) Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3644.

(26) Fitridge R, Chuter VH, Mills JL, Hinchliffe RJ, Azuma N, Behrendt C-A, et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in patients with diabetes mellitus and a foot ulcer. Diab Metab Res Rev. 2023; in press.

(27) Monteiro-Soares M, Hamilton EJ, Russell DA, Sirisawasdi G, Boyko EJ, Mills JL, et al. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diab Metab Res Rev. 2023;e3648.

(28) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease. Diab Metab Res Rev. 2023;e3657.

(29) Senneville É, Albalawi Z, Van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF/IDSA 2023). Diab Metab Res Rev. 2023;in press.

(30) Shibata T, Tada K, Hashizume C. The results of arthrodesis of the ankle for leprotic neuroarthropathy. J Bone Joint Surg Am. 1990;72(5):749-56.

(31) Chantelau EA, Grutzner G. Is the Eichenholtz classification still valid for the diabetic Charcot foot? Swiss Med Wkly. 2014;144:w13948.

(32) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;353:i2089.

(33) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

(34) Schunemann H, Brozek J, Guyatt G, Oxman AD. GRADE Handbook 2013 [Available from: *gdt.gradepro.org/app/handbook/handbook.html*.

(35) Dewidar O, Lotfi T, Langendam MW, Parmelli E, Saz Parkinson Z, Solo K, et al. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. BMJ Evid Based Med. 2022.

(36) Bus SA, Van Netten JJ, Apelqvist J, Fitridge R, Game F, Monteiro-Soares M, et al. Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot guidelines. Diab Metab Res Rev. 2023;e3656.

(37) Chantelau E. The perils of procrastination: Effects of early vs. delayed detection and treatment of incipient Charcot fracture. Diabetic Medicine. 2005;22(12):1707-12.

(38) Wukich DK, Sung W, Wipf SA, Armstrong DG. The consequences of complacency: managing the effects of unrecognized Charcot feet. Diabet Med. 2011;28(2):195-8.

(39) Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, et al. The Charcot foot in diabetes. Diabetes Care. 2011;34(9):2123-9.

(40) D. Hernandez-Contreras HP-B, J. Rangel-Magdaleno, J. Gonzalez-Bernal. Narrative review: Diabetic foot and infrared thermography. Infrared Physics & Technology. 2016;78:105-17.

(41) Bem R, Jirkovska A, Dubsky M, Fejfarova V, Buncova M, Skibova J, et al. Role of quantitative bone scanning in the assessment of bone turnover in patients with Charcot foot. Diabetes Care. 2010;33(2):348-9.

(42) Armstrong DG, Lavery LA, Liswood PJ, Todd WF, Tredwell JA. Infrared dermal thermometry for the high-risk diabetic foot. Physical Therapy. 1997;77(2):169-77.

(43) Jones PJ, Davies MJ, Webb D, Berrington R, Frykberg RG. Contralateral foot temperature monitoring during Charcot immobilisation: A systematic review. Diabetes Metab Res Rev. 2023:e3619.

(44) Macdonald A, Petrova N, Ainarkar S, Allen J, Plassmann P, Whittam A, et al. Thermal symmetry of healthy feet: a precursor to a thermal study of diabetic feet prior to skin breakdown. Physiol Meas. 2017;38(1):33-44.

(45) Macdonald A, Petrova N, Ainarker S, Allen J, Lomas C, Tang W, et al. Between visit variability of thermal imaging of feet in people attending podiatric clinics with diabetic neuropathy at high risk of developing foot ulcers. Physiol Meas. 2019;40(8):084004.

(46) Dallimore SM, Puli N, Kim D, Kaminski MR. Infrared dermal thermometry is highly reliable in the assessment of patients with Charcot neuroarthropathy. J Foot Ankle Res. 2020;13(1):56.

(47) Fletcher T, Whittam A, Simpson R, Machin G. Comparison of non-contact infrared skin thermometers. J Med Eng Technol. 2018;42(2):65-71.

(48) Gooday C, Gray K, Game F, Woodburn J, Poland F, Hardeman W. Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes. Diabetes Metab Res Rev. 2020:e3328.

(49) Armstrong DG, Lavery LA. Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. J Rehabil Res Dev. 1997;34(3):317-21.

(50) De Bruijn J, Hagemeijer NC, Rikken QGH, Husseini JS, Saengsin J, Kerkhoffs G, et al. Lisfranc injury: Refined diagnostic methodology using weightbearing and non-weightbearing radiographs. Injury. 2022;53(6):2318-25.

(51) Chantelau E, Poll LW. Evaluation of the diabetic charcot foot by MR imaging or plain radiography--an observational study. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2006;114(8):428-31.

(52) Chantelau E, Richter A, Ghassem-Zadeh N, Poll LW. "Silent" bone stress injuries in the feet of diabetic patients with polyneuropathy: A report on 12 cases. Archives of Orthopaedic and Trauma Surgery. 2007;127(3):171-7.

(53) Chantelau EA, Richter A. The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging--a review of 71 cases. Swiss medical weekly. 2013;143:w13831.

(54) Chantelau E-A, Antoniou S, Zweck B, Haage P. Follow up of MRI bone marrow edema in the treated diabetic Charcot foot - a review of patient charts. Diabetic foot & ankle. 2018;9(1):1466611.

(55) Gooday C, Game F, Woodburn J, Poland F, Sims E, Dhatariya K, et al. A randomised feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes (CADOM). J Foot Ankle Res. 2023;16(1):2.

(56) Ahluwalia R, Bilal A, Petrova N, Boddhu K, Manu C, Vas P, et al. The role of bone scintigraphy with SPECT/CT in the characterization and early diagnosis of stage 0 charcot neuroarthropathy. Journal of Clinical Medicine. 2020;9(12):1-14.

(57) Fosbol M, Reving S, Petersen EH, Rossing P, Lajer M, Zerahn B. Three-phase bone scintigraphy for diagnosis of Charcot neuropathic osteoarthropathy in the diabetic foot - does quantitative data improve diagnostic value? Clinical Physiology and Functional Imaging. 2017;37(1):30-6.

(58) Ruotolo V, Di Pietro B, Giurato L, Masala S, Meloni M, Schillaci O, et al. A new natural history of charcot foot: Clinical evolution and final outcome of stage 0 charcot neuroarthropathy in a tertiary referral diabetic foot clinic. Clinical Nuclear Medicine. 2013;38(7):506-9.

(59) Ludlow JB. Hand-wrist, knee, and foot-ankle dosimetry and image quality measurements of a novel extremity imaging unit providing CBCT and 2D imaging options. Med Phys. 2018;45(11):4955-63.

(60) Manning BT, Bohl DD, Idarraga AJP, Holmes GB, Lee S, Lin JL, et al. Patient Knowledge Regarding Radiation Exposure From Foot and Ankle Imaging. Foot Ankle Spec. 2020;13(4):324-9.

(61) Addala TE, Greffier J, Hamard A, Snene F, Bobbia X, Bastide S, et al. Early results of ultra-low-dose CT-scan for extremity traumas in emergency room. Quant Imaging Med Surg. 2022;12(8):4248-58.

(62) Petrova NL, Dew TK, Musto RL, Sherwood RA, Bates M, Moniz CF, et al. Inflammatory and bone turnover markers in a cross-sectional and prospective study of acute Charcot osteoarthropathy. Diabetic Medicine. 2015;32(2):267-73.

(63) Petrova NL, Moniz C, Elias DA, Buxton-Thomas M, Bates M, Edmonds ME. Is there a systemic inflammatory response in the acute charcot foot? Diabetes Care. 2007;30(4):997-8.

(64) Folestad A, Alund M, Asteberg S, Fowelin J, Aurell Y, Gothlin J, et al. IL-17 cytokines in bone healing of diabetic Charcot arthropathy patients: a prospective 2 year follow-up study. Journal of foot and ankle research. 2015;8:39.

(65) Schara K, Stukelj R, Krek JL, Lakota K, Sodin-Semrl S, Boulton AJM, et al. A study of extracellular vesicle concentration in active diabetic Charcot neuroarthropathy. European Journal of Pharmaceutical Sciences. 2017;98:58-63.

(66) Hingsammer AM, Bauer D, Renner N, Borbas P, Boeni T, Berli M. Correlation of Systemic Inflammatory Markers With Radiographic Stages of Charcot Osteoarthropathy. Foot Ankle Int. 2016;37(9):924-8.

(67) Gough A, Abraha H, Li F, Purewal TS, Foster AV, Watkins PJ, et al. Measurement of markers of osteoclast and osteoblast activity in patients with acute and chronic diabetic Charcot neuroarthropathy. Diabet Med. 1997;14(7):527-31.

(68) Lipsky BA, Senneville E, Abbas ZG, Aragon-Sanchez J, Diggle M, Embil JM, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3280.

(69) Zampa V, Bargellini I, Rizzo L, Turini F, Ortori S, Piaggesi A, et al. Role of Dynamic MRI in the follow-up of acute Charcot foot in patients with diabetes mellitus. Skeletal Radiology. 2011;40(8):991-9.

(70) Moura-Neto A, Fernandes TD, Zantut-Wittmann DE, Trevisan RO, Sakaki MH, Santos ALG, et al. Charcot foot: Skin temperature as a good clinical parameter for predicting disease outcome. Diabetes Research and Clinical Practice. 2012;96(2):e11-e4.

(71) Schlossbauer T, Mioc T, Sommerey S, Kessler SB, Reiser MF, Pfeifer KJ. Magnetic resonance imaging in early stage charcot arthropathy: correlation of imaging findings and clinical symptoms. European journal of medical research. 2008;13(9):409-14.

(72) Bus SA, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, et al. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3274.

(73) Pickwell KM, van Kroonenburgh MJ, Weijers RE, van Hirtum PV, Huijberts MS, Schaper NC. F-18 FDG PET/CT scanning in Charcot disease: a brief report. Clin Nucl Med. 2011;36(1):8-10.

(74) Vallier HA. Fractures of the Talus: State of the Art. J Orthop Trauma. 2015;29(9):385-92.

(75) Patel KA, Christopher ZK, Drakos MC, O'Malley MJ. Navicular Stress Fractures. J Am Acad Orthop Surg. 2021;29(4):148-57.

(76) Mandell JC, Khurana B, Smith SE. Stress fractures of the foot and ankle, part 2: site-specific etiology, imaging, and treatment, and differential diagnosis. Skeletal Radiol. 2017;46(9):1165-86.

(77) Begg L, McLaughlin P, Vicaretti M, Fletcher J, Burns J. Total contact cast wall load in patients with a plantar forefoot ulcer and diabetes. J Foot Ankle Res. 2016;9:2.

(78) Majid U, Argaez C. Off-Loading Devices for People with Diabetic Neuropathic Foot Ulcers: A Rapid Qualitative Review. CADTH Rapid Response Reports. Ottawa (ON)2020.

(79) Riopelle A, LeDuc R, Wesolowski M, Schiff AP, Pinzur MS. Risk of Complications With the Total Contact Cast in Diabetic Foot Disorders. Foot Ankle Spec. 2021;14(1):25-31.

(80) Game FL, Catlow R, Jones GR, Edmonds ME, Jude EB, Rayman G, et al. Audit of acute charcot's disease in the uk: The cduk study. Diabetologia. 2012;55(1):32-5.

(81) Lamb SE, Marsh JL, Hutton JL, Nakash R, Cooke MW, Collaborative Ankle Support T. Mechanical supports for acute, severe ankle sprain: a pragmatic, multicentre, randomised controlled trial. Lancet. 2009;373(9663):575-81.

(82) Milne TE, Rogers JR, Kinnear EM, Martin HV, Lazzarini PA, Quinton TR, et al. Developing an evidence-based clinical pathway for the assessment, diagnosis and management of acute Charcot Neuro-Arthropathy: a systematic review. J Foot Ankle Res. 2013;6(1):30.

(83) Kimmerle R, Chantelau E. Weight-bearing intensity produces charcot deformity in injured neuropathic feet in diabetes. Exp Clin Endocrinol Diabetes. 2007;115(6):360-4.

(84) Fabrin J, Larsen K, Holstein PE. Long-term follow-up in diabetic charcot feet with spontaneous onset. Diabetes Care. 2000;23(6):796-800.

(85) Christensen TM, Gade-Rasmussen B, Pedersen LW, Hommel E, Holstein PE, Svendsen OL. Duration of off-loading and recurrence rate in Charcot osteo-arthropathy treated with less restrictive regimen with removable walker. Journal of Diabetes and its Complications. 2012;26(5):430-4.

(86) Griffiths DA, Kaminski MR. Duration of total contact casting for resolution of acute Charcot foot: a retrospective cohort study. Journal of foot and ankle research. 2021;14(1):44.

(87) Duvivier BM, Schaper NC, Hesselink MK, van Kan L, Stienen N, Winkens B, et al. Breaking sitting with light activities vs structured exercise: a randomised crossover study demonstrating benefits for glycaemic control and insulin sensitivity in type 2 diabetes. Diabetologia. 2017;60(3):490-8.

(88) Sinacore DR. Acute Charcot arthropathy in patients with diabetes mellitus: Healing times by foot location. Journal of Diabetes and its Complications. 1998;12(5):287-93.

(89) NICE: Diabetic foot problems: prevention and management. *www.nice.org.uk/guidance/ng19*.

(90) Pinzur MS, Shields N, Trepman E, Dawson P, Evans A. Current practice patterns in the treatment of Charcot foot. Foot Ankle Int. 2000;21(11):916-20.

(91) O'Connor PJ, Sperl-Hillen JM, Johnson PE, Rush WA, Biltz G. Clinical Inertia and Outpatient Medical Errors. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Advances in Patient Safety. Rockville (MD)2005.

(92) Jude EB, Selby PL, Burgess J, Lilleystone P, Mawer EB, Page SR, et al. Bisphosphonates in the treatment of charcot neuroarthropathy: A double-blind randomised controlled trial. Diabetologia. 2001;44(11):2032-7.

(93) Bharath R, Bal A, Sundaram S, Unnikrishnan AG, Praveen VP, Bhavani N, et al. A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. Indian journal of endocrinology and metabolism. 2013;17(1):110-6.

(94) Pakarinen T-K, Laine H-J, Maenpaa H, Mattila P, Lahtela J. The effect of zoledronic acid on the clinical resolution of Charcot neuroarthropathy: a pilot randomized controlled trial. Diabetes care. 2011;34(7):1514-6.

(95) Pitocco D, Ruotolo V, Caputo S, Mancini L, Collina CM, Manto A, et al. Six-month treatment with alendronate in acute Charcot neuroarthropathy: a randomized controlled trial. Diabetes care. 2005;28(5):1214-5.

(96) Bem R, Jirkovská A, Fejfarová V, Skibová J, Jude EB. Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. Diabetes care. 2006;29(6):1392-4.

(97) Petrova NL, Donaldson NK, Bates M, Tang W, Jemmott T, Morris V, et al. Effect of Recombinant Human Parathyroid Hormone (1-84) on Resolution of Active Charcot Neuro-osteoarthropathy in Diabetes: a Randomized, Double-Blind, Placebo-Controlled Study. Diabetes care. 2021;44(7):1613-21.

(98) Das L, Bhansali A, Prakash M, Jude EB, Rastogi A. Effect of Methylprednisolone or Zoledronic Acid on Resolution of Active Charcot Neuroarthropathy in Diabetes: a Randomized, Double-Blind, Placebo-Controlled Study. Diabetes care. 2019.

(99) Busch-Westbroek TE, Delpeut K, Balm R, Bus SA, Schepers T, Peters EJ, et al. Effect of Single Dose of RANKL Antibody Treatment on Acute Charcot Neuro-osteoarthropathy of the Foot. Diabetes care. 2018;41(3):e21-e2.

(100) Rafiq S, Jeppesen PB. Is Hypovitaminosis D Related to Incidence of Type 2 Diabetes and High Fasting Glucose Level in Healthy Subjects: A Systematic Review and Meta-Analysis of Observational Studies. Nutrients. 2018;10(1).

(101) Greenhagen RM, Frykberg RG, Wukich DK. Serum vitamin D and diabetic foot complications. Diabet Foot Ankle. 2019;10(1):1579631.

(102) Chevalley T, Brandi ML, Cavalier E, Harvey NC, Iolascon G, Cooper C, et al. How can the orthopedic surgeon ensure optimal vitamin D status in patients operated for an osteoporotic fracture? Osteoporos Int. 2021;32(10):1921-35.

(103) Simon SR, Tejwani SG, Wilson DL, Santner TJ, Denniston NL. Arthrodesis as an early alternative to nonoperative management of charcot arthropathy of the diabetic foot. J Bone Joint Surg Am. 2000;82-A(7):939-50.

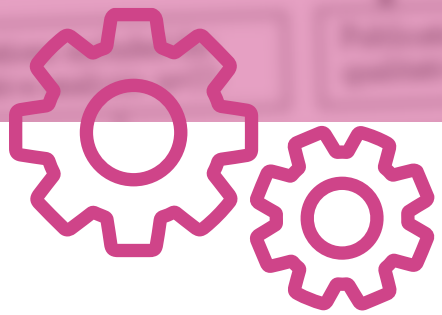
(104) Wang BK, Wukich DK, Sambandam S. Complications from ankle arthrodesis in diabetes-related Charcot foot syndrome. J Diabetes Complications. 2021;35(12):108071.

(105) Albright RH, Joseph RM, Wukich DK, Armstrong DG, Fleischer AE. Is Reconstruction of Unstable Midfoot Charcot Neuroarthropathy Cost Effective from a US Payer's Perspective? Clin Orthop Relat Res. 2020;478(12):2869-88.

(106) Gutekunst DJ, Smith KE, Commean PK, Bohnert KL, Prior FW, Sinacore DR. Impact of Charcot neuroarthropathy on metatarsal bone mineral density and geometric strength indices. Bone. 2013;52(1):407-13.

(107) Petrova NL, Edmonds ME. A prospective study of calcaneal bone mineral density in acute Charcot osteoarthropathy. Diabetes Care. 2010;33(10):2254-6

Standards for the development and methodology of the 2023 International Working Group on the Diabetic Foot Guidelines



Part of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease

IWGDF Guidelines

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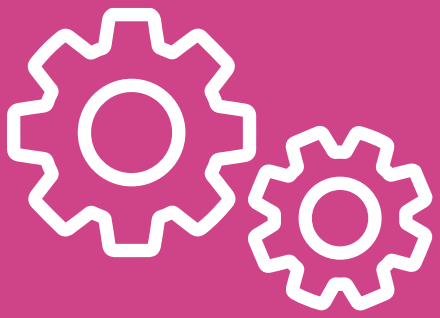

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ABSTRACT

Diabetes-related foot disease is a source of major patient burden and societal costs. Investing in evidence-based international guidelines on diabetes-related foot disease is important to reduce this burden and costs, provided the guidelines are focused on outcomes important to key stakeholders, evidence-based and properly implemented.

The International Working Group on the Diabetic Foot (IWGDF) has published and updated international guidelines since 1999. The 2023 updates were made using the Grading of Recommendations Assessment Development and Evaluation (GRADE) evidence-to-decision framework. This concerns formulating relevant clinical questions and important outcomes, conducting systematic reviews of the literature and meta-analyses where appropriate, completing summary of judgements tables, and writing recommendations that are specific, unambiguous and actionable, along with their transparent rationale.

We herein describe the development of the 2023 IWGDF Guidelines on the prevention and management of diabetes-related foot disease, which consists of seven chapters, each prepared by a separate working group of international experts. These chapters provide guidelines related to diabetes-related foot disease on: prevention; classification of diabetes-related foot ulcers; offloading; peripheral artery disease; infection; wound healing interventions; and active Charcot neuro-osteoarthropathy. Based on these seven guidelines, the IWGDF Editorial Board also produced a set of practical guidelines. Each guideline underwent extensive review by the members of the IWGDF Editorial Board as well as independent international experts in each field.

We believe that the adoption and implementation of the 2023 IWGDF guidelines by healthcare providers, public health agencies, and policymakers will improve the prevention and management of diabetes-related foot disease, and subsequently reduce the worldwide patient and societal burden this disease causes.

INTRODUCTION

The global prevalence of diabetes mellitus was 537 million in 2021 and is estimated to rise to 783 million by 2045; 75% of these people live in low- or middle-income countries (1). Diabetes-related foot disease is a source of major patient burden and societal costs. The frequency and severity of foot disease in persons with diabetes varies by region, largely due to differences in socio-economic conditions, cultural factors, and standards of and access to foot care (2). Foot ulcers are the most recognizable problem, with a yearly incidence of around 2%-4% in higher income (3), likely even higher in lower-income countries, and an estimated lifetime prevalence of 19-34% (4).

The most important factors underlying the development of foot ulcers are peripheral neuropathy, peripheral artery disease, foot deformities related to motor neuropathy, and minor foot trauma (4). These conspire to put the patient at risk for skin ulceration, making the foot susceptible to infection - an urgent medical problem. Only two-thirds of diabetes-related foot ulcers will eventually heal (5), and up to 28% may result in some form of lower extremity amputation (6). Every year, more than 1 million people with diabetes lose at least a part of their leg due to diabetes-related foot disease. This translates into the estimate that every 20 seconds a lower limb is lost to diabetes somewhere in the world (7).

Diabetes-related foot disease not only represents a personal tragedy for the affected patient, but it also affects that person's family and places a substantial financial burden on healthcare systems and society in general. In low-income countries, the cost of treating a complex diabetes-related foot ulcer can be equivalent to 5.7 years of annual income, potentially resulting in financial ruin for the patient and their family (8). Investing in evidence-based, internationally appropriate guidelines on diabetes-related foot disease is likely among the most cost-effective forms of healthcare expenditure, provided it is focused on outcomes important to key stakeholders and properly implemented (9).

INTERNATIONAL WORKING GROUP ON THE DIABETIC FOOT

The International Working Group on the Diabetic Foot (IWGDF; *www.iwgdfguidelines.org*), founded in 1996, consists of multidisciplinary experts involved in the care of patients with diabetes-related foot disease. The IWGDF aims to prevent the adverse effects of diabetes-related foot disease by developing and regularly updating international guidelines for use by all health care providers, public health agencies and policymakers involved in diabetes-related foot care. Developing and updating guidelines is managed by the IWGDF working groups. In 1999, the IWGDF published its first version of "International Consensus on the Diabetic Foot" and "Practical Guidelines on the Management and the Prevention of the Diabetic Foot". This publication has been translated into 26 languages, and more than 100,000 copies have been distributed globally. As healthcare systems and the prevalence of pathologies differ across regions in the world, the guidelines have to be adapted to local circumstances where applicable. These documents have been updated six times since then, in a 4-year cycle.

FROM CONSENSUS TO EVIDENCE-BASED GUIDELINES

While the core principles the IWGDF was founded on remain constant, the methodology by which the IWGDF guidelines have been developed has evolved over the past couple of decades. The initial guidelines, and each subsequent update, were developed by a consensus process and written by a panel of experts in the field. Systematic reviews were introduced in 2007 and formed the backbone of the guidelines' recommendations. Utilizing a multi-step review process, these guidelines were then revised by the IWGDF Editorial Board, followed by critical evaluation by global IWGDF representatives, culminating in an agreed-upon text. Finally, the IWGDF recruited representatives from over 100 countries around the world to help implement the recommended practices. In 2015, a new milestone was introduced to the IWGDF guideline development with the implementation of the GRADE framework to assess certainty of the evidence and formulate recommendations for clinical practice, based on both the available evidence and expert opinion. In 2019, we formulated clinical questions and relevant outcomes to guide the systematic review and writing of recommendations and introduced a definitions and criteria reference document for the most commonly used terms in diabetes-related foot disease (10).

THE 2023 UPDATE

For the 2023 IWGDF guidelines, the Editorial Board invited chairpersons being key investigators/clinicians in the field, with whom they selected international experts based on relevant specialty for the guideline and regional representation, to constitute seven multidisciplinary working groups, each tasked with producing a guideline on one of the following topics:

- Prevention of foot ulcers in persons with diabetes
- Classification of diabetes-related foot ulcers
- Diagnosis and treatment of foot infection in persons with diabetes
- Diagnosis and management of peripheral artery disease in persons with a foot ulcer and diabetes
- Offloading foot ulcers in persons with diabetes
- Interventions to enhance healing of foot ulcers in persons with diabetes
- Active Charcot neuro-osteoarthropathy

The first six guideline chapters are updates of the 2019 guideline on the topic, while the guideline on active Charcot neuro-osteoarthropathy is new for 2023. All can be found at *www.iwgdfguidelines.org*. As in earlier versions, the IWGDF Editorial Board produced a document titled "Practical Guidelines on the prevention and management of diabetes-related foot disease", based on these seven guidelines, intended as a brief outline of the essential parts of prevention and management of diabetes-related foot disease. We advise clinicians and other healthcare professionals to read the full guideline on each topic for the specific and detailed recommendations and the rationale underpinning them, as well as the associated systematic reviews for a detailed discussion of the evidence. In addition, this current

publication provides a more detailed description of the GRADE methodology followed and the process to develop the recommendations along with the rationale supporting them.

New in 2023, we took a more rigorous and strict approach by using the GRADE evidence-to-decision framework. Each member of the working groups was trained in guideline development through the International Guideline Development Credentialing & Certification Program (*www.inguide.org*) at the guideline panel member level (level 1) and at least two members of each working group at the guideline methodologist level (level 2). Each working group formulated clinical questions and defined important outcomes that were reviewed by an international panel of independent external experts (based on relevant specialty for the guideline and regional representation) and, for the first time, people with lived experience, as well as by the IWGDF Editorial Board. Summary of judgments were created based on a consideration of aspects that were important for determining the direction and the strength of the recommendation and included desirable and undesirable effects, resources required, for each of these the certainty of evidence, values, cost-effectiveness, equity, acceptability and feasibility.

Recommendations were thoroughly discussed within the working group, and reviewed again by the same external experts. New was a voting procedure, to improve transparency and clarity. The direction and strength were first voted on by each working group member, before the discussions started. Votes were repeated after discussion. The IWGDF Editorial Board members (the authors of this publication), a total of 69 working group members (including the Editorial Board members), and a total of 119 external experts and patient representatives from 63 countries and all continents were involved in the development of the 2023 IWGDF Guidelines.

The seven guidelines, the systematic reviews supporting them, the practical guidelines, this development and methodology document and the definitions and criteria document are all published as freely accessible articles online at *www.iwgdfguidelines.org*. We recommend that healthcare providers, public health agencies and policymakers use these guidelines as the basis for developing their own local (regional or national) guidelines, where the GRADE Adolopment approach can provide as framework for this.

METHODOLOGY USED FOR THE 2023 IWGDF SYSTEMATIC REVIEWS AND GUIDELINES

This section describes the various steps and methods set up by the IWGDF Editorial Board for use by the designated multidisciplinary working groups to develop guidelines for the prevention and management of diabetes-related foot disease. The aims were to produce high-quality systematic reviews to help inform each guideline, promote consistency among the guidelines developed, and ensure high-quality documents.

In the IWGDF guidelines, we have followed the GRADE evidence-to-decision framework. This is structured around developing clinical questions and relevant outcomes per question (in the PICO-format (Patient-Intervention-Comparison-Outcome)), conducting systematic searches and assessment of the available evidence, writing a summary of judgements, followed by developing recommendations and their rationale (11, 12). We will describe in detail the five key tasks in the development of the guidelines: i) establishing a diverse expert panel to develop the guideline, ii) defining key clinical questions and important outcomes , iii) performing systematic reviews and rigorous appraisals of all available evidence that address the clinical questions, iv) assessing key summary of judgements items for each clinical question and developing recommendations and their rationale based on these summaries of judgements, and v) consulting external stakeholders on each step.

1. Establishing a diverse expert panel to develop the guideline

First, a multidisciplinary working group of independent international experts for each of the seven guidelines was invited by the IWGDF Editorial Board to develop and author the guideline. International experts were defined as those having significant experience in practising or studying the topic of the guideline and have likely published on the topic. The working groups were comprised to ensure sufficient representation from different specialities (medical, science, professional practice) and different geographical regions in the world.

Each member of a guideline working group completed a declaration of interest for the guideline that they were involved in at the start of the guideline development process. These were published online at *www.iwgdfguidelines.org*. These declarations were monitored and kept up-to-date during guideline development as an item on the agenda of working group meetings.

2. Defining key clinical questions and important outcomes

Each working group started the guideline writing process by formulating the clinical questions they intended to address. This was to provide focus and structure to the setup of the evidence-based guidelines along the line of what a clinician or a patient would ask regarding the care provided in clinical practice to persons with diabetes-related foot disease. The questions generally involved diagnosis, prognosis, or treatment, and the members of the working group reached a consensus on the clinical questions they planned to address. The clinical questions were reviewed for their clinical relevance by the IWGDF Editorial Board and a panel of international external experts (including representatives of people with lived experience) from various geographical regions, to ensure global relevance to a wide

range of healthcare professionals and people with the disease so as to provide the most useful clinical information. These experts were selected by the working groups, under the guidance of the IWGDF Editorial Board. The final clinical questions were used for the systematic review and guidelines.

The clinical questions regarding interventions took the format of the "PICO", an acronym that at least includes the population (P) at risk (who are you studying?), the intervention (I) planned (what will you be doing?) and the outcome (O) of interest (what are the consequences of the intervention?). The C is for comparator or control and concerns the main alternative to the intervention considered, usual care, or nothing. The clinical questions regarding diagnosis or prognosis, take the format of the "PECO", which includes the population, exposure/assessment, comparator, and outcome.

Each working group devised specific outcomes following the GRADE process (13-15). Given the lack of a validated core outcome set for diabetes-related foot disease, the set of outcomes defined by the IWGDF-EWMA (16) was used as a guide to define the outcomes selected, and additionally expert opinion of the working group was used where such guidance did not exist. An extensive list of potential outcomes was rated on importance by the international external experts in the field (including the representatives with lived experience), with a score of 1 (not important), 2 (of some importance) or 3 (very important). Subsequently, each working group member independently rated these outcomes with a score ranging from 1 to 9, according to GRADE, and defined as 'not important for decision-making' (score 1-3.5), 'important but not critical for decision-making' (score 4-6.5), 'critically important for decision-making' (score 7-9) (17). Group means and medians were calculated, and discussed in a meeting with all working group members until a consensus was reached. Working groups were informed that critical outcomes, which have a larger effect on decision-making and recommendations, were the most important to address. As a last step, outcomes were matched with the interventions assessed as formulated in the clinical questions, with a maximum number of outcomes to be considered relevant per intervention, dependent on the question.

Following this multistep revision, the clinical questions and outcomes were finalized in February 2022.

3. Performing a systematic review (and meta-analysis)

Each working group undertook at least one systematic review of the medical literature that was designed to form the basis for the evidence-based guidelines. Each systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18, 19) (*www.prisma-statement.org*). Each working group used the AMSTAR tool to check that they were addressing the most important aspects of their systematic review (*amstar.ca/Amstar_Checklist.php*). Systematic reviews were prospectively registered in the PROSPERO database for systematic reviews before the literature search started (*www.crd.york.ac.uk/prospero*).

The literature databases used for each systematic review were PubMed (via Medline), and either EMBASE (via Ovid SP), the Cochrane database, or both. Each working group devised a search string for each database. Individual working groups could consult a medical librarian to help in devising their search string. Study designs included in the systematic review on interventions were randomized controlled trials. Depending on the number of papers found with this higher-level study design, working groups could also include lower-level designs, e.g., non-randomized controlled trials, case-control studies, cohort

studies, (controlled) before-and-after studies, interrupted time series, prospective and retrospective non-controlled studies, cross-sectional studies and case series. Case reports were excluded from the systematic reviews. For diagnostic and prognostic questions, observational study designs were included. If systematic reviews (with meta-analysis) were identified, reference checking of the papers identified in that publication was performed to cross-check (and as such validate) our search results, but the systematic review itself was excluded. Literature in all languages was searched for and included.

Trial registries
The working groups searched two trial registries for ongoing studies: The World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) (*apps.who.int/trialsearch/default.aspx*) and the ClinicalTrials.gov registry (*www.clinicaltrials.gov*). A sensitive search string derived from the original search string for the systematic review was used to search for relevant studies in these trial databases.

Validation set
To ensure that the search string used for the systematic review was robust, working groups created a validation set of 10-20 known key publications from the last four years for each systematic review before performing the literature search. If any of the papers in the validation set was not identified in the literature search performed, the working group modified the search string.

Date of search
The literature search for all systematic reviews was conducted in March 2022. At the discretion of the working group the full search could be updated in November 2022. Any trial that was identified in a trial registry and was published before November 1, 2022, was also included.

Assessing retrieved publications from the search
Two members of each working group independently reviewed publications by title and abstract to assess their eligibility for inclusion in the analysis based on four criteria that were tailored to thre specific question at hand: population; study design; outcomes; and intervention or exposure/assessment. Publications were listed in the online application Rayyan (20) (*www.rayyan.ai*) to help in the eligibility assessment of publications. At their discretion, the working groups could calculate Cohen's kappa values to test for agreement between the two reviewers. The two reviewers discussed any disagreement on which publications to include and reached a consensus. If necessary, a 3rd member of the working group was involved to arbitrate. The same two reviewers independently assessed selected full-paper copies of included publications on the same four criteria for final eligibility. Reference lists of included papers were not tracked. Regarding the population of interest, if a mixed population was present in the studies retrieved, the minimum proportion of the population of interest in the sample, as defined by the working group (e.g. 80%), was used for eligibility.

To assess for possible publication bias or selective reporting of results, the working groups assessed studies identified by trial registries in the WHO and ClinicalTrial.gov databases using the methodology as outlined in the GRADE handbook (17). From relevant trials identified from these databases, related publications were searched for in the original literature search database, using the trial registration number of these relevant trials. If no publications were identified, the principal investigator of the trial was contacted and asked about the status of the trial and any possible results from the trial. Funnel plots were constructed where possible.

Data extraction

Data were extracted from each included publication that had a controlled study design and were summarized in an evidence table. This table included participant and study characteristics, characteristics of the intervention and control conditions, and primary and secondary outcomes. One of the reviewers of the original team of two extracted the data, while the other reviewer checked the table for content and presentation. All members of the working group discussed the data in the evidence tables.

Each working group created a PRISMA flow diagram showing the process of selection of papers for the qualitative analysis, and a risk of bias table presenting in detail the risk of bias per included publication.

Classifying study design and level of evidence

For each included publication, we used the Scottish Intercollegiate Grouping Network (SIGN) algorithm for classifying study design for questions of effectiveness (*www.sign.ac.uk/assets/study_design.pdf*). The same two reviewers that reviewed publications for eligibility independently assessed included publications with a controlled study design for methodological quality (i.e., risk of bias), using scoring sheets developed by the Dutch Cochrane Centre (*netherlands.cochrane.org/beoordelingsformulieren-en-andere-downloads*).

The two reviewers discussed any disagreement regarding the risk of bias and reached a consensus. The SIGN level of evidence was determined based on the risk of bias for each publication using the SIGN Grading System for Levels of Evidence (*www.sign.ac.uk/assets/sign_grading_system_1999_2012.pdf*) (21). Level 1 refers to randomized controlled trials and Level 2 refers to case-control, cohort, controlled before-and-after designs or interrupted time series. Risk of bias was scored for each study as: ++ (very low risk of bias); + (low risk of bias); or, – (high risk of bias).

Additionally, working groups assessed all publications with a controlled study design for quality of reporting using the 21-item scoring system for reports of clinical studies developed by the IWGDF in collaboration with EWMA (16). To prevent any conflict of interest, reviewers who were one of the authors of any study assessed for inclusion did not participate in the assessment, data extraction or discussion of publications of that study. They were involved in the working group discussions of the summary of judgements and recommendation to which that study contributed.

Rating of the certainty of evidence

The certainty of the evidence obtained through the systematic review was rated per PICO and for all outcomes related to that PICO. The certainty of evidence was rated as high, moderate, low, or very low, based on the assessment of the following items:

- Risk of bias (scored from the risk of bias assessment per paper)
- Inconsistency of results (i.e., true differences in the underlying treatment effect may be likely when there are widely differing estimates of the treatment effect [i.e. heterogeneity or variability in results] across studies)
- Imprecision (i.e., results are imprecise when studies include relatively few patients and few events and thus have a wide confidence interval (CI) around the estimate of the effect, providing uncertainty about the results)

- Indirectness (i.e., direct evidence consists of research that directly compares the interventions in which we are interested, delivered to the populations in which we are interested, and measures the prioritized outcomes important to patients)
- Publication bias (as could be obtained from the Clinical Trials search or from funnel plots, see above), where appropriate

The starting point in the certainty of the evidence rating when >1 level 1 study (RCT) was involved was "high". When only one RCT was available, the certainty rating started at moderate, as inconsistency could not be assessed. When no RCTs were available, so only observational controlled studies (level 2, i.e. cohort, case-control), certainty rating started at low. When only non-controlled studies were available, the certainty rating started at very low.

For each of these five above items that were scored as 'present', the certainty of the evidence rating was lowered by one level. For example: the certainty of the evidence could be reduced from "high" to "moderate" when the risk of bias in included studies was high, and further to "low" whe also imprecision was present. The certainty of the evidence could be raised based on the presence of a large effect size or evidence of a dose-response relationship (for observational studies only). For each of these two items that were scored as "present", the certainty of the evidence rating was raised by one. For example, the certainty of the evidence was raised from "low" to "moderate" when the effect size was large. Many of the older papers identified in the systematic reviews lacked data to calculate or assess for indirectness or imprecision. If so, we did not take these older papers for these certainty of evidence rating items into account.

Meta-analysis

A meta-analysis for the intervention-based systematic reviews was done when >1 RCT was available that included the same or a similar intervention, the same or a similar comparator, and the same outcome. Each assessable outcome for each clinical question was meta-analysed if appropriate, and we followed the methodology as outlined in the GRADE and Cochrane Handbooks (15, 17). The aim of the meta-analysis was to generate a pooled effect estimate. For dichotomous outcomes, all meta-analyses were performed using Mantel-Haenszel's statistical method and random effect models anticipating substantial heterogeneity. The results were reported as risk ratios and 95% confidence intervals. For continuous outcomes, meta-analyses were performed using the inverse variance method and random effect models anticipating substantial heterogeneity. The mean difference was reported as the effect measure, with 95% confidence intervals. For statistical analyses, two-tailed tests with alpha set at 0.05 were used. Heterogeneity was assessed using the Chi-squared test and the I^2 statistic and interpreted as low (0–49%), moderate (50–74%) or high (75–100%). A forest plot was made to visualize outcomes. Meta-analyses were conducted using RevMan 5, version 5.4 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). If no meta-analysis was done, the reason(s) for doing so were provided.

Summary of findings

At the discretion of each working group, a summary of findings tables was created for each clinical question in accordance with Cochrane and GRADE handbooks (15, 17). The summary of findings tables display the key information addressing each comparison, including the population, interventions, controls, and outcomes. For each outcome, the working group members added the number of studies, the number of participants, the relative effect, anticipated absolute effects (as determined by the GRADEPro online application), the certainty of evidence assessment (with explanations), and evidence statements in a controlled language based on effect size and certainty of evidence assessment using the GRADEPro online application summary of finding table templates (*www.gradepro.org*) (17). Thus, each summary of findings table summarises the entire process for each comparison. For comparisons that did not have controlled trials reporting any outcomes, findings were narratively summarised.

Conclusions and evidence statements

Finally, the two assessors per intervention group drew conclusions for each intervention based on the available evidence per outcome, formulated as evidence statements for the group of outcomes and accompanying assessment of the certainty of the evidence, according to Cochrane and GRADE (15, 17). The assessors rated the certainty of the evidence for each formulated evidence statement as "high", "moderate", "low" or "very low". GRADE defines "high" as "We are very confident that the true effect lies close to that of the estimate of the effect"; "moderate" as "We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different"; "low" as "Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect", and "very low" as "We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect" (17). All members of the working group participated in the discussion of these conclusions, reaching a consensus on the content and formulation of the conclusions.

The content of the statement was based on the evidence, with a focus on point estimates of effect, as advocated by GRADE, rather than statistical significance or 95% confidence intervals (15, 17). The wording for each evidence statement was in accordance with the methods described by GRADE. For an effect with a moderate certainty of evidence, the statement contains "likely results in …"; for an effect with low certainty of effect, the statement contains "may result in …"; for statements with a very low certainty of effect, the statement contains "(very) uncertain"; when the effect or effect size could not be estimated, no evidence statement was provided. All members of the working group discussed these evidence statements until a consensus was reached.

Systematic review of diagnostic procedures

We obtained specific methods for the systematic review of diagnostic studies from Brownrigg et al (22) and PRISMA guidelines (19), and we asked all groups systematically reviewing studies and writing guidelines on diagnostic procedures to follow the methods used in this study (22). Working groups assessed the methodological quality of included studies against parameters included in the QUADAS tool, a consensus quality assessment tool designed specifically for diagnostic accuracy studies (23). Reviewers extracted data and entered them in a QUADAS data extraction form and calculated positive and negative likelihood ratios' for each test in each study (24, 25).

Systematic review on prognosis
The methods used for the systematic review on prognostics in peripheral artery disease were the same as the ones used in the 2019 systematic review on this topic (26). To assess the methodological quality of included studies we used the QUIPS tool, designed specifically for prognostic studies (27, 28). To assess the risk of bias we used the QUIPS Risk of Bias Assessment Instrument for Prognostic Factor Studies.

Archiving and record keeping
For archiving of papers and recording of screening decisions and study scores, a full audit trail was kept, so that the process, procedures used and decisions made were transparent, including the literature search, selection process, votes for clinical questions, outcomes, and recommendations, and all assessments (e.g. risk of bias) and pdfs of full papers.

4. Assessing key summary of judgements items and writing the recommendations and their rationale

Summary of judgement tables
Based on the systematic review and meta-analyses (when available), the summary of findings tables (if applicable) and expert opinion, teams of two members of the working group drafted the summary of judgements tables for each clinical question following the GRADE Evidence-to-Decision domains tables. These summary of judgement tables are tables in which aspects of the intervention that are important to consider for developing and writing the recommendation, are assessed and described. The summary of judgement items assessed included desirable and undesirable effects, values, the certainty of evidence of effects, the balance of these effects, resources required, the certainty of evidence for these required resources, cost-effectiveness, equity, acceptability and feasibility. For each item, a judgement was made, the research evidence was summarised and additional considerations could be described. Definitions for these items can be found in the GRADE handbook (17) and at the end of the summary of judgements tables used in the guidelines.

Writing the recommendations and their rationale
After careful weighing of the summary of judgements, the same teams of two members of the working group drafted the direction, strength, and wording of the recommendation(s) for the specific clinical question. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Recommendations were rated as 'for' or 'against' the particular intervention or 'either the intervention or the comparison', and the strength of each recommendation was rated as 'strong' or 'conditional'.

The certainty of evidence, rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE, as explained above, was added to the strength of the recommendation.

Summary of judgements tables and recommendations for each question were extensively discussed in online meetings of the working group. Judgements for individual evidence-to-decision domains could change based on these discussion and arguments provided. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention (or 'either the intervention or the comparison'), and the strength of each

recommendation as 'strong' or 'conditional'. A quorum of 60% of members was needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the summary of judgement tables in the supplemental material of each guideline.

Based on the summary of judgement tables, the rationales for the recommendations were written by the same team of two assessors of the working groups. These rationales are narrative (systematic) descriptions of how the working group came to the direction and strength of the recommendation and summarizes the research evidence for the items in the summary of judgement tables. (13, 14). In addition, expert opinion and aspects relevant to communicate to the reader regarding the intervention or recommendation could be added to these rationales.

Finally, all recommendations, with their rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same international external experts and persons with lived experience who reviewed the clinical questions and outcomes, as well as by the IWGDF Editorial Board. The working group then collated, reviewed and discussed all feedback on the consultation manuscript and revised it accordingly to produce the final guideline.

5. External review and feedback

The members of the IWGDF Editorial Board met online and in person on several occasions to thoroughly review each of the guideline chapters, which were then revised by the working groups based on this editorial review. The working groups then sent the guideline to the panel of independent international experts and people with lived experience for their critical review. The working group subsequently revised the document further based on these comments, after which the IWGDF Editorial Board did a final review of the recommendations and the rationale provided.

TIME INVESTMENT, EVALUATION AND UPDATING

The 2023 guideline development process for the seven guidelines developed took an estimated 10 years full-time working hour equivalent, involving working group and editorial board meetings, training, screening and assessment of the literature, completing tables, and writing and review of all documents. The 2023 process for guideline development will be evaluated a few months after publication of the guidelines within the IWGDF editorial board. Both the content, the process and methodology used will be evaluated and if needed, improvements or changes for the next round of guideline development will be defined. We will update each guideline and systematic review again in four years (2027).

CONCLUDING REMARKS

With the worldwide diabetes epidemic, it is now more imperative than ever that appropriate action be taken to ensure access to quality care for all people with diabetes, regardless of their age, geographic location, economic or social status. The IWGDF Guidelines on the prevention and management of diabetes-related foot disease are the result of a rather unique process that over 24 years has become more and more founded in a strong evidence base, with procedures to guarantee consistency, transparency and independency. The evidence base for how to help prevent and optimally manage diabetes-related foot disease is progressively growing, but it remains a challenge how to use this data to optimize outcomes in different healthcare systems, in countries with different resources and different cultures. The IWGDF hopes to see an increase in global awareness of diabetes-related foot disease and aims to stimulate this process of transforming global guidelines to local guidelines, leading to improved foot care throughout the world. Supported by limited published evidence of improved outcomes associated with using these IWGDF Guidelines (9, 29-33), we believe that implementation of the 2023 IWGDF Guidelines' recommendations will result in improved prevention and management of foot disease in people with diabetes and a subsequent worldwide reduction in the patient, the economic and societal burden caused by diabetes-related foot disease.

CONFLICT OF INTEREST

Production of the 2023 IWGDF Guidelines was supported by unrestricted grants from: Advanced Oxygen Therapy Inc., Essity, Mölnlycke, Reapplix, and Urgo Medical. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines, and have not seen any guideline or guideline-related document before publication.

Full conflict of interest statements of all authors can be found online at *www.iwgdfguidelines.org*.

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REFERENCES

(1) International Diabetes Federation, IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation, 2021, *www.diabetesatlas.org*.

(2) Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care. 2020;43(5):964-74.

(3) Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24.

(4) Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376(24):2367-75.

(5) Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care. 2006;29(8):1784-7.

(6) Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008;51(5):747-55.

(7) Time to Act: diabetes and foot care. A joint publication of the International Diabetes Federation and the International Working Group on the Diabetic Foot, 2005, *www.worlddiabetesfoundation.org/files/diabetes-and-foot-care-time-act*.

(8) Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu ZR. Cost of treating diabetic foot ulcers in five different countries. Diabetes Metab Res Rev. 2012;28 Suppl 1:107-11.

(9) Zhang Y, Carter HE, Lazzarini PA, Cramb S, Pacella R, van Netten JJ, et al. Cost-effectiveness of guideline-based care provision for patients with diabetes-related foot ulcers: A modelled analysis using discrete event simulation. Diabet Med. 2023;40(1):e14961.

(10) van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, et al. Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3268.

(11) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;353:i2089.

(12) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

(13) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ (Clinical research ed). 2016;353:i2089.

(14) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

(15) Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) 2022 [Available from: *www.training.cochrane.org/handbook*.

(16) Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC, et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. Lancet Diabetes Endocrinol. 2016;4(9):781-8.

(17) Schünemann HJ, Brozek J, Guyatt G, Oxman A. GRADE Handbook 2013 [Available from: *gdt.gradepro.org/app/handbook/handbook.html*.

(18) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

(19) McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, and the P-DTAG, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018;319(4):388-96.

(20) Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

(21) Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323(7308):334-6.

(22) Brownrigg JR, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. Diabetes Metab Res Rev. 2016;32 Suppl 1:119-27.

(23) Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.

(24) Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA. 1994;271(5):389-91.

(25) Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA. 1994;271(9):703-7.

(26) Brownrigg JR, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. Diabetes Metab Res Rev. 2016;32 Suppl 1:128-35.

(27) Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.

(28) Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-37.

(29) Buggy A, Moore Z. The impact of the multidisciplinary team in the management of individuals with diabetic foot ulcers: a systematic review. J Wound Care. 2017;26(6):324-39.

(30) Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab Res Rev. 2016;32 Suppl 1:195-200.

(31) Monteiro-Soares M, Vale-Lima J, Martiniano J, Pinheiro-Torres S, Dias V, Boyko EJ. A systematic review with meta-analysis of the impact of access and quality of diabetic foot care delivery in preventing lower extremity amputation. J Diabetes Complications. 2021;35(4):107837.

(32) Anichini R, Zecchini F, Cerretini I, Meucci G, Fusilli D, Alviggi L, et al. Improvement of diabetic foot care after the Implementation of the International Consensus on the Diabetic Foot (ICDF): results of a 5-year prospective study. Diabetes Res Clin Pract. 2007;75(2):153-8.

(33) Alvarsson A, Sandgren B, Wendel C, Alvarsson M, Brismar K. A retrospective analysis of amputation rates in diabetic patients: can lower extremity amputations be further prevented? Cardiovasc Diabetol. 2012;11:18.