Update on prevention of diabetic foot ulcer

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Abstract

The diabetic foot ulcer is the most important reason for non-traumatic limb amputation. Based on recent data, it has been estimated that up to 34% of type 2 diabetes patients may develop diabetic foot ulcers once in their lifetime. Risk factors for developing foot ulcers are distal sensorimotor peripheral neuropathy, peripheral arterial disease, previous ulcers, and/or amputations. Understanding the factors that place patients with diabetes mellitus at high ulceration risk and the early treatment of risk factors, and continuous education of the patient (and/or caregivers) are essential for the prevention and management of diabetic foot complications. Implementing strategies to prevent these complications is a key aspect of diabetes care, but the most effective strategy in prevention has to be investigated. More evidence from well-designed studies is needed on this topic.

Key words: prevention, amputation, peripheral neuropathy, diabetic foot ulcer, peripheral arterial disease.

Introduction

Diabetes mellitus represents a real pandemic. According to the International Diabetes Federation [1] by 2045, approximately 700 million people will live with diabetes. In Italy [2], more than 3 million people are diagnosed with diabetes, 5.3% of the total population, and about another million people have the condition but are not aware of it. It is estimated that the incidence of lesions is around 2% per year, while the lifetime incidence is between 19% and 34% [3].

The risk for ulcer recurrence is high, with recurrence rates of 40% in the first year and 65% in the first 3 years after healing [3]. The burden of diabetic foot disease is ranked in the top 10 of all medical conditions [4]. Direct and indirect costs for such a debilitating disease are very high [5–7].

Etiology and pathway to ulceration

In people with diabetes mellitus, the risk factors for developing ulcers are distal peripheral neuropathy, peripheral arterial disease, repeated trauma, previous ulcers, and/or amputation. The most affected are male subjects, with a longer duration of illness and low socio-economic level [8–10].
About 50% of people with type 2 diabetes have neuropathy and feet at risk. Neuropathy is defined as “the presence of signs and/or symptoms of peripheral nerve dysfunction in people with diabetes in the absence of other possible causes other than diabetes [11].

There are several forms of peripheral neuropathy, but the main forms associated with the diabetic foot are distal-symmetric sensorimotor neuropathy and autonomic neuropathy. Neuropathy causes a reduction in sensitivity up to complete loss, so even small traumas (improper nail cutting, inadequate footwear, burns) can cause an ulcer. The neuropathic foot has a deformed appearance, the skin appears dry and is warm to the touch with hyperkeratosis in the plantar surface, the veins are turgid, and arterial pulses are present. Autonomic neuropathy causes alterations in the control of capillary microcirculation, with shunts opening between arterioles and veins and turgidity of the veins of the foot with a hot but dry skin surface with a tendency to develop fissures, especially at the heels. Loss of sensitivity, deformity of the foot, and limited joint mobility cause biomechanical anomalies of foot loading, so thickened skin (callus) is formed, which is responsible for a further increase in the load and development of a subcutaneous hematoma, which by autolysis causes the formation of a severe or subcutaneous cavity, which opens to the outside and therefore leads to the formation of an ulcer.

The neuropathic ulcer is localized in areas of high plantar pressure, generally on the sole at the level of the metatarsal heads, on the plantar surface of the toes, the perilesional skin is hyperkeratotic (sometimes the hyperkeratosis overhangs the ulcer), the edges are high and jagged, the bottom appears bright red, tend to granulation and with a strong tendency to bleeding, and in most cases pain is absent.

Peripheral arterial disease (PAD) is defined as any atherosclerotic arterial occlusive disease below the level of the inguinal ligament resulting in a reduction in blood flow to the lower extremity [12].

In patients with diabetic foot ulcers, approximately 50% show signs of peripheral arterial disease [13]. Compared with subjects with PAD and no diabetes, subjects with diabetes and PAD are usually younger, have a higher body mass index (BMI), and have more cardiovascular comorbidities [14].

Other clinical peculiarities of PAD in subjects with diabetes are its rapid progression and distal prevalence. Indeed, PAD more frequently affects the level of the inguinal ligament resulting in a reduced or absent, the skin is dry, dystrophic, hair is absent, and there can be fissures in the heels.

Usually, the ischemic ulcer is localized on the toes, internal and external margins, heel, interdigital spaces, has a necrotic aspect or presents areas of necrosis, the edges are flat and well defined, the perilesional tissue is ischemic (absence of perilesional hyperkeratosis), and the background is usually pale or necrotic with little tendency to bleed. In contrast, perilesional skin is pale and atrophic, and pain is present.

Neuropathy and PAD often co-exist and may lead to neuroischemic ulceration, and symptoms may be absent, despite severe peripheral ischemia. The combination of two or more of the above risk factors commonly results in ulceration. The majority of injuries to the diabetic foot are caused by trauma in the presence of neuropathy and/or PAD: repetitive stress [3], thermal trauma (hot water bags, high-temperature footbaths), chemical trauma (inappropriate use of over-the-counter corn treatments) [21].

The management and prevention of diabetic foot ulcer takes a holistic approach and includes 1) standard care (glycemic control, management of peripheral arterial disease and cardiovascular risk factors), 2) identifying the at-risk foot, 3) regularly inspecting and examining the at-risk foot, 4) educating the patient, family and healthcare providers, 5) ensuring routine wearing of appropriate footwear, 6) treating risk factors for ulceration, 7) integrated foot care.

**Standards of care**

**Glycemic control**

Glycemic control is the proven primary prevention of microvascular complications [22]. The UK Prospective Diabetes Study (UKPDS) showed that intensive glycemic control reduced microvascular complications, including neuropathy, compared with standard regimens [23], while a long follow-up (≤ 20 years) is necessary to obtain a beneficial effect on macrovascular complications [24]. According to current guidelines, glycated hemoglobin (HbA1c) goals should be individualized, with more stringent goals (6.5% (48 mmol/mol)) in younger people with a short duration of diabetes mellitus and no evidence of cardiovascular disease, if achieved without significant hypoglycemia.
Less stringent HbA1c objectives (≤ 8% (64 mmol/mol) or ≤ 9% (75 mmol/mol)) may be appropriate for elderly persons with long-standing diabetes and limited life expectancy and frailty with multiple comorbidities, including hypoglycemic episodes [25, 26].

Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. Among patients with type 2 diabetes mellitus (T2DM) who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended [25, 26].

Instead insulin therapy is indicated if there is evidence of weight loss, if symptoms of hyperglycemia are present, or when A1c levels (10% (86 mmol/mol)) or blood glucose levels (≥ 300 mg/dl (16.7 mmol/l)) are very high [25]. Only a retrospective cohort study [27] has shown that insulin glargine therapy compared with neutral protamine Hagedorn (NPH) insulin significantly reduces the risk of diabetic foot ulcer.

**Management of PAD**

Diabetic people with PAD have a much higher risk of cardiovascular events than patients who have already had a myocardial infarction or stroke [28]. Hence, they should receive prompt and aggressive cardiovascular risk, including lifestyle changes and optimization of glycemic, lipid, and blood pressure control [15, 16].

Lifestyle changes include smoking cessation, regular exercise, a healthy diet, and weight management. For glycomic control in patients with diabetes mellitus and PAD, current guidelines recommend sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit independent of A1c [25, 26].

There is concern that SGLT-2 inhibitors may raise the risk of peripheral artery disease and lower extremity amputation. Two clinical trials, CANVAS and CANVAS-R, demonstrated an approximate doubling of the risk of minor amputations with canagliflozin compared to placebo (6.3 vs. 3.4 participants with amputations per 1000 patient-years) [29]. For this reason, in May 2017, the FDA issued a Drug Safety Communication regarding the increased risk of foot and leg amputations using canagliflozin [30]. However, after reviewing new data from three clinical trials, in August 2020, the FDA removed the boxed warning about amputation risk from the diabetes medicine canagliflozin [31].

Moreover, a sub-analysis of EMPAREG-OUTCOME showed that in patients with T2DM and PAD, empagliflozin reduced mortality, hospitalization for heart failure and progression of renal disease without increasing the risk of lower extremity amputation [32]. A meta-analysis showed that empagliflozin or dapagliflozin does not increase the risk of either peripheral artery disease or lower limb amputations [33].

A post hoc analysis of data from the LEADER trial demonstrated that treatment with lixisenatide did not increase the risk of diabetic foot ulcers and reduced amputations compared with placebo [34]. The mechanisms by which lixisenatide reduced the risk of ulcer are not known.

For lipid control, low-density lipoprotein (LDL) targets < 1.4 mmol/mol (< 55 mg/dl) or a 50% reduction in LDL cholesterol are recommended [26].

High-dose statins, when tolerated, are the treatment of choice.

Other drugs such as ezetimibe and PCKS9 inhibitors should be considered when goals are not met [28, 35, 36]. Evolocumab, a PCKS9 inhibitor, added to the statin, has been shown to significantly reduce the risk of major cardiovascular events, as well as reducing the risk of major adverse limb events such as acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia in patients with and without PAD [28].

A target < 140/90 mm Hg is recommended for blood pressure control, and angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be considered first-line therapy [37, 38].

In subjects with diabetes and symptomatic PAD, antiplatelet therapy is recommended [26]. Low-dose aspirin (ASA) (75–160 mg) is effective and safe during related complications such as gastrointestinal bleeding [39].

Aspirin (ASA) or clopidogrel is indicated for secondary prevention in patients with PAD and/or other cardiovascular diseases but some data encourage the use of clopidogrel over aspirin in patients with diabetes and PAD. In the CAPRIE trial, in which 20% of participants were diabetic, there was a reduction in PAD-related events in the clopidogrel 75 mg arm compared to the aspirin 325 mg arm [40].

In subjects with diabetes who undergo lower limb revascularization, dual antiplatelet therapy (ASA + clopidogrel or ticlopidine) is recommended for at least 1 month after the endovascular procedure; after 1 month, ASA or clopidogrel should be continued lifelong [41].

The effect of a low-dose antithrombotic therapy with the new oral anticoagulants in combination with ASA has been investigated. In the COMPASS study, in the subgroup of PAD patients with diabetes mellitus (44%), the combination of rivaroxaban 2.5 mg b.i.d. with aspirin 100 mg reduced major adverse limb events including amputation (HR = 0.54; p = 0.0037) [42].
Some drugs (cilostazol, naftidrofuryl) have been shown to increase walking distance in subjects with intermittent claudication, with no clear benefit from cardiovascular effects [38]. Furthermore, cilostazol is contraindicated in patients with clinically manifest heart failure, unstable angina pectoris and MI, or coronary intervention within 6 months, as well as severe tachyarrhythmia [43].

**Strategy for prevention of diabetic foot ulcer**

Prevention of first and recurrent foot ulcers in subjects with diabetes who are at risk for ulceration is essential to reduce the risk of amputation.

In the International Working Group on the Diabetic Foot (IWGDF) Guidelines 2019 [44], five key elements underpin prevention of foot problems: 1) identifying the at-risk foot; 2) regularly inspecting and examining the at-risk foot; 3) educating the patient, family and healthcare providers; 4) ensuring routine wearing of appropriate footwear; 5) treating risk factors for ulceration.

Several studies have demonstrated that introducing a multidisciplinary team for managing the diabetic foot headed by the endocrinology department is associated with a reduction in the frequency of major amputations in patients with diabetes [45–47].

**Identifying the at-risk foot**

The absence of symptoms does not mean that the feet are healthy; the patient could have a asymptomatic neuropathy, peripheral vascular diseases, or even an ulcer without evidence. Diabetic foot screening, conducted according to guidelines developed by the International Diabetic Foot Study Group, includes a detailed medical history, physical examination of the feet, screening for the loss of protective sensitivity (LOPS) and peripheral arterial disease (PAD) [12].

The screening of peripheral neuropathy aimed at identifying the loss of protective sensitivity (LOPS) can be conducted with a 10-gram Semmes Weinstein monofilament [48] or with the Ipswich Touch Test if a 10-gram monofilament is unavailable [49] and using a structured scoring system such as the Diabetic Neuropathy Index (DNI) [50], which includes inspection of the foot (detection of ulcers, dry skin, callusities, deformities, infections), examination of Achilles tendon reflexes and evaluation of the threshold of vibratory sensation with a tuning fork or biothesiometer/neurothesiometer applied to the big toe. Screening for PAD includes taking a cardiovascular history, palpating for foot pulses, obtaining pedal Doppler arterial waveforms, and blood pressure measurements [12]. In people with diabetic foot ulcers, it is recommended to evaluate pedal Doppler arterial waveforms in combination with systolic ankle pressure and systolic ankle-brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement [12].

According to the criteria proposed by the American Diabetes Association [15], the severity of the peripheral arterial disease is studied as follows: ABI > 1.30 high probability of medial arterial calcification, ABI in the range 0.91–1.30 normal, ABI in the range 0.70–0.90 mild arteriopathy, ABI in the range 0.40–0.69 moderate arteriopathy, ABI < 0.40 severe arteriopathy.

Although evidence for a screening interval is non-existent, the ADA recommends annual screening for a person with diabetes in whom LOPS or PAD has not yet been identified.

**Regularly inspecting and examining the at-risk foot**

**IWGDF Risk Stratification**

According to the screening results, patients can be stratified according to their risk for foot ulceration [44]. Category 0 is characterized by the absence of LOP and PAD, and it is very low risk for ulceration. These persons require only annual screening. Category 1 is characterized by LOPS or PAD but in the absence of additional risk factors, and it is at low risk for ulceration. These persons require screening once every 6–12 months. Category 2 is characterized by a combination of risk factors, and it is a moderate risk. These persons require screening every 3–6 months. Category 3 includes persons at high risk of ulceration because they have LOPS or PAD associated with the history of a foot ulcer or a lower-extremity amputation (minor or major) or end-stage renal disease. These persons require screening every 1–3 months.

**Educating the patient, family, and healthcare providers**

Therapeutic education, provided in a structured, organized, and repeated way, plays an important role in preventing foot problems. Therapeutic education has been defined by the WHO as a permanent process, integrated with care and centered on the patient, which aims to help patients and their families understand the disease and the treatment, collaborate with health personnel, live more healthily and maintain or improve their quality of life [51]. The goal of therapeutic education is to improve patients’ knowledge of foot care, awareness, and self-management, and improve motivation and skills to facilitate adherence to appropriate behaviors [52, 53]. People with diabetes should learn to recognize potential...
foot problems and be aware of the steps to take when necessary.

Patients at risk should understand the relationship between glycemic control, lifestyle and foot problems [54]. For subjects with neuropathy, daily foot monitoring is essential, as well as adequate foot care, including nail and skin care, and the selection of appropriate footwear.

Shoes are one of the most important elements in the development of lesions, in particular in the presence of internal seams or a shape not corresponding to the foot. Patients should be advised to use new shoes gradually to minimize blistering and ulcers. The educational intervention program requires the design and implementation of appropriate assessment tools that can assess the skills and performance of the subjects studied. The practical demonstration to the patients of some abilities such as cutting the nails or the treatment of calluses should always be done. The educational program must provide several educational sessions over time, use various methods (e.g., individual or group sessions) and different intervals (for example, single or weekly meetings). During the educational treatment, it is essential to assess whether the person with diabetes or a family caregiver has understood the messages and has sufficient self-care skills. The educator must demonstrate skills and knowledge, and be able to assess the effectiveness of education. A team member should provide education in various sessions over time, preferably using different methods. Also, health professionals providing the instructions should receive periodic training to improve their skills in caring for patients at high risk of foot ulceration [55].

The literature data on the effectiveness of therapeutic education in injury prevention are unfortunately scarce. The last Cochrane review [56] showed that only 5 of the 12 randomized controlled clinical studies reported the effects of therapeutic education on primary endpoints. One study [57] showed after one year of follow-up that the incidence of lesions and amputations was lower in the group of patients who received an hour of group education from a podiatrist than in the group of patients who only received routine education (p < 0.001). There were two main limitations of this study. First, the trial was conducted in a single center, performed by highly trained health professionals working in a diabetic foot clinic; the reproducibility of the program should be verified in different settings. Second, the therapeutic effects of patients’ education tend to fade with time [61]. The durability of beneficial effects needs to be formally tested in a study with a longer follow-up. Several studies have shown that a structured therapeutic patient education (TPE) can bring a significant improvement in several clinical, lifestyle, and psychosocial outcomes in people who have diabetes [62–64], while there are a few data regarding the potential direct and indirect role that a structured TPE may have in the prevention of diabetic complications [65, 66]. The best setup for patient education to be beneficial in prevention may yet have to be investigated because the education of the patient for the prevention of foot ulcers receives poor attention and is a neglected opportunity [67].

Ensuring routine wearing of appropriate footwear

People at moderate or high risk for foot ulceration (IWGDF risk 2-3) have often lost the sense of pain and may not adequately judge the fit of their footwear or the level of pressure on their foot. Their footwear must be appropriate for people at increased risk for ulceration, with adequate length, width, and depth [68]. In persons with foot deformity or pre-ulcerative signs, custom-made footwear, custom-made...
insoles, or toe orthoses may be used to reduce plantar pressure, while for people with a healed plantar foot ulcer (IWGDF risk 3), therapeutic footwear needs to reduce plantar pressure in high-risk areas. Two RCTs with very low risk of bias have shown a reduction in ulcer risk with custom-made orthopedic footwear [69] or custom-made insoles [70] in persons with diabetes and a previous plantar ulcer (IWGDF risk 3).

Treating risk factors for ulceration

Pre-ulcerative signs on feet (callus, blisters, fissures or hemorrhages, ingrown or thickened toenails, and fungal infections) require appropriate treatment by an appropriately trained foot care professional. Preventative surgery [71, 72], such as flexor tenotomy, Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection, metatarsophalangeal joint arthroplasty or osteotomy, may reduce the risk of a recurrent foot ulcer. However, after a full evaluation of nonsurgical treatment options, it should only be considered by an appropriately trained foot care professional [73–76].

Integrated foot care

Integrated foot care is a combination of key elements that underpin the prevention of foot problems, and it is defined as an intervention that at a minimum integrates regular foot care and examination by an adequately trained professional, structured education, and adequate footwear [44].

Integrated foot care may also integrate foot self-management and, as necessary, reconstructive foot surgery. Several studies have shown that the home monitoring of foot skin temperatures could effectively reduce the incidence of recurrent plantar ulcers [77, 78].

Foot surgery can reduce the risk of recurrent ulcers, both plantar and non-plantar, in selected patients who have not responded to nonsurgical treatment. No controlled or non-controlled studies have included all potential components of integrated foot care. Two reviews [5, 53] have investigated the effect sizes of the various components of integrated foot care and have shown that the largest effect sizes in ulcer prevention can be found for self-management and surgical interventions and a complete integrated approach should include these as well.

Conclusions

The foot ulcer is a complication of diabetes that can be prevented. Understanding the factors that place patients with diabetes mellitus at high risk of ulceration, together with tight glycemic control and the early treatment of risk factors and continuous education of the patient and caregivers, is essential for the prevention and management of diabetic foot complications.

This paper described and analyzed the available evidence and current clinical practice recommendations on this topic.

Table I. Flow diagram for prevention of diabetic foot ulcers

| Glycemic control | Management of PAD | Identifying the at-risk foot | Regularly inspecting and examining the at-risk foot |
|-----------------|------------------|----------------------------|---------------------------------|
| HbA1c target : | Lifestyle changes: | • Medical history | • IWGDF Risk Stratification Follow-up |
| • For most adults is < 7.0% (< 53 mol/mol) | • Smoking cessation | • Objective examination of the feet | |
| • For young patients is < 6.5% (48 mol/mol) | • Regular exercise | • Screening of peripheral neuropathy and PAD | |
| if this can be achieved without significant hypoglycemia or other adverse effects of treatment | • Healthy diet | | |
| • For elderly patients is < 8% (64 mmol/mol) or ≤ 9% (75 mmol/mol) may be adequate | • Weight management | | |

| Educating the patient, family and healthcare providers | Ensuring routine wearing of appropriate footwear | Treating risk factors for ulceration | Integrated foot care |
|--------------------------------------------------------|---------------------------------------------|---------------------------------|---------------------|
| • Design and implementation of appropriate assessment tools | • Footwear fits | • Pre-ulcerative lesion treatment | • Combination of key elements that underpin prevention of foot problems |
| | • Custom-made orthopedic footwear | • Preventative surgery | |
| | • Custom-made insoles | | |
The management of diabetic foot prevention ulcers takes a holistic approach to the patient (Table I), but the best setup for diabetic ulcers may yet have to be investigated. Diabetic foot ulceration poses a heavy burden on the patient and the healthcare system, but still ulcer prevention is a neglected opportunity [79].

In 2015, authors of guidelines from the International Working Group on the Diabetic Foot (IWGDF) [80] underlined that a shift in priority in care and research in diabetic foot disease was needed, while other experts argued that more evidence from properly designed studies on this topic is necessary [81].

However, after 4 years, diabetic foot ulcer prevention is still neglected in research. Between 2015 and 2019, 83 RCTs on diabetic foot were published, but only two RCTs were conducted on prevention while 72 were on ulcer healing [82].

We hope for more resources and investments in diabetic foot ulcer prevention in research and clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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