82162_Auto_Edited.docx

WORD COUNT 6456
TIME SUBMITTED 03-FEB-2023 05:59PM
PAPER ID 96225522

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 82162
Manuscript Type: MINIREVIEWS

Understanding the multifaceted etiopathogenesis of diabetic foot complications in individuals with chronic diabetic conditions

Diabetic foot complications in individuals diabetic

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Abstract

A chronic metabolic disease known as diabetes mellitus is characterized by a disorder in the production or use of insulin. Diabetic foot disease – a term that includes infections, diabetic foot ulcers, and gangrene – is one of the most severe complications of diabetes and the most common cause of hospitalization in individuals with diabetes. The aim of this study is to provide an evidence-based overview of diabetic foot complications in people with long-term diabetes. Due to neuropathy, diabetic foot infections can occur in the form of ulcers and minor skin lesions. In patients with diabetic foot ulcers, ischemia and infection are the main causes of non-healing ulcers and amputations. Hyperglycemia compromises the immune system of individuals with diabetes, leading to persistent inflammation and the delay in wound healing. In addition, the treatment of diabetic foot infections is challenging due to the challenges in accurate identification of pathogenic microorganisms and widespread issue of antimicrobial resistance. As a result, the warning signs and symptoms of diabetic foot problems can be easily overlooked. Other issues include peripheral arterial disease and osteomyelitis; hence, the risk of foot complications in people with diabetes should be assessed annually. Although antimicrobial agents represent the mainstay of treatment for diabetic foot infections, if the peripheral arterial disease is present, revascularization should be considered to prevent limb amputation. A multidisciplinary approach to the prevention, diagnosis, and treatment of people with diabetes – including patients with diabetic foot ulcers – is of utmost importance to reduce the cost of treatment and the adverse consequences of diabetic foot complications, particularly major amputations.

Key Words: diabetic foot; diabetes mellitus; foot ulcer; infection; peripheral arterial disease

Matijević T, Talapko J, Meštrović T, Matijević M, Erić S, Erić I, Škrlec I. Understanding the multifaceted etiopathogenesis of diabetic foot complications in individuals with chronic diabetic conditions. *World J Clin Cases* 2023; In press

Core Tip: Diabetic foot disease is a common and debilitating consequence of diabetes mellitus. Unfortunately, the recurrence rate of diabetic foot ulcers is exceptionally high, even after effective wound healing. Risk factors for foot ulcers include peripheral neuropathy, peripheral arterial disease, mild or recurrent foot trauma, infection, foot abnormalities, history of diabetic foot ulcers or amputations, and Charcot osteoarthropathy. However, poor wound healing is thought to be the major cause of long-term diabetic wounds, while the presence of polymicrobial infections may further compound this issue. Additional studies are needed to understand the underlying mechanisms and fill the knowledge gaps that would ultimately lead to successful treatment.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by insufficient insulin production or insufficient insulin use, currently affecting around 537 million people worldwide. It is forecasted to grow to 693 million by 2045 if adequate preventive measures are not implemented[1,2]. The increase in prevalence is higher in developing countries compared to developed high-income countries[3]. Two main and most prevalent types are diabetes mellitus 1 and 2, which have entirely different pathogenesis, but complications tend to overlap ultimately[4]. One of the most severe complications of diabetes and the most common cause of hospitalization of people with diabetes is diabetic foot disease, which is a term that includes infections, diabetic foot ulcers (DFU), and gangrene[5,6]. The risk of developing DFU is 25%, similar for patients with DM types 1 and 2[6,7]. Consequently, diabetes is one of the leading causes of limb amputations worldwide, as it accounts for more than 60% of non-traumatic lower extremity amputations, with approximately 80-85% being preceded by the DFU[8,9]. Translated to numbers, this means that more than 1 million people with diabetes suffer limb loss every year; to put it into perspective, every 20 s, there is a need for amputation somewhere in the world due to diabetes[8,9]. People with diabetes and diabetic foot

complications have a higher mortality rate than individuals with diabetes without foot complications[10,11]. Furthermore, individuals with diabetes have a more increased risk of mortality after an incident DFU compared to people of the same age and duration of diabetes without a DFU[12]. The mortality rate increases in people with diabetes and associated amputations[11]. Ischemic heart disease is a significant cause of premature mortality in patients with DFU[13], and patients with neuropathic DFU have even have even higher mortality burden[12,13]. Thus it is evident that diabetes represents a substantial public health and economic burden; more specifically, financial costs related to the treatment of diabetes reach up to 673 million USD annually, and 20-40% of the healthcare budget spent on diabetes is related to foot complications[5,14,15]. Apart from financial burden, diabetic foot disease (particularly DFU) is a major personal tragedy with a significant impact on patients' quality of life (with a considerable impact on their families as well) and a burden for health care professionals and institutions. Despite the generally accepted need for a multidisciplinary approach in the prevention, diagnosis, and management of individuals with diabetes, including patients with DFU, data related to financial cost and negative outcomes of diabetes foot complications (especially major amputations) is still rather insufficient[9]. Although guidelines related to the diabetic foot are available, there is only limited high-quality evidence for many critical questions on the one hand and the need for better implementation in clinical practice on the other. Therefore, a better understanding of diabetic foot complications by all involved clinical experts is fundamental for further improvement in the care of this group of patients.

PATHOPHYSIOLOGY

Foot ulcers in individuals with diabetes present with specific pathophysiology, which affects clinical presentation and management. Ischemia and neuropathy are two key pathological components that lead to diabetic foot complications, while infection usually arises as a secondary phenomenon. Nevertheless, all three components often have a synergistic role in the etiologic triad[6]. Peripheral neuropathy is present in

around 50% of people with diabetes, gradually developing "high-pressure" zones on foot with decreased protective sensation, which is considered the leading cause of DFU[16]. Although it seems changes are arising considering the most prevalent etiopathology, ischemia has an increasingly prominent role in causing DFU. Recent large-scale studies showed that in high-income countries, almost half of the DFUs are neuroischaemic or ischemic in origin, and patients presenting with manifest peripheral arterial disease (PAD)[17–19] and frank neuropathic ulcers are still more prevalent in low-income countries[3,20–22].

The pathogenesis of diabetic neuropathy is still not fully understood, but it is known that it can affect sensory, motor, and autonomic fibers [14]. Two accepted potential mechanisms include ischemic injury to the nerve due to changes to vasa nervorum and oxidative stress in the nerve caused by increased activity of the sorbitol pathway[6]. Sensory neuropathy causes decreased pain and pressure sensation, vibratory perception, proprioception, and altered temperature sensation. Motor neuropathy causes atrophy of foot muscles with secondary foot deformity and impaired gait, leading to high plantar pressure and elevated mechanical stress [23]. Finally, autonomic neuropathy causes anhidrosis, which makes dry skin susceptible to minor fissures and impaired microcirculation through arteriovenous shunts[6,24,25].

Microvascular dysfunction in patients with diabetes is also caused by structural and functional changes in endothelial cells resulting in impaired vasodilatory response, hypercoagulation, and inflammation in the wall[23,26]. Although ischemic complications in diabetes have been long prescribed to the changes in microcirculation, which mistakenly led to the pervasive opinion that people with diabetes will not benefit from revascularization, today it is known that microvascular dysfunction and PAD are the leading cause of vascular impairment in patients with diabetes[6,27]. Also, PAD and infection are instrumental in preventing the healing of DFU, as well as two main factors leading to significant amputations in people with diabetes[17,28,29]. PAD in diabetic individuals has some specifics compared to the general population. Atherosclerotic

plaques are usually multisegmental, bilateral, located infrapopliteal, involving anterior and posterior tibial arteries with relative sparing of foot arteries and impaired collateral formation[23,27,30].

People with diabetes are more susceptible to infections because of neuropathy, peripheral vascular disease, microcirculation dysfunction, and immunopathy[6,29]. Diabetic foot infections (DFI) most often occur in place of minor skin breaks due to neuropathy but most often in ulcers[31]. Although it can range from uncomplicated superficial infections, compared with infections in the general population, DFI are more prone to rapid progression into deep structures of the foot, including fascia, tendons, muscles, joints, and bones. In addition, because of specific foot anatomy with compartments, infection usually spreads along the tendons. At the same time, the ensuing inflammatory response can cause high pressures in compartments and further impairment of foot circulation, leading to a more rapid progression of infection[32–34]. Therefore, DFI can easily become a foot- and life-threatening condition and a direct cause of amputation in 25-50% of individuals with diabetes, especially if combined with PAD[5,23,31]. Risk factors for developing DFI are neuropathy, limb ischemia, chronic or recurrent deep foot ulcers, traumatic ulcers, chronic renal failure, and poor glycemic control[31,35].

Finally, it should be emphasized that not all patients with diabetes are at risk for DFU[8]. Established neuropathy, foot deformity, and peripheral arterial disease are the main risk factors. Additional risk factors are previous foot ulceration and minor or major limb amputation[36,37]. Patients who develop DFU are usually individuals with long-standing diabetes (>10 years), male, have poor glycemic control and have other diabetes-related comorbidities[38]. An incipient trigger for an ulcer is often a minor injury caused by repetitive trauma while walking in patients with decreased protective sensation, changed biomechanics, and foot deformity with high-pressure zones resulting from neuropathy. Furthermore, the skin of individuals with diabetes is dry because of autonomic neuropathy and is more prone to breakdowns and fissures[5,6]. Although foot ischemia as the causative factor in DFU was underestimated before, today we know that

at least half of DFU is neuroischaemic and ischemic in origin[17,19]. Ischemia and infections are the main contributing factors in non-healing ulcers and amputations in patients with DFU[17,28].

IMMUNE RESPONSE TO HYPERGLYCEMIA

The immune system regulates inflammation and maintains the organism's homeostasis[39]. In addition, the innate and adaptive immune systems have an essential function in properly developing all stages of wound healing[40]. The innate immune system consists of different types of cells (macrophages or monocytes, innate lymphocytes, basophils, natural killers (NK), granulocytes, and mast cells)[40]. It is activated quickly but with low specificity[40]. On the other hand, the adaptive immune system includes T and B lymphocytes and is activated more slowly with long-term memory and high specificity[40].

The immune system of individuals with diabetes is weaker than the immune system of those without diabetes, and hyperglycemia increases the number of macrophages and pro-inflammatory cytokines, directly affecting in turn phagocytosis, chemotaxis, and leukocyte activity[40,41]. The imbalance of immune cells leads to the deterioration of the immune environment of the wound, and it will remain in the inflammatory phase, which makes healing difficult[39]. A delayed and incomplete wound-healing process leads to impaired healing due to continuous inflammation leading to the development of diabetic wounds in DFU[42]. Acute wounds heal in time, while chronic wounds do not heal because they are in the stage of early inflammation[40]. Non-healing wounds are the main entry points for wound infection[43]. Controlling hyperglycemia accelerates wound healing and helps avoid adverse effects on cellular immunity and infections[41].

Dysfunctions of immune cells, such as neutrophils and monocytes, can lead to oxidative stress and inflammatory response during diabetic wound healing[42]. Diabetic wounds are permanently stopped in the inflammatory phase[43]. This is precisely why people with diabetes are more sensitive to wound infection, as well as due to a deficit in the mechanisms of the innate immune response[43]. In addition, hyperglycemia affects the

proliferation and migration of fibroblasts and keratinocytes, resulting in unsuccessful epithelization[43].

Neutrophils participate in the early stages of wound healing[42]. At the wound site, there are high levels of neutrophil elastase, which originates from neutrophil extracellular traps (NET) and contributes to the degradation of the wound matrix, thus delaying wound healing[42]. NETs interfere with wound healing, especially in people with diabetes[42].

Macrophages have two main types of polarization – namely inflammatory macrophages (M1) and wound-healing macrophages (M2)[42]. During normal wound healing process, there is a predominance of M1 macrophages in the initial stages, followed by their polarization into M2 macrophages[39]. Macrophages initiate the inflammatory phase of diabetic wound healing, while the delayed polarization of macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) leads to abeyant wound healing and chronic inflammation[42]. M1 macrophages eliminate pathogenic bacteria, cellular debris, and damaged matrix, promoting inflammation[39]. M2 macrophages are anti-inflammatory and have the ability to suppress the inflammatory response by releasing IL-4 and IL-10[39]. Hyperglycemia prevents the polarization of macrophages from the M1 to M2 phenotype[39]. This is important, as the polarization from M1 to M2 enables the timely restoration of damaged skin[42]. Furthermore, hyperglycemia and an immunosuppressive environment in individuals with diabetes lead to macrophage dysfunction and reduce phagocytic capacity[42]. The proportion of M1 macrophages in diabetic wounds increases[42]. Impaired polarization to the M2 phenotype in diabetic wounds is associated with reduced angiogenesis, poor collagen deposition, and decreased wound closure[42]. Depletion of anti-inflammatory M2 macrophages in the wound causes further tissue damage[42].

People with diabetes, especially those with DFU, have a significantly lower number of naïve T-cells[40,44] and an increased number of memory and effector T-cells[42]. In addition, the expression of inflammatory chemokine receptors is significantly reduced in individuals with diabetes[40,44]. The decrease in the diversity of T-cell receptors and

the proliferation of effector T cells can be seen as biomarkers of inflammation due to chronic DFU[42]. A subpopulation of regulatory T-cells (Treg) promotes the repair and regeneration of various tissues, including the skin[40]. Treg plays an essential role in angiogenesis and tissue regeneration in diabetic wounds[40], and people with diabetes have impaired Treg cell function[42]. Namely, people with diabetes have a constant pro-inflammatory environment, with elevated levels of IL-1, TNF-α, and IL-6 and regulation of regular T cell expression[42].

In a nutshell, wound healing is a complex process that results in the establishment of normal physiological function[43]. The wound healing process involves several overlapping phases (coagulation, inflammation, proliferation, and remodeling)[40,43].

During the normal wound healing process, there is an initial recruitment of platelets that create a fibrin clot, followed by the recruitment of inflammatory cells (monocytes and neutrophils) that release pro-inflammatory cytokines[40,43]. After the inflammation subsides, a proliferative phase follows, characterized by angiogenesis (i.e., the creation of new blood vessels) and the polarization of M1 macrophages into M2 macrophages[[43]. M2 macrophages promote the secretion of anti-inflammatory cytokines and angiogenesis, as well as the proliferation of fibroblasts and the formation of extracellular matrix[40]. Consequently, scar tissue formation and remodeling into healed tissue ensues[40].

In diabetic wounds, the process is somewhat different. Diabetic wounds have weak recruitment of platelets, and increased recruitment of neutrophils and M1 macrophages, resulting in increased pro-inflammatory response and damage to the surrounding tissue[40]. Due to the increased secretion of inflammatory cytokines, this phase is prolonged, making it more difficult to pass to the following[43]. As the inflammatory phase is prolonged, angiogenesis does not occur. Poor microcirculation creates a hypoxic environment, leading to oxidative stress, inflammatory polarization of M1 macrophages, and damage to fibroblasts[40]. Polarization in M2 macrophages is very weak[40]. Therefore, damaged cells remain in an inflammatory state, and re-

epithelialization does not occur, which can ulcerate the skin, and the wound does not heal[40,43].

MICROBIOLOGICAL PROFILE OF DIABETIC FOOT INFECTIONS

The microbiological aspects of diabetic foot infection, which is a frequent complication of this condition, have been increasingly understood with the pervasive utilization of both classical microbiological and molecular methods. One of the most important challenges is to delineate microorganisms that are purely incidental from those which are true pathogens, as it is known that the infections of diabetic foot may harbor a plethora of different species[45,46]. There is also a question of contamination, where the microbiological analysis of the diabetic foot is further hindered by the potential presence of commensal bacteria in clinical samples[46]. On the other hand, conventional culturing methods may also give rise to false negative results, as more than 37% of samples are considered culture-negative[45].

In accordance with the guidelines published by the Infectious Diseases Society of America (IDSA), diabetic foot infections can be classified into three distinct categories: limited superficial infections presenting with mild symptoms, deeper moderate infections leading to more pronounced symptoms, and severe infections with metabolic changes and true systemic response[47,48]. These differences in clinical presentation warrant different approaches in treatment, as superficial and moderate infections necessitate the administration narrow-spectrum antimicrobials orally or intravenously for only a short period of time, whereas severe infections require parenteral administration of broad-spectrum antibiotics[49]. However, the exact characterization of causative pathogens would enable a much more targeted approach, as antimicrobial sensitivity testing can also be pursued[49].

A recent meta-analysis has shown that the most frequent aerobic microorganisms isolated from a diabetic foot infection are *Staphylococcus aureus* (23.4%), *Escherichia coli* (11.5%), *Pseudomonas* spp. (11.1%), *Proteus* spp. (8.3%), *Klebsiella* spp. (6.9%) and *Enterococcus* spp. (5.4%)[46]. There was also a high frequency of coagulase-negative

staphylococci observed in this meta-analysis, likely indicating a combination of frank pathology and sample contamination when commensals are introduced into damaged and dysfunctional tissues. Within the *S. aureus* group, a significant prevalence of methicillin-resistant *S. aureus* (MRSA) has been observed in the same meta-analysis (18%), which is in line with previous estimates[46,50,51]. Literature has shown that harbingers of protracted infections and frequent relapses are usually two bacterial genera: *Acinetobacter* spp. and *Enterococcus* spp.[52,53], while *Citrobacter* spp. predominates in female patients[49]. Interestingly, a higher prevalence of Gram-positive microbial isolates in diabetic foot wounds is generally observed in high-income countries when compared to low- and middle-income countries where Gram-negative isolates predominate – reflecting in turn differences in hygiene, sanitation and footware usage[46,54,55].

In any case, the monomicrobial vantage point is rather narrow. The use of molecular techniques in recent studies have corroborated assumptions of polymicrobial nature of chronic wounds and processes, including diabetic foot ulcers[56–58]. More specifically, bacteria and other organisms found in foot infections may demonstrate specific non-random polymicrobial patterns which can correlate with clinical factors[59] and/or wound chronicity[60]. This could have direct clinical implications for the optimization of antimicrobial treatment (particularly if the aim is to cover all potential organisms pertinent for such processes) and understanding further evolution of polymicrobial diabetic foot infection (from the perspective of interactions that could have a synergistic or alleviating effect on microbial burden, expression of genes or pathogenicity)[61–63].

A very recent study by Barshes *et al* (2022)[63] suggested three species co-occurrence patterns: 1) the most pervasive *S. aureus*-dominant pattern (characterized with the absence of *Staphylococcus epidermidis* and other coagulase-negative or nonspeciated staphylococci), 2) the pattern where coagulase-negative staphylococci dominate (i.e., the inverse of the *S. aureus*-dominant pattern with the absence of *S. aurues*) and so-called 3) 'pattern C' characterized by the absence of *Bacteroides* and *Corynebacterium* species and the presence of two or more of the following bacterial groups, genera or species: alpha-

hemolytic streptococci, *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp. and *Enterococcus faecalis*. Simply put, these co-occurrence patterns show that *S. aureus* is rarely seen together with coagulase-negative staphylococci, while Proteobacteria can be seen with enterococci and alpha-hemolytic streptococci, but not corynebacteria. In addition, patients that have a polymicrobial diabetic foot infection that belongs to the aforementioned 'pattern C' present with substantially higher rates of treatment-recalcitrant osteomyelitis[63].

Similar patterns have been reported in other studies. Gardner *et al* (2013)[59] discerned a *Staphylococcus*-dominated pattern, streptococci-dominated pattern and a high-diversity pattern – the latter being characterized by many significant constituents of the phylum Proteobacteria. This means that diabetic foot infections are more habitually polymicrobial in nature when compared to bone and soft tissue infections in other locations, and that the spectrum of microorganisms from foot bone and soft tissue can be comparable among different individuals, but distinct from the spectra observed in other locations of the human body[63,64]. This is not just an academic exercise, because recognizing specific microbial profiles and signatures has true practical implications. For example, recognizing either polymicrobial 'pattern C' or isolating *P. aeruginosa* among different bacteria can be considered as a high risk for treatment failure, and a recent study shows that 15% of the patients with *P. aeruginosa* were ultimately subjected to amputation[49]. Understanding such nuanced interactions might prompt specific interventions; for example, the use of probiotics to fill the niche with beneficial bacteria and eliminate hazardous ones[65,66].

Finally, the high burden of antimicrobial resistance is becoming a true public health hazard[67,68], and will influence how we approach the treatment of diabetic foot infections[68]. Even studies published ten years ago have demonstrated a high prevalence (i.e., up to 33%) of resistant bacteria present in diabetic ulcers[69,70]. Together with the fact that patients with diabetes mellitus are inherently prone for developing foot infections[47,49], and that peripheral vascular disease and cigarette smoking may increase the risk of diabetic foot infection[53], the control may become increasingly

difficult and may lead to increased complications, with many downstream effects for the healthcare system.

In the progression of the disease and the formation of chronic lesions of diabetic foot ulcers, forming a biofilm plays the leading role, in which commensal and pathogenic bacteria symbiotically come together and maintain the chronic infection[71]. This is a significant pathophysiological moment that results in complex treatment and the emergence of antibiotic resistance[71]. The most common reason for the unsuccessful treatment of biofilm infections with conventional antibiotics is the inability of antibiotics to pass through the exopolysaccharide matrix formed by sessile cells in the biofilm[72,73]. The seriousness of such infections is demonstrated by the fact that 80% of lower limb amputations in patients with diabetes due to foot ulceration are caused by biofilm, and biofilm is present in 60% of chronic wounds and 6% of acute wounds[74]. For the detection of biofilm in deep tissues, the appropriate sample is a tissue biopsy[75–77], and techniques for quantifying biofilm in biopsy specimens include fluorescence in situ hybridization, scanning electron microscopy, or confocal laser scanning microscopy[78,79]. Due to the presence of biofilm, treatment of diabetic foot ulcers with conventional antibiotics is problematic as resistance to them develops[14,71]. Accordingly, new strategies must be found to solve the problem, and phage[72,80], silver nanoparticle[72,81], and antimicrobial peptides (AMP) therapy[72,82] is being introduced as an alternative.

We should not forget fungal pathogens that may compound the issue of diabetic foot infection. Their prevalence varies between 5% and 27%, with *Candida* species being the most frequently isolated strains[83–85]. Mold infections are much less pervasive, but more menacing in comparison to instances when only *Candida* is implicated. However, there are just a handful of case reports that show infections with *Aspergillus ochraceus* or species of the genera *Blastomyces* and *Fusarium*, with skin and nails being the main entry portals[84,86,87]. In any case, fungal diagnosis has to be included in the approach to diabetic foot infection to obtain a full microbiological profile.

CLINICAL PRESENTATION

Diabetic foot, at first glance, could have a seemingly normal appearance, and symptoms and signs of the diabetic foot and its complications can be easily missed. However, the clinical presentation of the diabetic foot has some specifics that are important for every clinician, especially those actively caring for these patients.

Due to atrophy of lumbricals and interosseus muscles caused by motor neuropathy, the anatomy of the foot changes in a way that the foot arch and toes are pulled in a "claw" position with prominent metatarsal heads, hammertoe contracture of digits and other bony prominences creating focal areas of high pressure susceptible for developing of an ulcer. Charcot neuroarthropathy (CN) is a severe diabetic foot complication that significantly increases morbidity and mortality, primarily in patients with concomitant DFU. Such patients can have reduced life expectancy by 14 years. CN is characterized by bone and joint destruction and can be asymptomatic or mimic other more common conditions such as cellulitis, osteomyelitis, deep vein thrombosis, inflammatory arthritis, or ankle sprain, which is why it remains a poorly recognized complication. In the acute phase, it presents as a warm, swollen red joint which is often not painful. In the early stages of CN, there are no clinical signs of bone fractures, but radiological examination usually shows microfractures. A total of 58% of patients with CN present with DFU. And CN can lead to mid-foot collapse, rocker-bottom foot (collapse and inversion of the plantar arch), acute fractures, and dislocation, if not treated[6,23]. Otherwise, the skin in diabetic foot is usually dry and cracked with calluses, which are signs of increased pressure. In addition, there could be pre-ulcerative signs such as localized redness, blisters, fissures, or hemorrhage[36,37] (**Figure 1**).

If concomitant with PAD, the diabetic foot appears pale and cold. However, sometimes in ischemia, it could be conversely warm and pink due to arterio-venous shunts or the previously mentioned early stage of Charcot's foot and fracture. Moreover, tissue ischemia can manifest as rest pain, claudication, gangrene, or ulceration. However, classical signs and symptoms of PAD are not obligatory to be seen in people with diabetes with PAD[20]. Therefore, the assessment of vascularization in people with

diabetes should not be done only by clinical examination. Also, clinical signs and symptoms of diabetic foot infection are often diminished due to PAD, neuropathy, and immunopathy[31]. This includes redness, warmth, swelling, pain, and purulent secretion. Furthermore, even in the presence of deep infection, usual systemic signs of infection include fever and elevated white blood cell count. In addition, CRP concentrations can be absent or diminished, resulting in a delay in diagnosis. If present, it should be alarming because it could mean severe infection, potentially limb- or life-threatening[5,31,88]. Sometimes, the only sign of infection can be unexplained hyperglycemia[6]. The most common infection symptom is excessive exudation if a foot ulcer is present. However, the accurate clinical picture can be masked by superficial eschar, which must be removed to reveal possible abscesses and involvement of deep structures[6,89,90].

DIAGNOSTIC EVALUATION

All patients with diabetes should be screened annually to assess the risk of foot complications (**Figure 2**). They should be stratified into high-risk and no-risk using the IWGDF Risk Stratification System to establish the frequency of further visits and examinations. This basic evaluation is part of the prevention strategy and includes foot inspection, evaluation of loss of protective sensation (neuropathy), and periphery arterial disease. For full risk assessment, this primary evaluation should also include general history and foot-specific history of previous foot ulceration, amputations, and comorbidities, especially end-stage renal disease[90].

Foot inspection should establish the presence of foot deformities, bone prominences, limited joint mobility, and pre-ulcerative signs. Also, the clinician should actively search for other signs of the foot at risk for ulceration or infection that are often hidden. This includes examining the areas between the toes for fissures, fungal infections, calluses, and nail problems[90].

Almost all working groups agree that the Semmes-Weinstein test is the most important test for evaluating neuropathy (considering the loss of protective sensation), as studies

have shown that it has a high sensitivity for identifying patients at risk and is predictive of developing foot ulceration[5,9,91]. Furthermore, it is performed under the pressure stimulation of defined areas on foot with nylon monofilaments[6,9]. Other tests (tuning fork test and neurothesiometer) can also asses the presence of neuropathy, but studies showed that they are less predictive of foot ulceration[6]. The deep tendon (Achilles) reflex should be examined[5,23].

In all patients with diabetes, vascularization should be assessed annually by taking relevant history (rest pain, claudication) and palpating foot pulses. The most valuable non-invasive diagnostic method for diagnosing PDA is the ankle-brachial index (ABI)[20]. It should be performed in all individuals with diabetes over 50 years, regardless of other risk factors, and in the presence of risk factors, it should be performed annually. This approach should also be used for all patients with diabetic foot ulcers[9], as it will not only aid in diagnosing PAD but also in evaluating the potential of ulcer healing, the need for revascularization, or the risk of limb amputation in patients with already established PAD[92]. ABI is usually combined with ankle and pedal arterial Doppler[20]. Because of frequent advanced arterial calcification in people with diabetes, ABI could falsely give higher values. Therefore, it is often recommended to measure toe or transcutaneous oxygen pressure where possible. Both proved to be good predictors of ulcer healing potential or the need for revascularization[5,20]. If the ulcer is not healing, when considering revascularization or at critical values of ABI, toe pressure, ankle pressure, or transcutaneous oxygen pressure (TcPO2) clinician should order one of the vascular imaging, including color duplex ultrasound, CT, or MR angiography and sometimes digital subtraction angiography (DSA)[20].

For the diagnosis of diabetic foot infection, including infection DFU, it is recommended to start with appraising classical clinical signs of infection such as redness, warmth, swelling, pain in the foot, and possible entry of pathogens through minor skin fissures[31]. Additionally, the most common sign of an infected ulcer is increased exudation. However, the severity of infection should be assessed after the debridement and evaluation of occasionally concealed extent and depth of infection by the superficial

eschar[5,88]. If clinical findings are unclear, laboratory examination with CRP, ESR, and sometimes procalcitonin should be performed. However, diagnosis of infection in individuals with diabetes can be challenging because of signs and symptoms that are frequently covert.

Further difficulties include diagnosing deep tissue infection, osteomyelitis, and Charcot's foot, which can mimic infection. If osteomyelitis is suspected, a metallic probe bone test should be performed[31]. If a sterile probe hits the bone, the diagnosis of osteomyelitis is highly possible, with a positive predictive value of 89%[93]. A positive probe test elevated CRP or procalcitonin, and plain X-ray findings compatible with osteomyelitis are sufficient for diagnosis. However, further diagnostic procedures should be performed in case of equivocal findings. The single basic radiographic study has low sensitivity and specificity for diagnosing osteomyelitis. Still, it should always be performed in patients with new DFI to detect possible foreign bodies, soft tissue gas, bone destruction, fracture, or deformities[9,94]. To diagnose osteomyelitis, it is better to perform two X-ray studies with an interval of at least two weeks to detect changes in radiologic appearance[48]. At the moment, magnetic resonance is considered the best diagnostic method, with 90% sensitivity and 79% specificity for osteomyelitis[94]. It is rarely necessary to obtain bone specimens by debridement or biopsy for diagnosis. Still, an appropriate sample of infected wounds should always be collected for culture purposes and microbiological evaluation before starting empirical therapy. Wound swabs should be avoided; the preferred method is curettage or biopsy of the ulcer[31].

If a diabetic foot ulcer is present, not only potential limb ischemia and infection should be assessed, but the characteristics of the ulcer alone should be described. The most significant are the localization, size, and depth of the ulcer, as well as the presence of gangrene. Following the reduction in the size of the ulcer, it is possible to predict treatment outcomes[95,96].

MANAGEMENT

If we understand the complexity of diabetic foot pathophysiology, the necessity of a multidisciplinary approach to treating its complications is very evident (**Figure 3**). Studies showed that adequate glycemic control with glycosylated hemoglobin (HbA1c) < 6.5-7% is important in preventing DFU and other complications, and it can also significantly decrease the risk of amputation and affect the wound healing rate[9,97,98]. The management should be directed towards all established contributing etiological factors to achieve adequate healing of the diabetic foot ulcer. In the case of purely neuropathic ulcers, off-loading and local wound care is most likely sufficient. Still, in the case of concomitant ischemia and infection, treatment is more complicated.

Off-loading strategies aim to relieve pressure on the extremity and prevent high-pressure focal zones, most often the place of ulcer development. A simple debridement of non-viable tissue or callus around the ulcer is often the best starting point for distributing some pressure off the point. There are many off-loading techniques available. If non-surgical off-loading fails to promote healing of the ulcer, even with appropriate standard wound care, surgical off-loading techniques must be considered. The ulcer localization navigates the selection of the suitable device. For example, suppose the ulcer is localized on the plantar side of the foot. In that case, non-removable knee-high devices like a total contact cast (TCC) or non-removable knee-high walker are usually recommended. Removable knee- or ankle-high devices are recommended in case of contraindications or patient intolerance. Additionally, they should be primarily addressed if moderate or severe infection and ischemia are present[16]. Plantar heel ulcers are less prevalent than plantar forefoot or mid-foot ulcers. Still, they are characterized by higher pressures, longer healing time, and more cumbersome pressure decrease by off-loading techniques[16,17,99]. If the ulcer is localized on the non-plantar side of the foot, removable ankle-high devices or footwear modifications, orthoses, or toe spacers can be used. It is extremely important to address patient compliance because they are often not very prone to wear those devices[9,100]. Few surgical techniques can help off-load the ulcer and promote healing in selected patients. In patients with plantar metatarsal head ulcer, Achilles tendon lengthening, metatarsal head resection, or joint

arthroplasty should be considered. Moreover, in patients with apex or digital plantar ulcers, digital flexor tenotomy can help decrease pressure[16]. Also, surgery corrections should be considered if there are foot deformities that the therapeutic footwear cannot manage[5].

In patients with diabetic foot ulcer and PAD, revascularization should always be considered, especially in those with a severe degree of ischemia established by one of the proposed tests (ABI, toe pressure, ankle pressure, TcPO2) or in patients with non-healing ulcer and PAD despite test results. ABI values 0.9-1.3 are considered to be the range where PAD is less likely, and ABI values < 0.8 are associated with an increased risk of limb amputation[92]. Usually, it is recommended to use Wound, Ischemia, and foot infection (WIfI) classification to predict which patients with diabetes and PAD are more likely to require and benefit from revascularization[9,20]. There are two approaches to revascularization: endovascular therapy and open surgical bypass. Randomized clinical trials on opting for one technique over the other in people with diabetes are lacking[5,101]. Today we witness significant progress in endovascular medicine, as there are emerging endovascular techniques (such as drug-eluting technologies); nevertheless, high-quality randomized studies to evaluate their efficiency in this specific group of patients are still lacking[102]. Furthermore, recent reports suggest an innovative treatment alternative for patients without endovascular or surgical options. Intravascular ultrasound (IVUS) – guided percutaneous deep vein arterialization with the creation of an arteriovenous fistula between the posterior tibial artery and its satellite deep vein showed promising results in such no-option patients with critical limb ischemia[103]. Special considerations should be taken in patients with DFU and PAD who are candidates for revascularization but have invasive foot infections, as they are at exceptionally high risk of amputation. In that case, the infection should be controlled before revascularization is pursued to avoid sepsis. Appropriate and aggressive therapy (surgical interventions and antibiotics) usually takes a few days to stabilize the patient; consequently, prompt revascularization should be considered to help solve infection with improved circulation to avoid limb amputation[20].

Antibiotics are the basis of treating diabetic foot infections, but they are often insufficient in controlling the infection; also, there is often a presence of polymicrobial infections, as described above. Hence, surgical treatment in managing DFI is often required because of the special features of diabetic foot infections. Indications for surgical interventions are the involvement of deep tissues (especially bones), abscess formation, the presence of necrotic tissue, compartment syndrome, and extensive gangrene. In such cases, the treatment of choice must be prompt surgical incision allowing abscess drainage and debridement of necrotic tissue. Uncomplicated osteomyelitis can be initially treated with antibiotics for no longer than six weeks. This regimen showed limited long-term results in controlling the infection[104,105]. Thus, surgical interventions – including partial bone resection and minor amputations – are often necessary to prevent infection. Selection, duration, and the route of antibiotic administration in treating DFI should be based on the likely causative pathogen and the clinical severity of infection. It is always preferable to prove a causative pathogen in infected tissue culture[31]. Using IDSA/IWGDF infection classification is recommended to guide the management of DFI[9,106]. Finally, amputation below the knee is necessary if minor amputation is insufficient to control infection or in case of extensive tissue loss or severe tissue ischemia after failed revascularization[5,107]. Nevertheless, generally, surgeons should try to preserve the knee joint if possible because of its significance for successful rehabilitation[6].

Finally, standards of good local wound care in individuals with diabetes should be followed to promote DFU healing. This involves frequent clinical evaluations with irrigation and debridement and modern dressings. There are different debridement methods, but sharp surgical debridement is usually recommended to remove necrotic tissue in DFU[9,108]. Other possible techniques are hydrogels, occlusive dressings, larval therapy, enzymes, ultrasound, and hydrotherapy, but studies have yet to prove that one method is better than the others[109]. Dressings should provide optimal conditions for wound healing: moist wound bed and exudate control with prevention of maceration of surrounding skin, prevention of infection, and promotion of granulations. They should

also be comfortable for the patients and enable atraumatic dressing changes. Modern (advanced) non-adherent dressings usually meet these requirements. The most commonly used dressings are hydrogels, hydrofiber dressings, hydrocolloids, foam dressings, and alginates. Still, studies showed that none is superior to others in promoting wound healing, and the choice is usually made based on the assessment of wound clinical characteristics, comfort, and cost[9,108].

If improvement in DFU healing is not seen after a minimum of 4 wk of the best standard of care, adjuvant methods should be considered. Hyperbaric oxygen therapy and negative pressure therapy are most often recommended[110]. However, before any other treatment modality, re-evaluation of vascular status, presence of infection, and high-pressure zones should be pursued[9,108].

CONCLUSION

Although knowledge about diabetic foot problems has grown tremendously in recent years, there are still unmet therapeutic needs. Diabetic foot ulcers, often associated with infection or ischemia, are thought to precede the majority of diabetes-related lower extremity amputations and are the leading cause of non-traumatic lower extremity amputations worldwide. In people with peripheral neuropathy or peripheral arterial disease, diabetic foot ulcers mainly result from mild or recurrent trauma to the foot. The pathophysiology of diabetic wound healing is complex and multidimensional. Thus, it remains to be fully understood. In addition, more than half of diabetic foot ulcers become infected, which impairs wound healing and increases the likelihood of foot amputation. The management of diabetic foot is complex for any healthcare provider; however, as the number of people with diabetes increases, so does the need for diabetic foot ulcer treatment. Hence, more targeted research endeavors are needed for an evidence-based approach to diabetic wound healing and improving patients' quality of life.

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