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Review

DIABETIC FOOT: OLD DISEASE, NEW CHALLENGES

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Summary

Diabetes is a socially significant disease that brings a significant burden to healthcare systems worldwide. The vicious nature of the disease affects almost all of the systems and organs of the body. The foot is one of the most important and clinically significant areas where these complications are manifested. Diabetic foot gangrene is a leading cause of non-traumatic foot loss worldwide. Although the disease has been known for over a decade, understanding it has gone through highs and lows, leading to suboptimal results in many cases. In this review article, we focused on diabetic foot and the methods for evaluation and assessment of the condition to properly initiate adequate treatment.
Keywords: diabetic foot, diabetic neuropathy, diabetic foot infection

Introduction

Diabetes is one of the most socially significant diseases worldwide. One conservative estimate is that around 170 million people suffer from it [1]. More detailed studies have concluded that as many as 415 million people across the globe are affected [2], and the percentage of the global population diagnosed with the disease shows a tendency to increase, irrespective of the efforts put into prevention steadily. The burden of diabetes is worsened due to the wide variety of complications in which no system is spared. In this review article, we focus on diabetic foot and the methods for evaluation and assessment of the condition to properly initiate adequate treatment.

The severity of the problem

The first written reports suggesting a correlation between diabetes and foot gangrene were published in 1852 by Marchal de Calvi and in 1854 by Thomas Hodgkin [3]. Since then, research on the disease has gone through success and failure. Advances in this area were almost entirely absent between World War II and the 1970s. Since the beginning of the 1980s, the number of scientists studying this complex condition has gradually increased [4]. Diabetic

foot is defined as any wound distal to the malleolus in patients with diabetes [5] and is one of the most common complications of diabetes mellitus. It is estimated that around 6.3% of diabetic patients are currently diagnosed with diabetic foot syndrome, with North America being most severely involved, with more than 10 % of diabetic patients suffering from this complication. Oceania is on the opposite end of the scale, with slightly more than 3% of all diabetic patients affected [6]. Europe is right between these numbers, with around 5.1% involvement, according to a large meta-analysis by Zhang et al. [7]. A Greek study also confirmed the European numbers, reporting a 4.8% prevalence among patients with diabetes [8]. These numbers draw a worrisome picture for the healthcare systems. It is estimated that diabetic foot infection and related complications are the single most significant contributor to health costs related to the treatment of diabetes [9]. M. Kerr et al. estimated that nearly 1% of the whole NHS budget is spent on treatment of the condition, which is more than the combined expenditures related to breast, lung, and prostate cancer. The same authors pointed out that if the UK could reduce the prevalence of the disease and initiate treatment earlier, this would shrink the cost of treatment for these patients by as much as 250 million GBP per year. Authors from the USA also supported this view [10]. According to a study by Driver et al., 116 billion USD was spent in 2007 to treat the complication. The cost of treating a patient with a diabetic foot was 5.4 times more expensive than a patient without it [11]. It has been estimated that the treatment of a patient with a diabetic foot ulcer in Germany costs more than 7000 euros for the year in which it is diagnosed. The healthcare system in Germany spends more than 10 000 euros per year on a patient undergoing amputation [12]. Since the diabetic foot is a leading cause of non-traumatic amputations worldwide with the related cost to the social system, it is clear that the condition requires close attention and efforts in prevention and early diagnosis to avoid severe outcomes.

The pathway to diabetic foot

Three major factors contribute to the development and evolution of the diabetic foot: neuropathy, angiopathy, and infection. Neuropathy is considered to be an initiating factor for the disease. It is estimated that 16% to 35% [13]peripheral vascular disease, history of ulceration or amputation, other microvascular complications (particularly end-stage renal disease on dialysis of people with diabetes have signs of neuropathy, and 10% are diagnosed with it when diagnosed with diabetes [14] affecting different parts of the nervous system that present with diverse clinical manifestations. They may be focal or diffuse. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN). Neuropathy pathogenesis is attributed to microvascular damage to the nerve fibers and pathologic metabolism, leading to increased sorbitol depositions in the nerves. The end result is damage to the function of both large and small nerve fibers. The first nerve fibers damaged are the sensory fibers for temperature and proprioception. In addition to these small fibers, large fibers of the autonomous nerve system also get involved in the process, manifested by reduced sweating and dryness of the skin. In the end, we can see that normal skin barrier function gets heavily compromised, leading to the development of skin wounds that go unnoticed by the patient [15]. The change in the mechanics of the foot itself is another way neuropathy takes part in the development of the diabetic foot. Damage to the nerve fibers results in changes in the muscle tone of the foot muscles. These changes the normal shape of the foot, mainly involving the foot arch and shifting the pressure points to new ones, which are not anatomically suitable to bear it [16] mean age 53.3 (range 17-77).

The second most important factor in the pathway to a diabetic foot is angiopathy, which is related to diabetes. Diabetes affects both small- and large-caliber blood vessels. In confirmation of the severity of the problem, Ierardi et al. report that 80% of the deaths in patients with diabetes are related to vascular disease. In the USA, 50% of all amputations are due to complications related to diabetes [17]. The prevalence of chronic limb ischemia (CLI) in patients with diabetes is considered to be 10 to 20 percent of the whole population [18], which is a two- to four-fold increase compared to the

non-diabetic population [19]. In patients with diabetes, the involvement is predominantly in the blood vessels below the knee.

In contrast to non-diabetic patients, diabetic patients tend to have diffuse involvement of the arteries by atherosclerosis which explains the poor prognosis in such patients. Also, the length of the involved segment is more than 10 cm in half of the patients, with occlusion of the arteries being more common than thrombosis. Occlusion in all tibial arteries is registered in up to ¼ of the patients with diabetic foot [20]. The same authors also noted the need for a unified classification system that describes infrapopliteal and proximal lesions of major blood vessels. So far, we have not found such a classification in the literature.

Regarding the pathogenesis of the changes in blood vessels, we found some differences when we compared these changes with those in non-diabetic CLI patients. Atherosclerosis follows the same pathway in both groups though the disease progresses much faster in the diabetic population and tends to deposit much more calcium [21]. The thickening of the vascular wall leads to impairment in the trans-membrane exchange. In addition, diabetes patients tend to have lower NO concentrations, which is crucial for vasodilatation and a vital antioxidant [22] S. Lange reported that only 5% of the patients with CLI and diabetes have intermittent claudication – a milestone symptom for the disease, suggesting that the majority of the patients with diabetes and CLI remain undiagnosed until more severe symptoms of the disease become manifest [23]. Besides major blood vessel damage, the changes in the small blood vessels are also significant. The blood vessels of the foot are responsible for metabolic exchange, normal immune system function, wound healing, and delivery of drugs. When these vessels are damaged, all these processes will be disrupted, which explains the problematic evolution of the disease. This problem, although well known, got little attention in the past and has been in focus only for the last 10 years. A report from Vanessa Cardenas et al. shed more light on the degree associated with such changes. In a study on 367 patients with diabetic foot, 251 (68.4%) were shown to have calcinosis of foot arteries, a morphologic expression of the disease of the small vessels. Interestingly, the study did not show a connection between calcinosis of the foot arteries and other risk factors such as smoking and poorly controlled diabetes [24]. A study by Francisco Javier Álvaro-Afonso et al. also confirmed the high percentage of patients with such a condition, adding that calcinosis of the arteries in patients with diabetes might interfere with the result of non-invasive vascular testing [25].

The last major factor in the development of diabetic foot is infection. The combination of neuropathy and CLI creates the perfect environment for the colonization and spread of bacteria. The most common causative bacteria in these cases are Staphylococcus aureus and Streptococcus spp. [26], although more recent studies have suggested a shift towards Gram-negative bacteria, especially in specialized centers [27]. Maria Demetriou et al. reported more than 55% of Gram-negative bacteria as the causative agent in a study held in Greece with 113 patients, further supporting the statement that this type of bacteria is more critical in diabetic foot infections [28]. Even more disturbing is the prevalence of polymicrobial infections, not uncommonly including both Gram-negative and Gram-positive isolates [26]. To add more complexity to the problem due to both micro- and macroangiopathy, it is typical for the i.v. antibiotics to reach a lower concentration in the soft tissues of the foot involved, thus making bacterial infection management even more challenging.

Finding the breadcrumbs

The most severe complication of the diabetic foot is major amputation on the level of the calf or thigh. To identify and adequately assess patients at risk for foot loss, it is mandatory to perform many tests before the initiation of the treatment process.

Regarding neuropathy, there is a readily available and widely spread test that is well-suited for clinical practice. The monofilament test with 10g pressure wire is the most commonly used. Boulton et al. reported that a 10 g monofilament test combined with a 128 Hz vibration test is 100% consistent with electromyography (EMG) data without needing specialized equipment. Preserved sensation to both tests reliably

excludes the possibility of neuropathy, while the lack of sensitivity towards one of the two tests confirms the diagnosis in 66% of the study group [38]. In another study, Kalish et al. reported that the 10 g test alone is 91% sensitive and 86% specific in diagnosing diabetic neuropathy. This data illustrates an easy and widely available option for examination for diabetic neuropathy. Dinesh Selvarajah et al. reported that 90% of patients referred to a foot clinic had data for neuropathy, and, basically, all patients who had had amputation also manifested damage to the peripheral nerves. The authors advocated annual examinations for neuropathy so that the issue is addressed timely and assumed that such practice could significantly reduce the complications related to diabetic foot [29].

The problem with vascular examination is much more complex in nature. The gold standards for vascular assessment usually include invasive studies. Application of i.v. contrast is not always possible and requires highly trained staff and expensive equipment. There are limited options regarding outpatient examinations and the identification of risk groups. Simple pulse palpation is the easiest and oldest method for examining blood vessels. Giurato et al. pointed out that simple palpation of the pulse does not yield enough information to clinical staff because a pulse does not mean an adequate blood supply to the foot. However, the lack of pulse does not always suggest thrombosis [24]. A Doppler examination for the presence of pulses is now widely available. It provides good information regarding the presence or absence of a pulse on a specific artery, but it provides poor information regarding the adequacy of the blood flow. CT angiography (CTA) and Direct Subtraction Angiography (DSA) are precise tests requiring expensive equipment and highly trained staff and are not widely available, especially in outpatient settings. These facts make them unusable for widespread monitoring and identification of patients at risk for limb loss. Thus the measurement of foot blood pressure comes into place: the examination of the Ankle-Brachial Index (ABI) and Toe-brachial Pressure Index (TBPI). The ABI compares the pressure measured on the ankle with that on the brachium. Values lower than average suggest vascular involvement with reduced blood flow, while ABI values higher than average indicate increased stiffness of the blood vessels proximal to the ankle and are thus a marker for calcinosis of those arteries. The ABI has a 95% sensitivity and is nearly 100% specific [19]. It is easily applicable in outpatient settings and is non-invasive. Graziani et al. even suggested that the test alone is enough for a patient to be diagnosed with peripheral vascular disease [20], i.e., ABI can be adequately used as a gateway to more specific and invasive tests that allow a proper assessment of the vascular status of a patient. ABI, though, has one major limitation: it does not adequately assess the pedal arteries, which are the ones concerned with direct blood supply to the foot. This is why a new method for evaluating foot blood flow is suggested: an examination of TBPI. This method has all the benefits of the ABI plus the fact that it does not give false high values because the mediocalcinosis of the foot arteries is not severe enough to increase the index value. A decrease in the value of the index indicates reduced blood flow of the foot itself and, according to data from Herraiz-Adillo, can identify vascular impairment in up to 25% of patients with normal ABI index. Wickstrom et al. further demonstrated the significance of the factor when examining a group of 732 patients, concluding that TBPI is a more sensitive predictor for future major amputations if the index has a value of less than 0.6 [30]. Despite the usefulness of TBPI, there is still much to be done to elucidate its use. Linton et al. performed a meta-analysis on 10 large-scale studies and could not find clear relevance between the values of the index and wound healing, thus suggesting that more effort must be put into clearing the matter [31]. Furthermore, although the method is widely used in developed countries, it plays little role in clinical practice in developing countries where the prophylaxis programs are generally less organized. The complexity of the matter gets more profound when one considers that the next step in clearing out the whole picture of the disease can be minimal for one reason or another. A major concern is the treatment of patients with end-stage kidney failure (ESKF) and diabetes. Diabetes itself severely damages the kidney and can lead to ESKF. Even initial changes in kidney function due to diabetes should bring forward the idea of generalized vessel damage. Such patients

are at high risk of developing diabetic foot. Moreover, vascular imaging with large volumes of contrast in such patients is problematic. In their review article, Lepäntalo et al. reported that these patients are prone to poor outcomes and have low survivability and poor limb salvage success [32].

Diagnosing the infection is also problematic when we consider patients with diabetes. Due to neuropathy and angiopathy, the medical staff cannot rely even on the most basic signs of the inflammation, which might be absent. Still, the presence of at least two of the five signs of inflammation, i.e., redness, heat, dolor, edema, and loss of function, should alert for inflammation [26]. The use of laboratory inflammatory markers is much more complex. Among patients with diabetes and diabetic foot infection, a high percentage of patients have normal white blood cell count (WBC), despite extensive foot involvement [33]. According to the same authors, the CRP poorly correlates with the severity of the infection, and it could not be reliably used in clinical practice. This thesis is not universally accepted. Vangaveti et al. analyzed the data of 16 studies on large cohorts, supporting the significance of CRP values when diagnosing low-to-moderate foot infection in patients with diabetes [34].

Empiric antibiotic treatment for patients with established diabetic foot infections is also debatable. There is no universally accepted approach to initial antibiotic treatment. Chisman et al. emphasized the need for every institution to make a local regimen for initial therapy after analyzing the most commonly isolated bacteria [35]. This assumption correlates well with the differences in most common isolates in different treatment centers [26-28]. This statement, supported by most diabetic foot specialists worldwide, shows the importance of constant research and analysis on a local level. There is a worrisome tendency: more antibiotics are used for initial therapy due to the high percentage of antibiotic resistance and a broader spectrum of isolates. A report by Lipsky et al. 20 years ago recommended using narrow-spectrum antibiotics against Gram-positive bacteria [36]. More recent studies from large centers for treating diabetic foot advocate for broad-spectrum antibiotics as initial antibiotic treatment [37, 38]. This reveals an unfavourable tendency for the future use of antibiotics in such patients.

Apart from the three major causative factors for the development of diabetic foot infection, some other factors can highlight patients at risk of limb loss. Moon et al., in a study among 1792 patients, examined the role of 88 risk factors and demonstrated a correlation between four risk factors and a risk of major amputation [39]. Of the four risk factors: level of gender, magnesium, platelet levels, and glycated hemoglobin (HbA1c), the level of the latter is most widely used to identify patients at risk since diabetes control plays a key role in developing its complications. Xiang et al. further examined the correlation between wound healing and levels of HbA1c, indicating that while treating a group of 298 patients, a target level for glycated hemoglobin between 7 and 8% facilitated wound healing. At the same time, values above 8 were related to a more significant percentage of amputations. These statements were also confirmed by Zhao et al. [40].

Another lifestyle risk factor that has no lesser role than diabetes control is smoking. Sayiner et al. reported a significantly higher percentage of smokers in patients who underwent amputation following diabetic foot gangrene. The authors also brought forward the problem of longevity related to the smoking habit: long-term smokers had significantly more episodes of re-amputations. A meta-analysis by Chunmei Lin backed up this statement [41]. In addition, smoking cessation reduces amputations by as much as 20% over 5 years [42].

Talking about the high cost of treatment and the burden on the healthcare system, we cannot ignore the fact that the strongest predictor for the recurrence of the disease is a previous episode of diabetic foot ulcer. Sicco et al. reported 40% recurrence in one year, 60% in 3 years, and 65% within 5 years, which is usually related to repeated hospital stays. In their article, the authors strongly suggest that more effort is needed in preventing and early identification of risk-group patients to prolong the ulcer-free days for patients and also reduce the need for hospital treatment [43]. In an article on the diabetic foot, William J. Jeffcoate stressed the need for the proper education of the patients, especially after the first episode of the disease, which can

significantly reduce the risk of another episode of ulceration or recurrence. [44]

A new approach to the disease

All the mentioned information above draws the picture of a complex disease with multiple factors affecting its onset, evolution, and prognosis. The variety of factors reported in the literature implies a consensus: the treatment of these patients should be carried out by a multidisciplinary team. Holstein et al. were the first to describe the need and effects of forming such a team in a retrospective study (1981 – 1995). They reported 98% of limb salvage after severe infection and a doubled number of revascularization procedures after the team had begun their work. The authors also reported improvement in prophylaxis, glycemic control, and control of the complication of diabetes [45]. In a more recent study analyzing the effect of building such a team, José Antonio Rubio et al. reported a reduction in major amputations from 6.1 to 4 per 100 000/year. At the same time, there was an increase in amputations to 10.9 per 100 000 in other centers [46]. All of the latter studies advocate for including general, orthopedic, and vascular surgeons in addition to specialists in clinical infections or clinical microbiologists and endocrinologists in the team. Where possible, a podiatrist is a valuable asset to the team.

Conclusion

Based on all the information above, it is clear that the topic of diabetic foot is not closed yet. With the development of novel techniques for diagnostics and monitoring in recent years, the accent is put on prevention, prophylaxis, and early identification of the disease. Therefore, an inevitable shift is required in the mindset of those who treat this treacherous condition.

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