DIABETIC FOOT SYNDROME – DERMATOLOGICAL POINT OF VIEW

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SUMMARY – Patients with diabetes mellitus often suffer from diabetic foot syndrome, a condition leading to foot ulceration or even amputation of lower extremity. Peripheral neuropathy combined with repetitive trauma to the foot and peripheral vascular disease are the main etiological factors in the development of foot ulcers. Other major contributive factors include the effects of callus, increased plantar pressures, and local infections. Patient education concerning their disease has a central role in the prevention of foot ulcers. Ordinary preventive measures taken by the patient include regular self-inspections, appropriate daily hygiene of the feet, appropriate footwear to reduce plantar pressures, and medical pedicure performed by a pedicurist experienced in diabetic foot patients. The importance of callus in diabetic patients has been shown in several studies by high predictability of subsequent ulcer development in patients with plantar calluses. For removing callus, urea based preparations are considered to be the treatment of choice. In case of local bacterial and fungal diabetic foot infections, systemic antibiotic and systemic antimycotic therapy is indicated, respectively. Wound dressings of various types are the mainstay in the treatment of chronic foot ulcers with avoidance of occlusive dressings in infected ulcers. Since the vast majority of ulcers and amputations can be prevented in diabetic patients, proper diagnosis and multidisciplinary approach are essential.

Key words: *Diabetic foot syndrome; Foot ulcer; Neuropathy; Vasculopathy; Callus; Wound infections; Patient education*

Introduction

Patients with diabetes mellitus are known to be prone to many serious complications in the course of their disease. One of the most devastating of these conditions is certainly the diabetic foot syndrome (DFS), which is the leading cause of nontraumatic lower extremity amputations in developed countries[1]. The combination of peripheral neuropathy and repetitive trauma is the essential part in the complex pathophysiological mechanism that ultimately leads to foot ulceration[2]. Whereas in normal skin the ulcer caused by physical trauma heals relatively rapidly under appropriate conditions, in diabetics the healing process is impaired and therefore significantly prolonged (Fig. 1). Foot ulcer affects one of six diabetic patients during the course of their disease[3]. Furthermore, approximately 20% of diabetic patients with foot ulcers also have underlying osteomyelitis, whereby the forefoot (metatarsal head and distally) is the involved site in 90% of cases[4]. The average onset of foot ulceration in diabetic patients is about 14 years after the initial diagnosis of diabetes mellitus and the amputation rate in western countries is 2.5-6 *per* 1000 patients *per* year[5]. Diabetics as opposed to nondiabetics also have a 15- to 46-fold greater risk of lower extremity amputation[1] and 20- to 50-fold greater risk of gangrene[5]. Finally, economic costs of treating foot ulcers in patients with diabetes mellitus are enormous[6]. The

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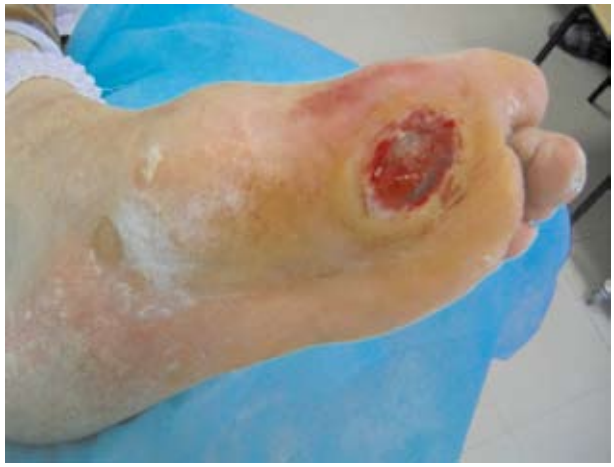

Fig. 1. Diabetic foot ulcer.

fact that foot ulcerations can be prevented in the great majority of diabetic patients with an estimated 85% of amputations preventable, highlights the importance of appropriate foot care, the use of appropriate footwear and patient education in this condition[1,7].

Pathophysiology of Diabetic Foot Syndrome

Diabetic foot can be classified according to the extent of lesion, from stage 0 with no visible defect to the skin, to stage 5 with gangrene of the whole foot (Table 1)[1]. Peripheral neuropathy is considered to have a central role in the development of DFS, acting together with repetitive physical trauma, usually due to inappropriate footwear[2,7]. Other important pathophysiological components include vascular micro- and macroangiopathy, deformity of the foot, and especially the formation of callus[5,7]. Noticeably, almost two-thirds of foot ulcer patients have concomitantly trauma, deformity and neuropathy[7].

Some diabetic patients develop the so-called Charcot neuroarthropathy, an inflammatory syndrome characterized by varying degrees of bone and joint destruction, fragmentation and remodeling, ultimately leading to bone fractures as well as to subsequent deformity, large ulcers and infection[5,8,9]. This condition usually involves the tarsus but can also affect the metatarsus and can ultimately lead to amputation[5]. According to published data, the prevalence of Charcot foot syndrome among diabetic patients varies from 0.15% to 6.8%[9].

Role of Neuropathy in the Pathogenesis of Diabetic Foot Syndrome

The central role of neuropathy in the development of foot ulceration in patients with diabetes mellitus is due to its three main types: sensory, motor and autonomic[10]. Sensory neuropathy renders the foot insensitive to pain, temperature, vibration and pressure[10]. The gradual loss of protective sensitivity, which includes sensitivity to pain and temperature, leads to further reduction in the perception of pain stimuli[9]. Therefore, the lesions that would otherwise be noticed in a healthy person, can escape notice up to the point of severe necrosis lasting for a number of weeks in diabetic patients[5]. Typical features of sensory neuropathy also include a symmetric, stocking-like loss of sensation, as well as diminished patellar and Achilles tendon reflexes[5].

Motor neuropathy is another crucial component of peripheral neuropathy that contributes to the development of foot ulceration. The contributive mechanism of motor neuropathy is the weakening of interosseous and lumbrical muscles within the foot, causing abnormal flexion of the toes and foot deformation, thus leading to the formation of areas of high plantar pressure, especially beneath the metatarsal heads and toes[5,9]. According to Gefen[11], plantar pressure under the first metatarsal head was four times higher in diabetic patients compared to nondiabetics and almost eight times higher on the second metatarsal head. Forefoot to ground contact increases by 38% under the first metatarsal head and by 50% under the second metatarsal head. It was also shown that pressures within the internal plantar soft tissues rose even more significantly: by 82% and 307% under the first and second metatarsal heads, respectively[11]. This pathological increase in plantar pressures as a final consequence of motor neuropathy is clearly associated with the development of foot ulceration, as it was shown in a prospective study in which plantar ulceration occurred in 35% of diabetic patients with high foot pressures, while there was no plantar ulcer recorded in patients with normal plantar pressure[12]. Peripheral motor neuropathy in diabetic patients also causes altered gait with a prolonged support time, thus further aggravating plantar pressures and increasing the risk of developing foot ulcerations[13].

The third, autonomic component of peripheral neuropathy causes vasodilatation and anhidrosis that

leads to the impairment of vascular circulation and skin perspiration. As a result, the skin becomes dry, therefore more susceptible to multiple minor physical traumas, infections, as well as to subsequent formation of callus[5,10].

Importance of Callus in the Development of Diabetic Foot Ulcer

According to Dorland's Medical Dictionary, callus is defined as localized hyperplasia of the stratum corneum of the epidermis due to pressure or friction[14]. Although of special importance in diabetic patients, callus is very common in otherwise healthy, nondiabetic individuals. According to a published report by Sage *et al.*[15], 82.4% of diabetic patients with foot ulcer have previously had callus formation. Another report by Murray *et al.*[16] found a relative risk of 11.0 for an ulcer developing under an area of callus in a neuropathic diabetic foot, showing plantar callus to be highly predictive of subsequent ulcer development. The highest relative risk (56.8) involved the sites of previous ulceration[16]. Clinically, callus is seen as a thickened, hyperkeratotic plaque with little or no ability of pain perception[5]. This particular feature of callus only worsens the already present peripheral neuropathy in diabetic patients, making them less able to sense pain or early signs of inflammation[14]. Due to its thickened structure, callus increases pressure on the underlying tissues, contributing to new lesion formation, thus creating a vicious cycle. Increased mechanical pressure finally separates the nonelastic callus from underlying tissue creating skin tears and blisters, which form the basis of an ulcerative lesion[5]. The development of ulcer within the callus region may be accompanied by surrounding inflammation whose symptoms are easily overlooked since the typical signs of inflammation such as erythema, warmth or swelling occur in the plantar region, which has a particularly thickened stratum corneum[14]. In addition to that, diabetic patients with sensory neuropathy have a lack of pain sensation, which allows further development of callus, progressive tissue destruction, and ultimately ulcer formation[5]. For this reason, new techniques for detecting early signs of inflammation have recently been used, as reported by Nishide *et al.*[14] in their cross-sectional study of 60 patients with asymptomatic foot callus (30 diabetic patients as opposed to 30 nondiabetics). The study used thermography and ultrasonography to detect signs of inflammation that could not be identified by physical examination performed by wound care specialists. Latent inflammatory changes were found by both techniques in 10% of the calluses in diabetic group, while no inflammation was noted in nondiabetic group of patients (inflammation was defined as skin temperature elevation on thermography and hypoechoic lesion on ultrasonography). The results suggested a high risk of ulceration in diabetic group of patients having asymptomatic foot callus, as well as the use of thermography and ultrasonography as the possible effective diagnostic tools in the prevention of inflammation[14].

Vascular Disease in Patients with Diabetic Foot Syndrome

Vascular pathology is a common complication in diabetic patients and it affects all types of blood vessels. Peripheral vascular disease (PVD) is considered to play a significant role in the development of DFS and diabetic foot ulceration, and the risk of suffering from PVD in diabetic patients is approximately fourfold compared to nondiabetics, with a 5 to 10 years earlier onset in diabetics[5,17]. Various reports from the USA, UK and Finland have confirmed the significance of PVD in the pathogenesis of foot ulceration and have also shown PVD to be a major risk factor for subsequent foot amputations[10]. According to a study by Pataky *et al.*[18], related to diabetic patients with both peripheral neuropathy and peripheral vascular disease, PVD contributes to an increase in plantar pressures as well as to a prolonged foot to floor walking contact. In such patients, severe ischemia increases the risk of foot ulceration and amputation, especially when combined with local foot infection[18,19]. Concomitant arterial hypertension and/or hyperlipidemia in diabetic patients, as well as tobacco smoking increase particularly the risk of developing peripheral artery disease (PAD), which can be classified according to Fontaine into four stages: PAD without subjective symptoms (stage I), presence of intermittent claudication (stage II), ischemic pain at rest, including pain at night (stage III), and ischemic ulceration or gangrene of the foot (stage IV)[1]. Preventive and therapeutic measures for PVD therefore include firstly and most importantly good glycemic regulation, cessation of smok-

ing, physical activity, appropriate treatment of other diseases that contribute to the progression of PVD, eventually thrombolytic and antiaggregation medications, and revascularization as early as Fontaine stage II, as well as newer techniques such as percutaneous interventions[20,21].

Infections of Diabetic Foot

Patients with diabetes mellitus are especially vulnerable to foot infections due to the effects of peripheral neuropathy and peripheral vascular disease[22]. Sensory neuropathy causes the patient to be insensitive to minor trauma, which in case of diabetic patients mostly occurs during walking due to inappropriate footwear. Motor neuropathy causes deformities of the foot making it even more vulnerable to injury. Finally, autonomic neuropathy causes dry skin as well as other trophic changes of the skin and nails, thereby significantly impairing the barrier functions of the skin[5]. All these factors combined create a favorable environment for the invasion and colonization of microorganisms into the superficial and deeper tissues of the foot. The resolution of such an infection in diabetic patients is further compromised by the same mechanisms that caused the infection, as well as by diabetic vascular insufficiency[22]. Clinically, foot infection can be defined as the presence of two or more local signs of infection (erythema, warmth, pain, edema), or the presence of purulent secretion or the presence of systemic signs of infection[7]. Furthermore, a number of scoring systems have been developed for assessing foot ulceration and infection[22]. These include, for example, Wagner score[23], which classifies the wound according to the depth and severity of ulceration, regardless of etiology. A more useful classification system for clinical practice may be that of the Infectious Diseases Society of America (IDSA) that ranks infected wounds as mild, moderate or severe, which allows clinicians to assess therapy and diagnostics needed for treating the patient[22].

Once an infection has been diagnosed, further clinical and microbiological findings are necessary in determining the causative pathogens for the purpose of instigating appropriate and efficacious therapy. The nature and duration of the lesion itself is a valuable lead for that purpose. Recently developed, superficial ulcers for which no therapy has been used so far are most likely to harbor aerobic gram-positive cocci, such as *Staphylococcus aureus*[22]. On the other side of the spectrum, chronic, persistent ulcers that have often extended into deeper tissues and usually have already had extensive antimicrobial therapy are a much greater diagnostic and therapeutic challenge, as they are more likely to harbor more than one kind of bacteria[22]. These often include both gram-positive and gram-negative cocci, as well as various kinds of therapy resistant microbes. For an accurate and clinically relevant microbiological analysis, it is important to take into account the indigenous microbial flora of the skin, which naturally interferes with the pathologic flora, complicating the interpretation of swab culture findings. Adequate debridement of the lesion and swab culture or even biopsy from the base of the lesion is crucial for proper analysis and clinical interpretation[22].

Fungal Infections in Diabetic Foot Syndrome

Fungal infections play a crucial role in the development and course of foot infections in diabetic patients since their influence is twofold. Fungi act as infectious agents themselves, contributing to the pathogenesis of foot ulceration, while at the same time, they facilitate bacterial infections[5]. The prevalence of fungal infections in diabetic foot patients as well as specific fungal pathogens isolated in such patients varies considerably. According to Mayser *et al.*[24], 82.1% of 95 patients with type 1 diabetes mellitus had clinical signs of dermatomycosis or onychomycosis and 84.6% of these patients tested positive microscopically or by culture. In this study, the most commonly isolated fungal pathogen was the dermatophyte *Trichophyton rubrum*. Other studies performed by Eckhardt *et al.*[25] and Romano *et al.*[26] have also found *Trichophyton rubrum* to be the most common pathogen. Contrary to these findings, a number of other studies have demonstrated *Candida* spp. to be the most commonly isolated fungal species in diabetic foot patients[27]. Fata *et al.*, for example, found a 20% prevalence of fungal infections in diabetic foot patients, caused mainly by various species of *Candida* spp., especially *Candida albicans*[26]. Mlinarić-Missoni *et al.*[28] report on *Candida parapsilosis* as the most frequent causative agent in diabetic foot ulcers, followed by seven other *Candida* species. They also found pure fungal infections in only one-third of patients, while

the other two-thirds had a mixed fungal-bacterial infection. The majority of patients with mixed infections (80% of patients) presented also with a more severe clinical picture, which may partly be explained by a greater ability of *Candida* spp. to cause infections when acting together with other microorganisms[28]. Characteristic of diabetic foot ulcers are also infections caused by otherwise low pathogenic yeasts, many of which are part of the normal mycobiotic flora of the skin[28]. Certain mold species, i.e. *Aspergillus* spp., *Fusarium* spp., *Penicillium* spp. and *Scopolariopsis* spp., have also been found in patients with diabetic foot ulcers[27]. Another important factor in the development and course of fungal infections is the influence of certain therapeutic measures that are common in diabetic foot patients. This includes topical application of antibiotics, especially when combined with the often prescribed measure of long wrapping of the foot. Thus, choosing the proper antibiotic requires compliance with therapy guidelines, as well as an individualized approach to the patient. The resulting increased temperature and sweating of the skin, as well as the immunomodulating influence of antibiotics, increases the number of yeasts in the affected area[28]. Because of the complex nature and often chronic duration of the lesion, systemic antifungal therapy is considered to be the treatment of choice for diabetic patients with fungal ulcer infection.

Treatment of Patients with Diabetic Foot Syndrome

Prevention of foot ulcerations is the main goal of treatment for diabetic patients with a high risk of developing DFS. For that part, patient education in both prevention and prompt treatment of a newly occurred lesion plays a fundamental role. Overall, preventive measures include regulation of diabetes, hypertension and hyperlipidemia, as well as a regulated physical activity and cessation of smoking[29]. Patients also have to be educated in performing appropriate hygiene, preferably daily washing of the feet, daily self-inspection, wearing appropriate footwear, including shoe inlay devices that would reduce plantar pressures, i.e. correct the biomechanical abnormalities for the purpose of redistributing increased plantar pressures from particular portions of the foot onto the whole foot. As for the maintenance of foot care, i.e. pedicure, the patient has to inform the pedicurist of their diabetic condition in order to apply appropriate medical pedicure, since an incompetent pedicure can cause lesions leading to chronic ulcers in diabetic patients. For removing callus, various preparations containing urea are the treatment of choice. These include urea moisturizers with concentrations of 10% to 40%[5]. The main effect of such urea preparations is twofold: reducing transepidermal water loss and keratolysis without reactive activation of basal cells[30,31]. Keratolysis prevents the formation of callus or leads to its removal, which further reduces plantar pressure, ultimately preventing foot ulceration since an elevated plantar pressure is a known risk factor for the development of foot ulcers[12]. The keratolytic effect of urea is furthermore important when dealing with frequently occurring dermatomycosis and/or onychomycosis in diabetic foot patients. The required topical antimycotic therapy for such patients is severely impaired by the presence of callus or other forms of hyperkeratotic, scaly skin, which prevents adequate absorption of the antifungal agent. Here, the combination of topical antimycotics with urea containing preparations, preferably in higher concentrations, i.e. 40%, can significantly increase the absorption and the efficacy of the topical antimycotic, as it was shown in the case of moccasin type tinea pedis patients in the study by Elewski *et al.*[32]. Contrary to urea preparations, any topical preparation containing salicylic acid should be avoided, since there is a greater risk of injury to nerve fibers and blood vessels in patients with DFS.

Once a foot ulcer has occurred, closure of the lesion as swift as possible becomes the main objective of treatment. Due to the complex etiology of diabetic foot ulcer, as well as various comorbidity associated with diabetes mellitus, a multidisciplinary approach is essential. This includes a combined diabetologic, surgical and dermatologic expertise. Surgical debridement of necrotic tissue and removal of callus is usually the first step in foot ulcer therapy, accompanied by appropriate systemic antibiotic therapy and, in case of a proven fungal infection, systemic antimycotic therapy. Wound dressings are, further on, an important part of managing diabetic ulcers. Here, the experience in treating chronic wounds is most valuable in choosing the appropriate dressing among the various types that exist. In general, occlusive dressings should

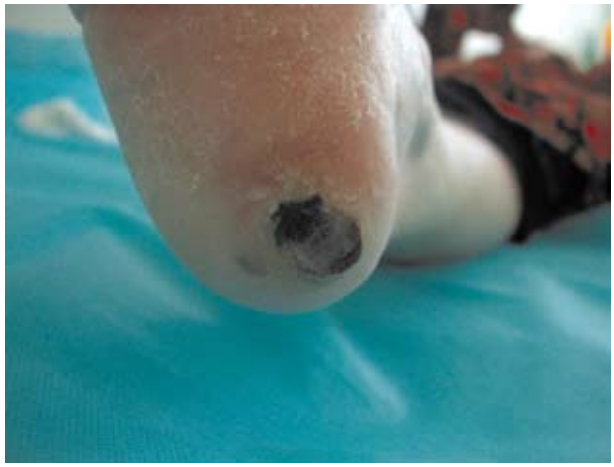

Fig. 2. Malignant melanoma ulcer on the foot of a diabetic patient.

not be applied to infected diabetic foot ulcers, since occlusion worsens the infection, as mentioned above. Infected ulcers in particular often have a heavy exudate, thus requiring dressings with a greater absorption capacity, such as foam and alginate dressings[33]. Various dressings containing silver are also often used for infected wounds, since the antimicrobial actions of silver include direct inhibition of bacterial cell respiration, inactivation of intracellular enzymes, and alterations to the cell membrane[33]. Necrotic ulcers, for example, respond well to hydrogels due to their ability of autolysis[33]. Any type of dressing, however, should be frequently changed and the wound inspected. In summary, an 'ideal' wound dressing should facilitate wound healing, reduce pain, and at the same be cost effective and comfortable for the patient. Not to ignore are also non-antimicrobial agents for the treatment of diabetic foot ulcers, such as human skin equivalents (Dermagraft, Apligraf) or the recombinant human platelet-derived growth factor[20,34]. Finally, all health care providers involved in the treatment of foot lesions in diabetic patients should be aware of the possibility of other nondiabetic pathologic conditions, such as skin or soft tissue cancers, arising within the primary diabetic lesion (Fig. 2). Hence the importance of frequent and careful inspection of foot ulcers in diabetic patients, as to avoid improper or negligent treatment.

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Table 1. Classification of diabetic foot according to the extent of ulceration[1]

Stage 0	No visible ulcerations, foot deformities, or sensation disorder present.
Stage 1A	Superficial ulcerations without cellulitis or signs of infection.
Stage 1B	Ischemia in addition to superficial ulcerations. No cellulitis or signs of infection.
Stage 2A	Deep ulcerations until the tendon, bone and ligaments or joint capsule. No signs of infection. Sensation disorder present.
Stage 2B	Ischemia in addition to deep ulcerations until the tendon, bone and ligaments or joint capsule. No signs of infection. Sensation disorder present.
Stage 3A	Deep ulcerations with abscess formation or signs of osteomyelitis. Signs of comprehensive cellulitis and systemic intoxication, loss of sensation, foot deformities.
Stage 3B	Vascular disturbances in addition to deep ulcerations with abscess formation or signs of osteomyelitis. Signs of comprehensive cellulitis and systemic intoxication, loss of sensation, foot deformities.
Stage 4	Gangrene of the toes accompanied by cellulitis and systemic intoxication. Deep ulcerations with bones exposed accompanied by severe peripheral vascular disease. Complete loss of sensation. Surgical intervention and revascularization needed.
Stage 5	Gangrene of the whole foot. Surgical revascularization or amputation needed.

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Sažetak

SINDROM DIJABETIČNOG STOPALA – DERMATOLOŠKO GLEDIŠTE

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Bolesnici s dijabetes melitusom često pate od sindroma dijabetičnog stopala, stanja koje dovodi do stvaranja ulkusa na stopalu ili čak do amputacije donjeg ekstremiteta. Periferna neuropatija udružena s ponavljajućom traumom stopala, te periferna vaskularna bolest su glavni etiološki čimbenici u nastanku ulkusa stopala. Drugi značajno doprinoseći čimbenici uključuju utjecaj kalusa, povećani plantarni pritisak i lokalne infekcije. Središnju ulogu u prevenciji ulkusa stopala ima izobrazba bolesnika o njihovoj bolesti. Jednostavne preventivne mjere koje bolesnik može poduzeti uključuju redovite samopreglede, odgovarajuću dnevnu higijanu stopala, odgovarajuću obuću radi smanjenja plantarnih pritisaka te medicinsku pedikuru koju treba provoditi pediker s iskustvom u obradi bolesnika s dijabetičnim stopalom. Važnost kalusa kod dijabetičnih bolesnika je pokazana u nekoliko studija s obzirom na veliku vjerojatnost naknadnog nastanka ulkusa kod bolesnika s plantarnim kalusima. U svrhu odstranjenja kalusa terapija izbora su pripravci na bazi ureje. U slučaju lokalne bakterijske ili gljivične infekcije dijabetičnog stopala indicirana je sistemska antibiotska, odnosno sistemska antimikotična terapija. Različite vrste obloga za rane su stožerna terapija za kronične ulkuse stopala uz izbjegavanje okluzivnih zavoja kod inficiranih ulkusa. S obzirom na to da se velika većina ulkusa i amputacija kod dijabetičnih bolesnika može spriječiti, neophodna je ispravna dijagnostika i multidisciplinarni pristup.

Ključne riječi: *Sindrom dijabetičnog stopala; Ulkus stopala; Neuropatija; Vaskulopatija; Kalus; Infekcije rane; Izobrazba bolesnika*