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Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities

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Abstract

Diabetic foot ulcers (DFU) are a debilitating and severe manifestation of uncontrolled and prolonged diabetes which present as an ulceration, usually located to the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop one of these ulcers, and out of these individuals, 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications. The pathologic mechanisms of DFU are described in terms of a triad: Neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease amputations, and prevent mortality from DFU. In this manuscript, we review the literature for the current pathophysiology, preventive options, and definitive management of DFU.

Key Words: Diabetes; Ulcer; foot; Antibiotics; Revascularization; Cell therapy

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Core Tip: Diabetic foot ulcer: Pathophysiology: - Neuropathy - Vascular insufficiency - Secondary infection Overview of management: I. Preventive care II. Non invasive modalities including cell therapy III. Invasive modalities including revascularization.

INTRODUCTION

Diabetes is a global pandemic affecting about 422 million people worldwide and resulting in estimated 2 million deaths per year[1]. It affects 11.3% of the United States population[2]. Diabetic foot ulcers (DFU) are a debilitating and severe manifestation of uncontrolled and prolonged diabetes which present as an ulceration, usually located to the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop one of these ulcers, and out of these individuals, 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications[3]. With such a high level of morbidity stemming from debilitating osteomyelitis and amputations in patients with DFU, it is of the utmost importance to properly address and treat the underlying causes of DFU. In this paper, we review the literature for the current pathophysiology, preventive options, and definitive management of DFU.

PATHOPHYSIOLOGY

DFU is a full-thickness wound, involving the dermis, located in the weight bearing or exposed area below the ankle. The Wagner system aids in categorizing the severity of the ulcer, ranking it on a scale of 1 to 5 (Table 1). The pathologic mechanisms of DFU are described in terms of a triad. This includes neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot[4] (Figure 1).

First, the lack of protective sensation in the feet predisposes patients with diabetes to developing trauma and ulcers. This sensory impairment occurs due to hyperglycemia-induced upregulation of aldose reductase and sorbitol dehydrogenase production which in turn increase fructose and sorbitol. These glucose products accumulate and induce osmotic stress thereby reducing nerve cell myoinositol synthesis and nerve conduction[5]. Also, from a pathological stance, Advanced glycation end-products (AGEs) must be considered. AGEs are non-enzymatic protein and amino acid adducts as well as DNA adducts which form from dicarbonyls and glucose. AGE formation is enhanced in diabetes and is associated with the development of diabetic complications[6]. In addition to the sensory neuropathy, diabetes can induce neuronal autonomic dysfunction which results in impaired sweat production and makes the foot susceptible to dryness, skin cracking and fissuring[7]. Furthermore, motor neuron dysfunction can give rise to muscle wasting and structural abnormalities of the foot[8]. This causes focally elevated pressures at various zones of the plantar foot and increase the risk of ulceration[9].

In addition to the triad, impaired wound healing has been established as a key means of DFU progression[10], importantly, molecular changes at the site of DFU precede the grossly visualized tissue abnormalities[11]. In fact, the route from hyperglycemia to DFU involves complex molecular dysfunctions in wound healing. Ordinarily, wounds undergo several healing stages involving hemostasis, inflammation, proliferation, and remodeling. Acute wounds advance linearly through these stages; however, chronic nonhealing DFU stall in one phase or more. In early phases of wound healing, neutrophils normally release their granular molecules to kill foreign pathogens in a process known as neutrophil extracellular traps (NETosis)[12]. However, under the diabetic microenvironment, NETosis becomes dysregulated causing a proinflammatory cascade and overproduction of cytokines and superoxide which delays wound healing[13,14]. Moreover, hyperglycemia induces formation of AGEs that cause structural and functional changes of key proteins[15]. Specifically, AGE can bind to its receptor, RAGE, which is normally expressed minimally in normoglycemic

conditions[16]. This in turn activates NF-κB. Ultimately, cytokine release is enhanced with a self-sustaining cascade that prolongs inflammation and favors apoptosis[17]. Overall, hyperglycemia induces a proinflammatory environment largely due to the dysregulation of cytokine release, NETosis and AGEs.

Along with inflammation, the substantial alterations of the extracellular matrix (ECM) play a significant role in perpetuating the non-healing DFU. In cases of normal wound healing, the production and degradation of ECM proteins such as collagen and fibrin are tightly regulated[18]. Collagen comprises most of the soft tissue ECM; and thus, abnormalities of collagen metabolism have significant consequences on wound healing. Specifically, collagen-degrading enzymes known as matrix metalloproteinases (MMPs) become hyperactive resulting in a highly proteolytic environment with reduced collagen content[19,20]. Overall, the ECM becomes disorganized and insufficient to support wound healing. Alongside elevated MMP activity, the accumulation of AGEs results in a reduction of fibroblast growth factor (FGF) and transforming growth factor-beta[21,22]. This has a similar effect of reducing the collagen content by way of also inducing apoptosis of fibroblasts[23].

Lastly, impaired angiogenesis plays a key role in the disruption of diabetic wound healing. Angiogenesis ordinarily occurs during the proliferative phase of wound healing and is responsible for both the formation of granulation tissue and delivery of nutrition and oxygen to the wound[24]. In the case of DFU, there is a reduction of angiogenic growth factors such as vascular endothelial growth factor (VEGF) 20 and FGF-2[25]. Essentially, VEGF initiates angiogenesis and mediates endothelial cell proliferation while FGF-2 facilitates migration of new blood vessels through the ECM[26,27]. When VEGF and FGF-2 expression is compromised, wound healing declines. Furthermore, endothelial progenitor cells (EPCs) have been implicated as expressors of pro-angiogenic factors and receptors including VEGF and FGF[28]. A deficiency of function and number of EPCs has been demonstrated in patients with type 2 diabetes which is also due to AGEs[29-31]. Overall, the dysfunction of EPCs and circulating growth

factors contributes significantly to the development and progression of DFU by way of disrupting angiogenesis.

MANAGEMENT

Management of DFU involves preventative care as well treatment modalities inclusive of both non-invasive and invasive management strategies (Figure 2).

Preventative care

Due to diabetes being a risk factor for development of underlying peripheral vascular disease, the majority of DFUs are asymptomatic until advanced enough to recognize more severe symptoms. During diagnosis of DFUs, neuropathy may mask ischemia, and the converse relationship is also possible. Therefore, the primary preventative strategy is regular diabetic foot screening to allow early identification of DFU and proceed with more effective treatment, ultimately avoiding further complications such as gangrene and amputation[32]. Screening encompasses self-screening of the foot for trauma or ulceration everyday by the patient and routine screening during health care visits.

Noninvasive care

The more common route with DFU is local care, in which many potential avenues of treatment can be utilized. These include wound dressings, human skin equivalents, pressure off-loading, total-contact casting (TCC), systemic hyperbaric oxygen, Larvae Therapy (Maggot Therapy) and topical growth factors.

Wound dressings

Wound dressings are the most basic and common treatment measure, and although they serve their purpose well in approaching DFU, other methods have proven vastly more effective in comparison or adjunction with wound dressings.

Human skin equivalent

Human skin equivalent (HSE) is more effective compared to the standard treatment of saline-moistened gauze across amputation rates, ulcer healing rates, and infection rates. One Randomized Controlled Trial (RCT) assessed the effectiveness of Graftskin, a living skin equivalent in noninfected nonischemic DFU. Graftskin was applied weekly for a maximum of four weeks or until complete healing occurred. The results of the trial highlighted the increased effectiveness of the HSE in comparison to the control group, which only treated the ulcers with saline-moistened gauze. The HSE resulted in an 18% increase in complete wound healing when compared to the control group[33]. Despite this impressive results, one limitation to this treatment is that HSE may not be widely available.

Offloading, TCC

Pressure offloading serves as one of the primary treatments of DFU, primarily ones that have a neuropathic nature, with many variants being utilized. For ischemic DFUs, however, revascularization is more commonly used. Common methods include bed rest, wheelchair, crutch-assisted gait, total contact casts, felted foam, therapeutic shoes, and removable cast walkers[34]. The most effective offloading treatment is TCC, in which full casts are applied by an experienced physiotherapist and are changed weekly for 2-3 wk or until healing has occurred. One RCT found that TCC was extremely effective in increasing ulcer healing and reducing infection when compared with traditional dressing changes and other offloading methods. The study reported a 91% rate of healing within the TCC population, compared to a 32% rate of healing in the control group. This rate was reported following a 65-d period. Furthermore, the TCC group reported 0% of infection, and the control group reported 26% of infection[35]. Multiple other studies indicate similar results, with TCC being an extremely effective treatment to DFU, particularly when compared to traditional dressing changes. One adverse effect of this treatment, however, is fungal infection development, but this was addressed with topical treatment and did not prevent continued casting. Despite the evident

success of the TCC method, one national survey evaluating 901-foot clinics in 48 states and the District of Columbia indicated that TCCs were used only by 1.7% of the centers, potentially due to the tedious nature of this treatment option. The option requires an experienced physiotherapist, and constant replacing and tending to. The application of the cast is a timely and intricate endeavor and tends to cause patients discomfort according to the survey. The survey indicated that the primary treatment across the foot clinics was shoe modifications.

Hyperbaric oxygen therapy

Another treatment for DFU is systemic hyperbaric oxygen therapy (HBOT), which is reserved for advanced cases of DFU, aimed at reducing the risk of amputation. This treatment is prevalent particularly in treatment of infected DFU, where one systematic review identified six RCTs that evaluated chronic DFU. The systemic hyperbaric oxygen treatment sessions are usually conducted from 45 to 120 min once or twice daily at pressures between 1·5 and 3·0 ATA. This method resulted in significantly reduced rates of major amputation compared with usual care of said ulcers. It tends to be presented as an adjunctive therapy to normal wound care measures[36]. However, HBOT is quite expensive, and still not fully researched, and may warrant further trials.

Larvae therapy (maggot therapy)

Maggot therapy is another well-researched technique when treating chronic wounds in which maggots are placed on the wound area. This treatment method has been shown to facilitate debridement efficiency significantly. Maggot therapy also enabled faster development of granulation tissue and increased reduction in the wound surface area compared to other topical treatments such as hydrogel dressings. Maggot therapy also had no effect on disinfection or complete healing rate for the wound[37].

Topical growth factors

Topical growth factors also prove to be effective in increasing ulcer healing rates when compared with placebo, particularly platelet-derived growth factors. The growth factors serve as the principal immediate mediators of wound healing, thus propagating the healing of DFU. One meta-analysis evaluated 26 RCTs with 2088 participants, and focused on recombinant epidermal growth factor, autologous platelet rich plasma, and recombinant human platelet-derived growth factor. Overall, all three treatments significantly improved healing rate when used alongside standard treatment, with a slight favoring of recombinant human epidermal growth factor compared to other growth factors[38].

Shock wave therapy

Extracorporeal shockwave therapy (ESWT) has been reported to accelerate the healing of soft tissue wounds when treating DFU. The ESWT is utilized to stimulate osteoblasts and in turn facilitate soft tissue healing. There have been promising trial results indicating ESWT as a more effective treatment for DFU when compared to more traditional methods. Two multi-national RCTs were conducted to compare the efficacy of ESWT when used adjunctively with standard care and other DFU treatments. The trials both lasted 12 wk and showed reduction of wound volume by more than 50% in the ESWT treatment when compared with standard practice alone[39].

Stem cell therapy

The cornerstone of available treatment options currently includes infection treatment, surgical debridement, and revascularization[40]. Better understanding of the tissue remodeling process, which comprises of inflammation, cell migration, neovascularization, and proliferation has paved the way for stem cell- based therapy to be a viable option in treatment of DFU[41]. Stem cells aid wound healing by secretion of cytokines that play an important role in cell migration, angiogenesis, remodeling of extracellular matrix, and regeneration of nerves[42]. Also, their inherent property of

differentiation into various cell types including myofibroblasts and endothelial cells optimize wound healing[43].

The stem cell types that have been studied to aid in diabetic foot treatment are mainly adult stem cells (ASC). Bone marrow derived mesenchymal stem cells (BM-MSC) is the most extensively studied among the different ASC which include adipose-derived stem cells, umbilical cord-derived mesenchymal stem cells (UC-MSC), and peripheral blood-derived mesenchymal stem cells[44] (Table 2). BM-MSC use demonstrated improved wound ulcer healing, with improvement in Ankle-Brachial Index (ABI), angiogenesis, and increase in blood flow when compared to local treatment[45-47]. Even functional improvement with decrease in rest pain and increase in claudication distance was demonstrated. Decreased amputation when compared to conventional treatment was also seen. Furthermore, combining UC-MSC stem cell therapy with traditional angioplasty resulted in improvement in ABI, claudication distance, and improvement in skin temperature[48].

Embryonic stem cells (ESC) are usually derived from blastocysts from the inner cell mass usually by *in vitro* fertilization[49]. The controversial ethics behind obtaining ESC and their inherent high rate of proliferation, the risk of tumor formation or immunological rejection has limited them from widespread research[50]. Though an animal model study showed that use of ESC did not increase chances of tumor formation in rats[51], further clinical studies are required to test the efficacy of ESC treatment in diabetic feet. Thus, stem cell therapy shows promise as a viable therapeutic option in the treatment of diabetic foot ulcer. They can be used alongside conventional therapies like angioplasty to obtain better outcomes.

Systemic and local antibiotics

Systemic and local antibiotics in infected DFU serve as a noninvasive treatment of infection caused by the ulcer formation. The antibiotics can be administered topically through sponge applications or through gauze wrapping as well as through usage of a circulator boot. The presence of infection is determined by ≥2 classic findings of

inflammation or purulence. There are three classifications of infection severity, mild (superficial and limited in size and depth), moderate (deeper and larger in area), and severe (overexpressed and beginning to affect metabolic perturbations). Most DFU have a microbial cause, with aerobic gram-positive cocci and staphylococci being primary microbial pathogens causing said infections. Wounds that lack infection do not require antibiotic therapy, whereas infected wounds may. If the wound is infected, a post-debridement specimen must be collected for both aerobic and anaerobic cultures. Following testing and potential imaging (includes radiographs and MRIs if necessary), antibiotics may be prescribed[52]. If the infection is mild or moderate, narrow-spectrum oral antibiotics may be administered, and if the infection ranks as high moderate or severe, broad-spectrum parenteral antibiotics should be utilized[53].

Negative pressure wound therapy

One of the most recent developments in DFU treatment is the utilization of negative pressure wound therapy (NPWT). NPWT utilizes vacuum pressure to draw fluid from the wound and increase blood flow to the affected area, thus stimulating the healing process. While being primarily a treatment for burn patients, NPWT has begun being used on DFU patients as well, and promising results have been shown. NPWT results in two primary types of tissue deformations: macro deformation, which is exemplified by wound contraction, and micro deformation, which occurs on the microscopic level. Both deformations stimulate blood flow and ensue a wound-healing cascade which includes tissue granulation promotion, vessel proliferation, neo angiogenesis, epithelialization and excess extracellular fluid removal. NPWT also results in increased anti-inflammatory conditions in the patient. Clinical studies in DFU patients showed that NPWT is more efficient compared to standard therapy, particularly when observing wound healing and amputation rate, without a rise in adverse events[54].

INVASIVE TREATMENT STRATEGIES

Debridement

Debridement is one of the primary steps in the protocol of treating DFU, particularly due to its ability in changing the environment of the chronic wound through the removal of necrotic and nonviable tissue and foreign debris, which impede the healing process. Thus, their removal quickens healing. This removal may not always lead to complete healing of the DFU, but it serves well as a preliminary step in the treatment. Following debridement, the wound is further analyzed and if necessary, other treatment paths are pursued[55]. Debridement is commonly used alongside other treatments.

Revascularization (angioplasty)

When patients with DFU also have a history of peripheral arterial disease (PAD), delayed healing may take place, and thus lead to higher complication risks and an increased chance of potential amputation. Thus, when patients have both DFU and chronic limb ischemia, revascularization can serve as a promising treatment option. According to past studies, the ulcer-healing rate after the revascularization procedures ranges from 46% to 91% and showcases an improvement in healing rate compared to patients that do not undergo revascularization[56]. Revascularization options include stenting and surgical bypass if intervention is not possible. Interventions like atherectomy, shockwave for calcified lesions, balloons (cutting, drug coated, cryoplasty) can be used in unison with stenting or alone to revascularization[57]. According to another clinical trial in which 80 patients who underwent foot revascularization procedures, promising results were also shown. All patients in this study underwent endovascular procedures (balloon angioplasty). The patients were followed for 12 mo after the procedures, and the results showed that 56.2% of the patients fully recovered, 58.7% had minor amputations, and only 16.2% ended in having major amputations following the procedures. Overall, revascularization is an effective treatment for DFU especially when the patient is at risk of amputation[58]. However, the effectiveness of the vascular procedure differs among patients, and it also does not reduce the risk of death associated with PAD. It is important to consider along revascularization the role of

complex therapy, specifically medicinal control. This includes close monitoring of glucose levels, lipid levels, blood pressure and even antiplatelet therapy following the surgical procedure. Compared with initial supervised exercise training (SET) only, endovascular therapy in combination with SET is associated with significant improvement in total walking distance, ABI, and risk of future revascularization or amputation. On the other hand, only endovascular therapy was not associated with any improvement in functional capacity[59]. It is also important to note that post-endovascular procedure patients must be started on dual anti-platelet therapy, including aspirin and clopidogrel or ticagrelor for a few months. Statin therapy has also been proven to stabilize the plaques before and after revascularization.

Skin grafting

Skin grafting may serve as a solution when the DFU become more severe, offering a chance to replace the infected skin and thus propagate the healing process. There are a variety of skin grafting techniques that may be used, which include bioengineered or artificial skin, autografts (taken from the patient), allografts (taken from another person) or xenografts (taken from animals). A review article that analyzed 17 RCTs concluded that skin grafting and tissue replacements when used in adjunction with standard treatment led to an increase in the healing rate of DFU and slightly lowered the chance of amputation. However, evidence of long-term effectiveness is uncertain[60].

Amputation

Amputation serves as the final front when treating DFU and is reserved for the most chronic levels of infection or deformity that renders the foot as non-functional. Amputation can be classified as either minor or major, with minor amputation being the removal of a smaller area. For example, removal of a toe or part of the foot is classified as minor amputation. Major amputation, however, can be performed above or below a major joint, like a knee or an elbow. According to a clinical trial, minor amputation was

performed for 38.4% while major amputation was performed for 6.8% of the patients with DFU[61].

CONCLUSION

DFU renders substantial morbidity and mortality in patients with diabetes. It also, results in increased hospitalization leading to increased health care spending. Thus, prompt diagnosis and catered management is essential. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease amputations, and prevent mortality from DFU. Further research into newer modalities that aid in prompt and effective management will further help alleviate the healthcare burden of DFU.

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