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REVIEW

Diabetic foot ulcers in conjunction with lower limb lymphedema: pathophysiology and treatment procedures

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Abstract: Diabetic foot ulcers (DFUs) are complex, chronic, and progressive wounds, and have a significant impact on morbidity, mortality, and quality of life. A particular aspect of DFU that has not been reviewed extensively thus far is its management in conjunction with peripheral limb edema. Peripheral limb edema is a feature of diabetes that has been identified as a significant risk factor for amputation in patients with DFU. Three major etiological factors in development of lymphedema with concurrent DFU are diabetic microangiopathy, failure of autonomic regulation, and recurrent infection. This review outlines the pathophysiology of lymphedema formation in patients with DFU and highlights the cellular and immune components of impaired wound healing in lymphedematous DFU. We then discuss the principles of management of DFU in conjunction with lymphedema.

Keywords: diabetic foot ulcer, lymphedema, chronic wound, wound management

Introduction

Globally, approximately 370 million people have diabetes and this number is on the rise.[1] Diabetes UK estimates that by 2030, nearly 552 million people worldwide will have diabetes.[2] In the UK alone, approximately 2% of the population is estimated to have diabetes, of which 15% will develop foot ulceration at some point in their lives.[3] Overall, 8% of hospital admissions involve patients with diabetes.

Diabetic foot ulcers (DFUs) are complex, chronic, and progressive wounds, and have a significant impact on morbidity, mortality, and quality of life.[4,5] Diabetic patients have a 20-fold increased risk of amputation compared with non-diabetics, and DFU directly leads to 6,000 amputations per year in England alone.[6] The prognosis often remains poor despite amputation. Historical data demonstrate 50% mortality at 2 years following major amputation,[7] and an overall decrease in 5-year survival of 41%–70% has been reported.[8] Even between diabetic populations, the presence of DFU represents an approximately 50% increased mortality risk.[9]

The economic burden of DFU management is significant. In the UK, an estimated £639–£662 million was spent in 2010–2011 on the management of DFU and subsequent amputation, representing 0.6%–0.7% of the entire National Health Service annual budget.[6] In the USA, 33% of the $116 billion total health care spend on diabetes is on the management of foot ulceration.[10]

Peripheral limb edema is a feature of DFU and despite the lack of an estimate of its incidence or prevalence in DFU, it has been identified as a significant risk factor for amputation in patients with DFU.[11,12] Diabetes, however, has been identified as a comorbidity in 23.5% of patients with lymphedema in a multicenter study of 1,000 patients

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with chronic leg ulcers and is also reported to be a significant comorbidity in breast cancer survivors with lymphedema.[13,14] The resistance of diabetic ulcers to healing is undoubtedly multifactorial, but having concurrent lymphedema further impairs the wound healing process.[11,12] This review outlines the pathophysiology of lymphedema formation in DFU and the principles of management of DFU in conjunction with lymphedema.

Pathophysiology of lymphedema formation in DFU

DFU has traditionally been linked to peripheral vascular disease, peripheral neuropathy, and infection.[3] Peripheral vascular disease is more common in patients with diabetes and is traditionally classified into macrovascular and microvascular complications. Neuropathy affects the motor, sensory, and autonomic nerves and their associated functions, with local trauma and pressure in the neuropathic foot being the leading factors in the development of DFU. Recurrent infection in the functionally immunosuppressed diabetic can have devastating sequelae.[15]

Lymphedema is a condition of localized fluid retention and tissue swelling caused by a compromised lymphatic system. Primary lymphedema develops as result of lymphatic abnormalities from congenital hypoplasia, aplasia, or valvular incompetence that could present at birth or later in life. Secondary lymphedema occurs due to recurrent infection and inflammation, parasitic infection, malignancy, trauma, or iatrogenic causes, resulting in failure to drain protein-rich lymphatic fluid from the interstitium, leading to edema of the affected site. Secondary lymphedema is seen in patients with lymphedematous DFU.

The pathophysiology of DFU in conjunction to lymphedema has not been widely discussed, although several studies have been undertaken to better understand the development of peripheral limb edema in diabetes. This section explores the pathophysiology of lymphedema in DFU, focusing on the three major underlying etiologies of DFU, ie, diabetic microangiopathy, failure of autonomic regulation, and recurrent infection. We then highlight the cellular and immune component of impaired wound healing in lymphedematous DFU.

Diabetic microangiopathy and lymphedema

The important role of hyperglycemia in the development and progression of microvascular complications has been clearly established.[16] In the hyperglycemic state, abnormal glucose metabolism leads to production of advanced glycation end products. These, among other consequences, interfere with vascular remodeling, which has been proposed as a mechanism for development of diabetic microangiopathy.[17] Microangiopathy alters the structure and function of the microvasculature, leading to loss of the vascular barrier and tone regulation, resulting in increased capillary filtration of fluid into the tissues.[17]

When the capillary filtration rate exceeds the rate of lymphatic drainage, fluid accumulates in the intercellular space, leading to edema, which is governed by Starling's principle of fluid exchange (equation 1). Starling's principle states that fluid transport across the exchange vessel wall is driven by the hydraulic pressure gradient and opposed by the colloid osmotic pressure gradient between the plasma and the interstitium.[18] In diabetic microangiopathy, the hydraulic conductance of the capillary wall (L_p) is increased due to structural and functional impairment, resulting in an increased capillary filtration rate.

$$\text{Starling's equilibrium: } J_v = L_p S ([P_c - P_i] - \sigma [\pi_p - \pi_i]) \quad (1)$$

where J_v is the capillary filtration rate, L_p is the hydraulic conductance of the capillary wall, S is the surface area, P is the pressure within the capillary (c) or interstitium (i), σ is the osmotic reflection coefficient of the capillary wall, and π is the osmotic pressure of plasma (p) or interstitial fluid (i).

This is further exacerbated by the increased resting blood flow in the skin, the capillary filtration rate, and the hydrostatic pressure in the lower limbs compared with the upper limbs, leading to lower limb lymphedema.[19–21]

Microangiopathy also affects endothelial function with increased capillary permeability to large proteins and molecules in diabetic patients, a feature that can be seen by the transcapillary escape rate of radiolabelled albumin.[22,23] Removal and drainage of interstitial albumin appears to be delayed in diabetic patients, suggesting a defect in lymphatic function due to overflow saturation of the lymph pumps.[22] Hence, although diabetes does not cause direct damage to the lymphatic vessels, the processes of normal interstitial fluid homeostasis are affected with the increase in transport capacity that overwhelms the drainage system. This has been demonstrated by the improvement of edema and notable reduction in local capillary filtration with drugs acting on capillary permeability such as O-(beta-hydroxyethyl)-rutosides and Pycnogenol in subjects with diabetic microangiopathy.[24–26] Reduction in lymphedema was accompanied by improvement in ulcer healing.[25]

Diabetic neuropathy and lymphedema

The pathogenesis of diabetic neuropathy is thought to involve disturbance in the metabolism and vasculature of nerve tissue due to excessive glucose uptake, leading to damage of peripheral nerves.[27] The functional subunit in lymphatic vessels is the lymphangion, wall of which consists of smooth muscle cells that propel lymph in a peristaltic manner, contraction of which is under neural control.[22] Analogous to the blood vessels, the peripheral lymphatic vessels and smooth muscle subunits are under autonomic control. Diabetic neuropathy can lead to lymphatic pump failure, impairing interstitial fluid uptake from the distal part of the limb and disrupting lymphatic fluid transport along the lymphatic vessels.[22] The disorder in absorption and transport of lymphatic fluid is analogous to direct neural injury with sympathetic denervation interruption seen in trauma where management by complex physical decongestion therapy with manual lymphatic drainage (MLD) results in clinical improvement.[28]

Recurrent infection and lymphedema

Patients with DFU are predisposed to recurrent wound infections, contributed to by the open wound and immunological perturbation. The shift in balance between the host defense system and bacterial load in the wound favors soft tissue infection which leads to destruction of host tissue. Recurrent soft tissue infection invariably damages the lymphatic system located in the dermal layer of the skin. The affected lymphatics become inflamed, dilated, and filled with exudate, chiefly neutrophils and monocytes. Abnormal accumulation of interstitial fluid, proteins, growth factors and other active peptide moieties, glycosaminoglycans, and particulate matter also includes bacteria. The overload and failure of lymphatic intestinal drainage with accumulation of these larger elements leads to occlusion of the lymphatic system and stasis, providing an ideal microenvironment for bacterial growth, commonly group A β-hemolytic *Streptococcus* and *Staphylococcus aureus*.[29–31] Accumulation of lymphatic fluid within the interstitium stimulates fibroblasts, keratinocytes, and adipocytes, leading to deposition of collagen and glycosaminoglycans within the skin and subcutaneous tissue.[31] This is accompanied by chronic inflammation, involving lymphocytes, monocyte/macrophages, and dendritic cells. These inflammatory cells produce several inflammatory cytokines related to fibrosis, such as connective tissue growth factor, transforming growth factor-β, and platelet-derived growth factor, besides upregulating the cellular proliferation and migration of fibroblasts.[31] The outcome of this is further soft tissue destruction, which exacerbates the lymphedema. Lymphatic dysfunction also impairs the local immune response, which plays a permissive role in propagation of bacterial and fungal invasion, further worsening the existing lymphatic dysfunction leading to a chronic state with reduced reversibility of the edema.[31]

Impaired wound healing in lymphedematous DFU

Wound healing is a complex physiological process involving numerous types of cells, growth factors, and cytokines, each of which is required at the correct time and for the appropriate duration. Impaired wound healing in the lymphedematous DFU is attributed to altered function at the cellular level, compounded by the inflammatory reaction and impaired immune system. This section exemplifies the cellular and immunological aspects of impaired wound healing in lymphedematous DFU through two important mechanistic processes of wound healing: the gap junctional protein and the Toll-like receptors (TLRs) of the innate immune system.

Cellular component in DFU and lymphedema

Accumulation of fluid in the interstitial space results in abnormal function at both the tissue and cellular level.[32] The ensuing increase in physical distance between tissue channels can affect metabolic exchange, impairing the delivery of oxygen and nutrients and the discharge of toxins and inhibitory factors, with a resultant shift toward anaerobic metabolism. Likewise, the wider separation between cells affects the exchange of gases between plasma membranes. Given that the rich microvascular network in the skin is located in the papillary dermal layer, formation of interstitial edema that increases intercellular spaces affects oxygenation to the epidermal layer of the skin.[33] This leads to alteration of the tissue properties in response to external pressure, predisposing to ulcer formation. This is particularly true in weight-bearing areas such as the plantar surface of the foot, which is the commonest location for DFU.[33]

Important transmembrane proteins involved in the passage of nutrients between cells and gaseous exchange are the connexin family of gap junctional proteins. Gap junctions are highly specialized structures, made up of channels spanning adjacent cell membranes, leaving a 2–4 nm extracellular "gap", hence their name.[34] These channels are assembled of transmembrane proteins called "connexins", which are described in terms of molecular mass (Cx43 represents the connexin protein of 43 kDa). As the key mechanism of cellular communication, connexins are involved in epidermal

innate immunity, inflammation control, and wound repair.[35] A wide range of connexins are found within the skin (including Cx26, 30, 30.3, 31.1, 32, 37, 40, 43, and 45), with Cx43 being the most ubiquitous and found in dermal fibroblasts, blood vessels, and appendages such as sweat glands, sebaceous glands, hair follicles, mast cells, and activated leukocytes, as well as epidermal keratinocytes.[36,37] Connexins are associated with the pathogenesis of both type 1 and type 2 diabetes, and are directly linked to wound healing. Abnormal upregulation of Cx43 seen in diabetic wounds binds cells together and prevents migration of keratinocytes from the wound edge, delaying re-epithelialization and the wound healing process.[38,39] Preventing upregulation of Cx43 expression in a diabetic wound has been reported to increase the rate of re-epithelialization in a mouse model.[40]

Three connexin isoforms, Cx37, Cx43, and C47, have been shown to be involved in development and function of the lymphatics.[41] Loss of function in knockout mice results in widely dilated superficial lymphatics in the skin and severe lymphedema due to complete absence of valve formation.[41,42] Mutation experiments on connexins, on the other hand, resulted in impaired uptake of lymphatic fluid without obvious anatomical defect involving the lymphatic vessels.[43] Data suggest that coordinated function of gap junctions is needed to mediate the propagation of spontaneous contractions in the lymphatic vasculature.[44] Although these in vivo studies have demonstrated the effect of deletion of connexin, it is still unknown if the changes in expression of connexin seen in chronic wounds affect lymphangiogenesis.

Innate immune system in DFU and lymphedema

Persistent and excessive inflammation results in disruption of wound healing in diabetes. DFU become stalled in the inflammatory phase of wound healing, fails to progress, and a chronic ulcer results. This excessive "hyperinflammation" is mediated in part by the TLRs of the innate immune system. TLRs are key pattern recognition receptors of the innate immune system, which confer specificity to the innate immune system through recognition of discrete molecular patterns such as microbial cell wall constituents.[45] Stimulation of TLRs results in activation of a variety of cell-dependent responses, including antigen presentation and activation of a potent pro-inflammatory cascade, with release of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, and phagocytosis.[46]

In addition to exogenous microbial ligands known as pathogen-associated molecular patterns, TLRs also recognize endogenous "self" patterns that are released in response to tissue damage, known as damage-associated molecular patterns (DAMPs).[46] DAMPs act as danger signals triggered by tissue damage, and initiate a TLR-mediated inflammatory response, that in turn alerts the immune system to the presence of tissue injury.[47] Under normal circumstances, the resulting influx of inflammatory cells and stimulates a sterile inflammatory reaction to control bacterial infection and remove debris. Activation of DAMP TLRs is regarded as essential for initiation of the wound healing process.[48] However, in diabetes, controversy exists as to whether TLR-mediated inflammation has a beneficial or inhibitory effect on wound healing.[49] In animal studies, TLR2 and TLR4 inhibition or knock-out has a detrimental effect on the wound healing process for up to 7 days following injury, indicating the importance of TLR2 and TLR4 in the early phases of wound healing.[50,51] However, in diabetes-induced mice, TLR2 and TLR4 deletion conferred an apparent protective effect, demonstrated by significantly improved wound healing and a reduction in the pro-inflammatory environment of the wound, compared with wild-type diabetic rodents.[52,53]

In lymphedema, DAMPs such as high-mobility group box 1 and heat-shock protein appear elevated in response to lymphatic stasis.[54] Inhibition of high-mobility group box 1 leads to a significant reduction in inflammatory lymphangiogenesis, suggesting a negative role for DAMPs in promoting lymphangiogenesis besides provocating chronic inflammatory response in chronic lymphedema.[54] Studies in a mouse model of post-surgical lymphedema deficient for TLR2, TLR4, and TLR9 demonstrated significantly worse effects post injury compared with those in a wild-type model, as evidenced by increased tissue edema, reduced lymphangiogenesis, increased fibrosis, and increased leucocyte infiltration but reduced monocyte infiltration.[55] The data suggest a role for TLRs in the normal repair of lymphatic injury and resolution of lymphedema.[55]

Consequently, although TLRs appear to have a role in normal inflammation and swelling, their role in the diabetic patient with lymphedema may be confused, and the excessive TLR-mediated inflammation associated with diabetes is counterproductive with resultant chronic lymphedema.

Principles of management

While the current standard of care for DFU is well established by clinical guidelines and pathways and a recent systematic review by Braun et al, there remains a lack of high-quality evidence on the management of DFU in conjunction with lymphedema.[5,56]

Best practice management for DFU with or without lymphedema includes rapid assessment and correction where possible (or necessary) of macrovascular arterial insufficiency. The importance of wound assessment, debridement and cleansing, recognition and treatment of infection, revascularization, and selection of an appropriate dressing to achieve optimal healing is undeniable. However, managing DFU requires comprehensive attention with good diabetic control, offloading strategies, and an integrated approach to wound care.[56] This section highlights the principles of management of DFU in conjunction with lymphedema.

Glycemic control

Evidence for the benefit of good glycemic control is well established.[57] Randomized controlled trials (RCTs) such as the Diabetes Control and Complication Trial in type 1 diabetes demonstrated a significant reduction in development of microvascular complications such as retinopathy, nephropathy, and microalbuminuria and in neurological complications such as neuropathy in the intensive therapy groups.[16] The UK Prospective Diabetes Study in type 2 diabetes similarly demonstrated a significant reduction in "any diabetes related end-point", progression of retinopathy, and microalbuminuria in the tightly controlled treatment arm, regardless of treatment modality.[16] While no studies have examined the effect of tight glycemic control on the development, progression, and treatment of lymphedema in DFU, it seems intuitive that a reduction in the risk of diabetes-related microangiopathic complications and in the secondary consequences of hyperglycemia, such as cellulitis and other skin infections, through long-term close glycemic control will benefit the prevention and treatment of lymphedema.

Decongestion therapy

Decongestion therapies, including compression bandaging, MLD, and physical exercises, improve dermal lymphatic plexus lymph flow and have been the accepted non-surgical method to manage lymphedema.[58] MLD involves specialized rhythmic pumping techniques to massage the affected area and enhance the flow of lymph from the peripheries toward the heart. This gentle skin massage encourages superficial lymphatic contraction, thereby increasing lymph drainage.[59] Current imaging studies with near-infrared fluorescence have demonstrated the positive effect of MLD in increasing lymphatic vessel contractility and lymph velocity, leading to resolution of clinical symptoms.[60,61] The benefit of MLD in lymphedema secondary to complex regional pain syndrome, a clinical condition characterized by post-traumatic diffuse pain with autonomic and vasomotor changes, indicates that MLD could also benefit edema due to autonomic impairment as seen in DFU.[62] Conversely, a recent systematic review of the RCTs evaluating the effects of MLD on breast cancer-related secondary lymphedema indicates that MLD does not prevent or treat lymphedema.[63] However, there were clinical and statistical inconsistencies between the various studies, confounding the evaluation of the reviewed studies.[63]

Compression therapy has been advocated for the management of lymphedema and in the management of high perfusion microangiopathy in patients with DFU. Compression therapy with elastic stockings reduces capillary leakage and formation of edema, and may retard the progression of diabetic microangiopathy.[64] Use of stiff, short-stretch bandages with high working pressure and low resting pressure provides resistance to the accumulation of interstitial fluid while stimulating the rhythmic contraction of lymphatic collectors during exercise.[65] Working pressure is determined by the resistance provided by the bandage against the underlying muscle contraction, while the pressure exerted on tissue at rest is the resting pressure.[65] Two RCTs have shown that compression therapy with the use of intermittent pneumatic compression (IPC) is effective in reducing healing time for DFU in addition to reducing lymphedema.[66,67] The mechanism of action of IPC is believed to include enhancement of fibrinolysis and venous outflow, thereby reducing edema.[67,68] IPC simulates the effect of walking and weight-bearing on the venous system by the intermittent compression-decompression cycle. However, compression therapy is limited in the presence of peripheral vascular disease. One RCT evaluated the effect of compressed air massage on the rate of diabetic ulcer healing, with all patients receiving standard medical and surgical treatment, while in addition, one group received air massage at 100 kPa for 15–20 minutes for 5 days per week. This study found a significant reduction in time to DFU healing, with an average time of 58.1 days in patients (n=28) receiving compressed air massage, while those patients (n=27) receiving only standard wound care averaged 82.7 days until ulcer healing.[66] Compressed air massage has been shown to significantly improve local skin blood flow measured using laser Doppler fluxmetry.[66] Another double-blind RCT compared healing at 12 weeks between a pulsatile pneumatic foot compression system with a bladder that inflates to 160 mmHg for 2 seconds to empty the veins of the foot, repeating the cycle every 20 seconds for 8 hours a day in 52 patients, against a non-functioning

foot compression device in 45 patients. This study found a significant increase in healing efficacy in patients with DFU,[67] along with a significant reduction in edema in the study arm receiving IPC therapy.

Limb offloading is a common strategy in the management of diabetic foot disease, and standard offloading devices are believed to reduce edema by enabling patients to remain relatively mobile; however, there are no objective published data confirming this.[69] An alternative view is that immobilization of the ankle reduces function of the calf muscle pump, impairing venous return, potentially resulting in increased foot edema.[69]

Surgical management

Surgical management of DFU with lymphedema can be divided into debridement, debulking, and a microsurgical approach. Wound debridement is considered part of standard DFU care. Debridement, the most important intervention for decreasing the risk of limb amputation in patients with DFU, involves the removal of callus and necrotic tissue, and reduction of bacterial biofilm.[70] Debridement may be surgical, enzymatic (collagenase), autolytic (ie, occlusive), or biologic (larval). The different types of debridement for DFU, along with their advantages and disadvantages, have been recently reviewed by Yazdanpanah et al.[71]

Debulking surgery, such as the Charles procedure, which involves extensive excision of subcutaneous tissue followed by skin grafting, may be the simplest approach to reducing the volume of lymphedematous limbs but often results in substantial morbidity. Treatment of secondary lymphedema in the presence of DFU using the Charles procedure was described in a case report; however, it is an aggressive treatment with a prolonged treatment course.[72] The debulking procedure is particularly useful for ulcers with deep sinuses in the presence of chronic lymphedema where excision of the ulcer along with the sinus tract can be performed as a combined debulking procedure.[73]

Microsurgical techniques for treating lymphedema consist of lymphovenous anastomosis and vascularized lymph node transfer. Lymphovenous anastomosis creates a detour route from the lymphatics to the vein at the peripheral region of the affected limb, thereby increasing lymphatic drainage. Lymphovenous anastomosis has minimal morbidity; however, several studies have found that it is less effective in advanced-stage lymphedema, hence less likely to benefit patients with both lymphedema and DFU.[74] Vascularized lymph node transfer, a relatively new surgical treatment for lymphedema, involves transfer of lymph nodes to the lymphedematous limbs followed by microanastomosis of blood vessels. Despite promising outcomes in the clinical setting, the interaction between the transferred lymph nodes and the lymphatic system in the transfer site is not yet well understood.[74] Lahteenvuo et al and Honkonen et al showed that the transferred lymph nodes produce vascular endothelial growth factor-C, inducing lymphangiogenesis which may facilitate canalization of recipient lymphatic vessels to the lymph node.[75,76] Lin et al and Cheng et al hypothesized that the transferred lymph nodes act as "lymph pumps", ejecting the absorbed lymph fluid from the surrounding interstitial tissue into the venous circulation via the lymphovenous communication.[77,78] Despite the encouraging results in treating lymphedema, the reported clinical studies involve only patients with chronic lymphedema secondary to iatrogenic injury, which does not reflect the exact pathophysiology of lymphedema associated with a DFU. Furthermore, the surgical complexity and potential morbidity at the donor site of vascularized lymph node transfer may complicate its application.

Conclusion

Foot ulceration represents a significant burden of morbidity and excess mortality for diabetic patients, and is an enormous challenge for health care providers. There is significant overlap in the pathophysiology of both DFU and lymphedema, but further research is needed to better our understanding. The treatment strategies outlined here address the management of DFU in conjunction with lower limb lymphedema; however, novel strategies such as manipulation of innate immune inflammatory pathways through modulation of TLR and connexin regulation therapies have the potential to benefit both these pathologies. Our understanding of lymphatic biology in relation to chronic ulcers has to be advanced with further research, as it holds immense benefit for both patients and the health care system.

Disclosure

None of the authors have any commercial associations or financial relationships that would create a conflict of interest with regard to the work presented in this article.

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