ORIGINAL ARTICLE

Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections

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Abstract

Diabetes mellitus affects 284 million adults worldwide and is increasing in prevalence. Accelerated atherosclerosis in patients with diabetes mellitus contributes an increased risk of developing cardiovascular diseases including peripheral vascular disease (PVD). Immune dysfunction, diabetic neuropathy and poor circulation in patients with diabetes mellitus, especially those with PVD, place these patients at high risk for many types of typical and atypical infections. Complicated skin and soft-tissue infections (cSSTIs) are of particular concern because skin breakdown in patients with advanced diabetes mellitus and PVD provides a portal of entry for bacteria. Patients with diabetes mellitus are more likely to be hospitalized with cSSTIs and to experience related complications than patients without diabetes mellitus. Patients with PVD requiring lower extremity bypass are also at high risk of surgical site and graft infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a frequent causative pathogen in cSSTIs, and may be a significant contributor to surgical site infections, especially in patients who are colonized with MRSA on hospital admission. Patients with cSSTIs and diabetes mellitus or PVD experience lower clinical success rates than patients without these comorbidities, and may also have a longer length of hospital stay and higher risk of adverse drug events. Clinicians should be vigilant in recognizing the potential for infection with multi-drug-resistant organisms, especially MRSA, in these populations and initiating therapy with appropriate antibiotics.

Keywords: Burden, complicated skin and soft-tissue infection, diabetes mellitus, methicillin-resistant *Staphylococcus aureus*, peripheral vascular disease

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Epidemiology and pathophysiology of peripheral vascular disease and diabetes mellitus

It is estimated that over 284 million adults were living with diabetes mellitus worldwide in 2010, and this number is expected to increase by 54% by 2030 [1]. Comorbid peripheral vascular disease (PVD) is present in 9.5% of patients ≥40 years old with diabetes mellitus [2], and the risk of developing PVD is up to four-fold higher in patients with diabetes mellitus compared with patients without diabetes mellitus [3]. The

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prevalence of PVD increases with the duration of diabetes mellitus, with a relative risk of 1.39 for patients diagnosed with diabetes mellitus 1–5 years ago, and 4.5 for patients diagnosed more than 25 years ago [4].

The pathophysiology of atherosclerosis leading to PVD in patients with diabetes mellitus is multifactorial [5,6]. In the blood vessels, hyperglycaemia is thought to impair nitric oxide-mediated vasodilatation and enhance the formation of advanced glycation endproducts, leading to increases in pro-inflammatory factors. Hyperglycaemia may also lead to atherosclerotic plaque instability by enhancing the oxidation of glycated low-density lipoprotein. Pro-coagulant effects may arise from elevated levels of C-reactive protein and coagulation factors, in addition to platelet hyper-reactivity. Taken together, these processes result in accelerated atherogenesis and diabetic atheropathy, leading to microvascular and macrovascular complications, including PVD [5].

Altered immune function in diabetes mellitus and PVD

Potential mechanisms for altered immune function in patients with diabetes mellitus are shown in Table 1. Changes in leucocyte function figure prominently and are believed to result from hyperglycaemia, as they are ameliorated by adequate glycaemic control [7]. It is believed that, in the presence of elevated blood glucose, polymorphonuclear lymphocytes are continually activated at baseline and so are less responsive to infectious stimuli [8]. Increased resting levels of pro-inflammatory cytokines contribute both to an insufficient immune response to pathogens and to vascular inflammation [8].

Both PVD and diabetic neuropathy may contribute to a propensity for infection and poor outcomes among patients with diabetes. Substance P and nerve growth factor promote immune cell chemotaxis and proliferation, and decreased production of these neuropeptides in patients with diabetic neuropathy can slow wound healing [9]. In addition, leucocyte migration may be impaired in denervated tissues [9,10]. Movement of immune cells and nutrients to the site of infection may be further impaired in patients with PVD as the result of prolonged inflammation resulting in thickening of capillary basement membranes [9]. Comorbid renal impairment in patients with PVD and diabetes mellitus is associated with further impairment in host defences [11].

TABLE 1. Mechanisms of altered immune function in patients with diabetes mellitus [7,8]

Humoral mechanisms	Cellular mechanisms
Decreased levels of complement C4 Increased background levels of tumour necrosis factor-α, interleukin-6 and interleukin-8 with impaired response to stimulation	Impaired polymorphonuclear cell and neutrophil chemotaxis and phagocytosis Impaired killing by polymorphonuclear cells Decreased lymphocyte proliferative response to pathogens including *Staphylococcus aureus*

Infection risk and outcomes

Altered immune function in patients with diabetes mellitus leads to an increased risk of multiple types of infections. Atypical infections that occur more frequently in patients with diabetes mellitus include streptococcal and Fournier's gangrene [12], rhinocerebral mucormycosis [8] and malignant otitis externa [8]. However, because these infections are relatively rare, the burden of infection in patients with diabetes mellitus lies primarily with more common infection types (Table 2).

A number of studies have evaluated infection risk among patients with diabetes mellitus. Shah and Hux conducted a retrospective cohort study matching over 500 000 patients in Ontario with diabetes mellitus to non-diabetic controls using administrative claims data [13]. Almost half of the patients with diabetes had at least one hospitalization or physician claim for an infectious disease during the study year (risk ratio (RR) = 1.21; 95% CI 1.20–1.22 versus non-diabetic patients), with 5% being hospitalized (RR = 2.01; 95% CI 1.96–2.06). Risk of nearly every type of infection studied was higher among patients with diabetes, with the highest risk ratios seen for osteomyelitis (RR = 4.39; 95% CI 3.80–5.06), sepsis (RR = 2.45; 95% CI 2.23–2.68), post-operative infections (RR = 2.02, 95% CI 1.80–2.27) and cellulitis (RR = 1.81; 95% CI 1.76–1.86). Only herpes simplex virus infection, mastoiditis, human immunodeficiency virus infection and appendicitis did not occur more frequently in patients with diabetes mellitus [13]. These findings were confirmed by Hamilton *et al.* in a prospective cohort study in Australia, with risk of hospitalization for an infection increased two-fold among patients with diabetes mellitus (incident rate ratio = 2.13; 95% CI 1.88–2.42) [14]. In a Danish population, Benfield *et al.* found that patients with

TABLE 2. Common infections with at least two-fold increased risk in patients with diabetes mellitus [13–15]

Osteomyelitis
Sepsis
Post-operative infections
Skin and soft-tissue infections/cellulitis
Urinary tract infection