

## Review Article

# Diabetes mellitus and burns. Part I-basic science and implications for management

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**Abstract:** The number of diabetic patients presenting to burn services is predicted to increase significantly over the next decades. Diabetes mellitus represents an independent risk factor for sustaining burn injuries and mediates alterations to key physiological systems including the vascular, renal, nervous, gastrointestinal and immune system. The effects of the pathophysiological permutations need to be carefully considered during both the acute as well as the long-term rehabilitation phase of injury. The purpose of the first part of this review is to outline the metabolic permutations observed in diabetes mellitus pertinent to the clinical presentation and management of burn patients.

**Keywords:** Diabetes, burn, management

## Introduction

Diabetes Mellitus (DM) is one of the largest global health problems of the 21<sup>st</sup> Century. It is anticipated that the number of Americans diagnosed with the disease will continue to increase by 165% from the year 2000 to 2050 [1]. DM represents a spectrum of metabolic disorders characterised by chronic hyperglycaemia, resulting either from endogenous insulin insufficiency/defective production or from diminished effectiveness at peripheral receptors [2]. There are several different subtypes of DM with the commonest being type 1 and 2.

Type 1 DM (T1DM), which results from the autoimmune destruction of insulin-secreting pancreatic  $\beta$ -cells, has a typically acute juvenile onset and requires lifelong insulin treatment [3]. Despite being the subject of intensive study over the last decades, the causes of T1DM are still not fully understood; nevertheless a combination of environmental and genetic factors has been associated with disease pathogenesis. The chromosomal loci believed to influence T1DM susceptibility can be broadly categorised into those relating to immune function [including the Human Leukocyte Antigen (HLA) region], insulin expression (polymorphisms in promoter gene regions) and  $\beta$ -cell function [including the

protein tyrosine phosphatase, non-receptor type 22 gene] (PTPN22) [4].

Type 2 DM (T2DM) is characterised by excessive insulin secretion, tissue insulin resistance and subsequent  $\beta$ -cell dysfunction. It tends to present in later life and affected patients are frequently diagnosed on the basis of diabetic complications [3]. The pathogenesis of type 2 DM has a strong environmental component with obesity being one of the most important modifiable risk factors [5, 6]. Genetics are also believed to play an important role in the pathogenesis of T2DM; over 36 genes have already been linked to disease development, many of which are associated with differing degrees of beta cell dysfunction. Of particular note, the transcription factor 7 like 2 (TCF7L2) gene nearly doubles the risk of developing T2DM most likely through the pathway, which regulates proglucagon gene expression in enteroendocrine cells [7]. The American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus are shown in **Table 1** [3].

## Similarities between the metabolic features of diabetes mellitus and stress induced hyperglycaemia (SIH) of acute illness

The hormonal profile of diabetic patients has multiple facets, which augment the primary perturbations in glucose metabolism.

## Diabetes mellitus and burns. Part I

**Table 1.** American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus [3]

Test	Diagnostic levels	Comments
Fasting plasma glucose (FPG) level	≥ 126 mg/dl (7.0 mmol/l)	Fasting is defined as no caloric intake for at least 8 hours
2 hour plasma glucose following oral glucose tolerance test (OGTT)	≥ 200 mg/dl (11.1 mmol/l)	Test to be performed using glucose load with equivalent of 75 g glucose dissolved in water
Random plasma glucose level	≥ 200 mg/dl (11.1 mmol/l)	To be used in presence of symptoms of hyperglycemia or hyperglycemic crisis
Glycosylated hemoglobin (HbA1c)	≥ 6.5%	To be performed using a standardized assay

Fasting as well as plasma glucose levels following an oral glucose tolerance test are widely used tests for the initial diagnosis of diabetes; nevertheless in patients with severe classic hyperglycemic symptoms/hyperglycemic crisis, a random plasma level is considered adequate. Glycosylated haemoglobin (HbA1c), although widely used as a marker of chronic glycemia (reflecting levels over a 2-3 month period), is currently considered valid in diagnostic terms provided it is performed in a standardized manner.

In T1DM, in addition to the lack insulin secretion, there are increased levels of glucagon [8], which exacerbate hyperglycaemia by reducing hepatic glucose uptake and increasing glucose release [9]. Elevated levels of fasting catecholamines, especially found in poorly controlled DM, contribute to hyperglycaemia by stimulating glucagon production and impairing the action of insulin [10, 11]. Additionally, enhanced lipolysis (in the presence of high cortisol levels) predisposes towards increased concentrations of circulating free fatty-acids (FFAs) and ketone body formation, which can lead to ketoacidosis [12-15].

Type 2 DM is characterised by marked insulin resistance with underlying mechanisms including the deranged expression of liver enzymes and changes in signalling pathways (e.g. c-Jun amino terminal kinase) due to the increased release of TNF-alpha and IL-6 by adipose tissue macrophages [16]. Additionally, the elevated levels of fatty acid metabolites (including diacylglycerol) decrease insulin receptor signalling by activating the phosphorylation of insulin receptor substrates 1 and 2 [17].

Furthermore, under normal physiological conditions, insulin plays an important role in the upregulation of protein synthesis by enhancing the uptake of amino acids into muscle. In DM, the low levels and tissue insensitivity to circulating insulin (especially in poorly controlled patients), mediates an enhancement in proteolysis causing disturbances in nitrogen balance [18].

Burn injuries are associated with a profound hypermetabolic response. Metabolic features

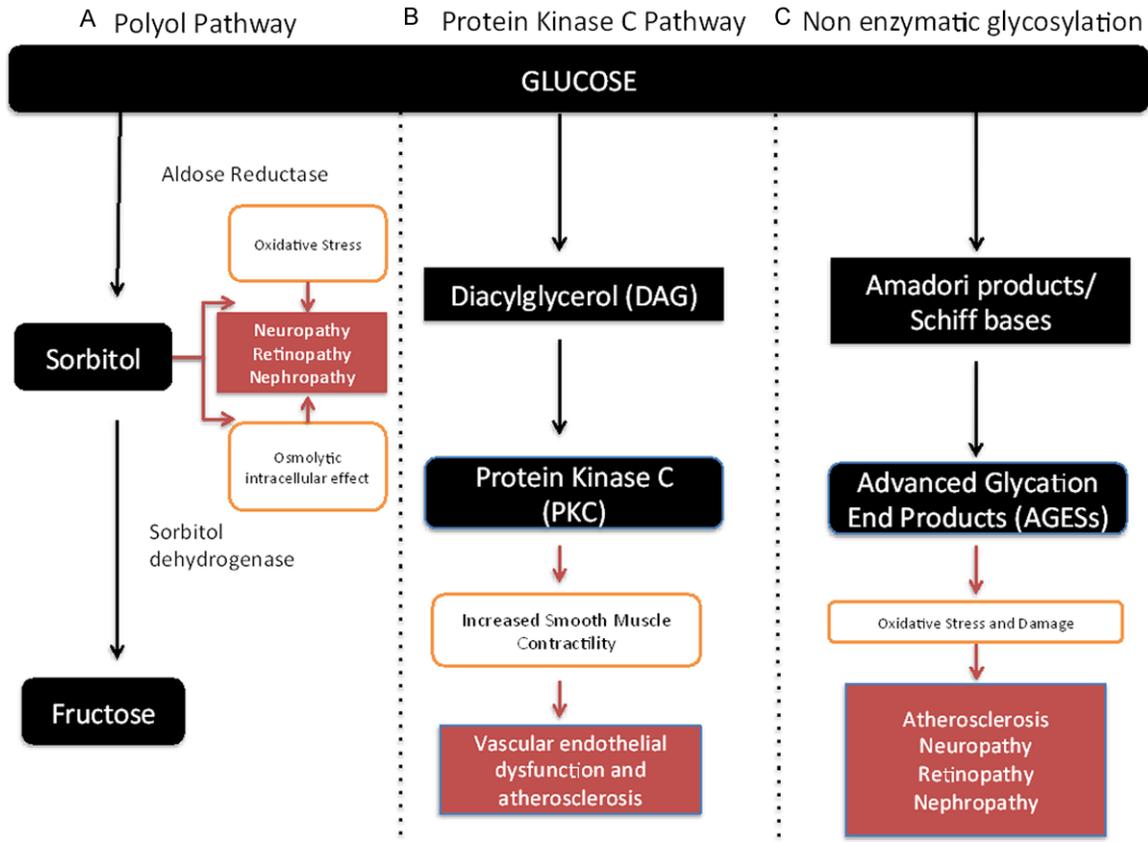
include increased energy expenditure, a negative nitrogen balance as well as stress-induced hyperglycaemia and decreased peripheral insulin sensitivity. Key mediators for these derangements include the augmented secretion of catabolic hormones (cortisol and catecholamines), the suppression of endogenous activity of anabolic agents (growth hormone and testosterone) as well as cytokine release (interleukins 1, 6 and tumour necrosis factor-TNF) [18-27].

It is striking that the metabolic profile of diabetes mellitus mirrors changes occurring in critical illness (e.g. hyperglycaemia, insulin tissue insensitivity, negative nitrogen balance), hence burn patients with pre-existing diabetes mellitus may be theoretically subjected to a 'second hit' phenomenon. In other words, they may be prone to enhanced metabolic disturbances due to the combined effects of the acute burn injury and the premorbid diabetic pathophysiology. It is interesting to review the different mechanisms by which DM affects the different physiological systems, since this forms the basis for investigating a potential 'second hit' phenomenon. The latter will be further elucidated in the second part of this work, which focuses on morbidity and mortality in this cohort of burn patients.

### Key physiological system alterations in diabetes mellitus

#### *Vascular system*

A variety of biochemical derangements have been identified as contributing factors to end organ tissue damage in diabetes. These include the utilisation of excess glucose along the poly-



**Figure 1.** Pathways involved in end organ tissue damage in diabetes mellitus [28]. A. Polyol pathway-Increased blood glucose is converted via sorbitol into fructose. Due to the slow absorption of sorbitol, its accumulation has a significant intracellular osmolytic effect as well as (via interaction with the inositol pathway) increases cellular oxidative stress. B. Protein Kinase C pathway-Glucose handling via the glycolysis pathway leads to an increase in the intermediate product diacylglycerol (DAG). This activates intracellular signalling via protein kinase C and this leads to a variety of cellular effects (including increased smooth muscle contractility, altered calcium homeostasis and sensitivity to growth factors) contributing to vascular dysfunction. C. Non-enzymatic glycosylation pathway-Glucose interacts with reactive amino groups in cellular proteins and forms advanced glycosylation end products (AGEs) via intermediate compounds (Amadori products and Schiff bases). The AGEs interact with fixed tissue elements and circulating cells and lead via a variety of mechanisms to oxidative stress/cellular damage contributing to diabetic complications.

ol pathway, the stimulation of the diacylglycerol-protein C kinase pathway as well as the non-enzymatic glycosylation of tissues (Figure 1) [28].

Macrovasculature

Atherosclerosis is more prevalent in diabetic patients with underlying contributing factors relating to abnormalities in the vessel wall, circulating cells/factors and blood flow.

*Vessel wall:* Increased non enzymatic glycosylation of lipoprotein leads to the accumulation of cholesterol ester in ‘foam’ macrophages [29]; the modified lipoproteins result in the formation of autoantibodies and the ensuing lipo-

protein immune complexes activate the endothelium and smooth muscle cells contributing to accelerated atheromatous plaque formation [30].

*Circulating cells:* Platelets in diabetes are characterised by reduced deformability and propensity to adhesion/aggregation; the latter is due to the enhanced release of  $\alpha$  granule contents and hypersensitivity to aggregating agents (including collagen and arachidonic acid) [31]. Furthermore, red blood cells are more prone to oxidative stress contributing to a reduced cellular life span [32-36] and their decreased oxygen affinity has profound effects on tissues by limiting the supply of oxygen [37-40].

*Impaired rheological characteristics:* Plasma viscosity is increased considerably in diabetic patients, which is thought to promote atherosclerosis and thrombosis in blood vessels [41-43]. Additionally, the elevated levels of coagulation factors (including fibrinogen and factors 7, 8), decreased levels of protein C and S and the impaired fibrinolytic activity contribute towards a pro-coagulant state in the vasculature [28].

The three main macrovascular disease manifestations include coronary artery, cerebrovascular and peripheral vascular disease. The increased risk of diabetic patients from macrovascular complications needs to be carefully considered during the acute and rehabilitative stage of burn injuries. Meticulous attention must be given to careful fluid management in order to balance the risk of under-resuscitation versus cardiac overload (incidence of congestive heart failure is 2-5 times higher in diabetics) [44]. The risk of cerebrovascular accidents needs to be addressed with attention to normotension, normovolaemia and thromboprophylaxis. The implications of impaired peripheral vasculature concern both the acute stage of healing (impaired perfusion of tissues) as well as the mobilisation in later phases of recovery (decreased exercise tolerance).

### Microvasculature

Microvascular complications are particularly prominent sequelae of chronic DM, caused by prolonged exposure of a wide variety of cells to high levels of glucose in the circulation via a variety of pathways shown in **Figure 1**. Chronic intracellular hyperglycaemia of endothelial and mesangial cells, coupled with hypercoagulability secondary to increased platelet and adhesion, causes progressive narrowing, microthrombus formation and eventual occlusion of vascular lumina. This leads to ischemia and dysfunction of the affected tissues with common microvascular complications including nephropathy and peripheral neuropathy [45-47].

### *Renal system/diabetic nephropathy*

Diabetic nephropathy is a chronic, progressive condition characterized by increasing urinary albumin excretion, hypertension and declining glomerular filtration rate. It is a relatively late complication of T1DM, but often established at the time of diagnosis of T2DM. Nephropathy is

a marker for other diabetes related complications, including cardiovascular disease and cerebrovascular accidents [48-50] and can lead to end stage renal insufficiency necessitating renal replacement therapy or transplantation [51, 52]. The implications of diabetic renal impairment are multiple and apart from the need for careful fluid management include:

### Pharmacokinetic/dynamic considerations

Careful administration and monitoring of medications (especially those with a narrow therapeutic range excreted by the kidneys) is paramount in order to avoid deteriorations of renal function in diabetic patients. This becomes more pertinent given the complex effect of the burn injury on drug metabolism; for instance the 'ebb' phase of the metabolic response is characterised by a reduction in renal perfusion/glomerular filtration rate (GFR) whereas during the subsequent 'flow' phase, the GFR is considerably increased [53]. Furthermore, comorbid conditions including obesity can further impact upon pharmacological strategies; the comparatively higher fat content in obese individuals mediates an increased volume of distribution for lipophilic drugs mandating the need for close liaison between clinicians and pharmacists in order to determine optimal drug dosing [54].

### Blood product replacement

Anaemia is one of the common sequelae of diabetic renal disease; judicious transfusion practices are recommended in this subgroup of patients especially those who are candidates for renal transplantation. Administration of transfusions renders patients prone to immune sensitisation, which can limit the range of potential donor organs ahead of renal transplantation [55]. In cases of planned delayed surgery, increasing the dose of erythropoietin administration is a valid option; nevertheless several weeks are needed for the hormone to raise the haematocrit considerably [56, 57]. It is clear that decisions regarding the maintenance of haematocrit levels in this cohort of patients need to be made in close liaison with renal physicians.

### *Nervous system/diabetic neuropathy*

Diabetic neuropathy affects 30-50% of people with established diabetes [58-60]. Its patho-

physiology is thought to result from the combined effects of microangiopathy and direct osmotic axonal damage from elevated levels of glucose [61]. Diabetic distal symmetrical sensory polyneuropathy (DPN) is the most relevant manifestation; it classically presents with a “glove and stocking” distribution of sensory loss and is a major contributor towards ulceration as well as burn injuries to the lower limb [62]. The loss of normal neurofeedback contributes to arch flattening and leads to abnormal pressure distribution in the feet. Sympathetic autonomic neuropathy results in dryness and skin fissuring and contributes to increased susceptibility to trauma and infection. Neuropathic arthropathy (Charcot’s joints) and oedema are further contributory factors towards tissue injury, which can lead to limb amputation [63, 64].

Neuropathic pain symptoms are quite common in diabetes affecting up to one third of patients [65, 66]. Burn injuries can be associated with severe symptoms of pain and pruritus, which in the context of established neuropathy, can present the burns team with unique management challenges. Given the emerging evidence implicating neuropathic mechanisms in post burn sensory disturbances, it appears prudent for burn teams to utilise therapeutic agents acting on the central nervous system (including gabapentin or pregabalin) early on for symptom control in this subgroup of patients [67, 68].

### *Gastrointestinal system*

Longstanding hyperglycaemia in diabetes mellitus causes enteric nerve damage and dysregulation of vagal activity resulting in abnormal motility, gastric paresis, and bacterial overgrowth [69]. Clinical manifestations of abnormal motility include diarrhea, nausea and vomiting, which can precipitate significant additional fluid and electrolyte abnormalities.

Poor glycaemic control is also strongly associated with gastrointestinal infections such as oral candidiasis, which can be exacerbated by the antibiotic polypharmacy often practised in the management of burn patients. Consequent symptoms of dysphagia and odynophagia can lead to on-going poor nutrition, with implications on delayed wound healing and subsequent rehabilitation [70]. Fluid replacement, judicious antibiotic therapy and nutritional support should therefore be carefully tailored in the care of the diabetic burn patient.

Additionally, obesity (a frequent association with type 2 diabetes) is associated with a higher incidence of gastroesophageal reflux disease, large residual gastric volumes and comparatively lower pH secretions; these factors predispose patients to gastric ulceration/bleeding as well as aspiration pneumonitis and underlie the importance of gastroprophylaxis in this patient cohort [71-73].

### *Immune system*

Many components of the immune (both innate and adaptive) system show significant perturbations in patients with diabetes accounting for the increased susceptibility to infective complications.

#### *Innate immune system*

Complement system deficiencies along with a diminished activity of natural killer cells are prominent in diabetes mellitus [74, 75]. Furthermore, significant disturbances in the activity of polymorphonuclear leucocytes are observed; these include reduced chemotaxis, adherence, phagocytosis, and bactericidal activity of neutrophils, monocytes and macrophages [76-81].

#### *Adaptive immune system*

Lymphocytes responsible for the production of antibodies against pathogens show decreased mitogenic responses. In addition, the production of interleukin 2 (which is vital in sustaining the post-injury inflammatory response via T cell activation) is significantly reduced [82, 83]. Interestingly, insulin administration appears to increase the activity of adenosine triphosphate and uptake of glucose in lymphocytes [84], a finding, which highlights the importance of good glycaemic control in minimising the effects of diabetic metabolism on immune function.

### *Healing in diabetics*

Wound healing comprises three overlapping phases: inflammation, proliferation and remodelling [85, 86].

Diabetes exerts a detrimental effect on wound healing via extrinsic and intrinsic mechanisms. The term ‘intrinsic’ refers to mechanisms relating to the abnormal expression/activity of local growth factors and wound healing constitu-

ents. 'Extrinsic' parameters include peripheral vascular disease (resulting in decreased oxygen supply to tissues), neuropathy (disruption of neurogenic control of small vessels interfering with the inflammatory response) as well as infection and oedema [87-89].

### Inflammation

The defects in neutrophil chemotaxis and function, result in defective tissue debridement and impaired secretion of a variety of growth factors and cytokines important in wound healing [90-92]. The pattern of macrophages is also altered in DM. Under normal circumstances, activation shows two distinctive phenotypes: classical (caM), which predominates in the initial inflammatory phase and alternative activation (aaM), which predominates in the proliferative stage of healing [93]. In diabetic wounds, there is insufficient caM in the early stage but excessive aaM in the later proliferative phase alongside the predominance of a T helper 2 (TH2) over T helper 1 (TH1) cytokine response. These factors are believed to play a significant role in stalling diabetic wounds in an abnormal inflammatory state (comprising an increased number of inflammatory cells, albeit a marked absence of growth on cellular level) and hindering the transition into the proliferative stage [94, 95].

### Proliferation

This phase is characterised by fibroplasia, neovascularisation and epithelialisation involving fibroblasts, endothelial cells and keratinocytes.

*Fibroplasia:* Diabetes mellitus is associated with excessive production of advanced glycation end products, which interferes with normal extracellular matrix deposition; additionally, fibroblasts show impaired proliferation and premature senescence. As a result, diabetic wounds have decreased levels of glycosaminoglycans as well as collagen (which is also characterised by an abnormal molecular structure) contributing to a lower wound breaking strength [90, 94, 96-100].

*Neovascularisation:* This is a vital process implicated in healing and comprises endothelial proliferation, migration and capillary formation regulated by angiogenic factors including angiopoietins [101]. Angiopoietin 2 (Ang-2) is

considered as an angiogenesis 'starting mediator', which initially is present in high concentrations but gradually in the course of angiogenesis returns to normal levels [102]. Another important growth factor involved in new vessel formation is vascular endothelial growth factor (VEGF), which promotes endothelial cell proliferation and migration [103]. There is normally a synergistic action between Ang-2 and high levels of VEGF inducing 'sprouting' angiogenesis, whereas absence of VEGF results in capillary regression in the early stages [104]. The regulation of neovascularisation in deep partial thickness scalds in diabetic rates has revealed marked impairment in wound healing at 2 weeks following injury with inhibition of vascularisation at the wound edges due to a sustained abnormally high expression of Ang-2 and downregulation of VEGF between day 14-21 post injury [105]. Insulin has been found to stimulate human microvascular endothelial cell migration and tube formation [95], a finding, which further highlights the impact of good glycaemic control on diabetic wound healing.

*Epithelialisation:* Epithelialisation is a process, which is attenuated in DM [106]; porcine burn models suggest that low levels of insulin growth factor 1 (IGF-1) and tumour growth factor beta (TGF- $\beta$ ) in the first week post injury are most likely implicated in this abnormality [90, 107].

IGF-1 has been shown to induce chemoattractant activity in endothelial cell lines, stimulate keratinocyte and fibroblast proliferation and re-epithelialisation [108], whilst TGF-beta is thought to be important in chemoattraction of monocytes, keratinocytes, fibroblasts and induction of these cells to release further growth factors [109, 110].

### Remodelling

This phase is characterised by cessation of fibroblast proliferation/collagen production as well as diminishing vascularisation and myofibroblast mediated wound contraction.

Important factors contributing to disturbances in the remodelling phase of diabetic wounds include: increased levels of proteolytic enzymes reduced activity of growth factors due to non enzymatic glycosylation as well as the imbalance between metalloproteases and their tissue inhibitors (responsible for collagen remodelling) [85, 90, 111, 112].

### *Diabetes mellitus as a risk factor for burn injuries*

Diabetes mellitus represents a significant risk factor for burn injuries due to a variety of reasons. Peripheral neuropathy and retinopathy result in decreased tactile sensation as well as visual impairment. This implies that diabetics are less able to detect and avoid sources of burn injury hence are more susceptible to sustaining injuries and presenting to medical care in a delayed manner with deeper burns. Additionally, gait abnormalities stemming from neuropathy and pre-existing amputated limbs can predispose an individual to injuries by increasing the risk of falling and limiting the ability to remove oneself from a source of injury.

The ability of the skin to dissipate heat energy relies on passive conduction to lateral and deep tissues as well as dispersion via the increase in blood flow in the affected tissues [113]. Studies have confirmed that diabetes is characterised by diminished heat energy transfer to the surrounding skin as well as a weaker hyperaemic response [114]. The conductive properties of skin in DM are reduced by virtue of a comparatively thinner dermal and thicker subcutaneous fat layer [115] as well as physiological disturbances in vasoregulation [116].

The main vasodilating factors include nitric oxide, substance P, calcitonin gene-related peptide and prostaglandins [116-119]. Diabetes (as well as ageing) makes the skin more dependent on nitric oxide for vasodilation, whereas the ability to vasoconstrict remains unaltered [113, 117, 120-122]. Interestingly, the nitric oxide pathway is impaired in diabetes most likely due to a combination of reduced L-arginine in endothelial cells as well as diminished production of nitric oxide/bioavailability due to the presence of high concentrations of free radicals in vascular endothelial cells [116, 123].

### **Conclusion**

Diabetes mellitus is responsible for a host of physiological disturbances affecting most bodily systems and represents a significant risk factor for sustaining burn injuries. The effects of diabetes as a premorbid condition have an impact on both the acute phase of the injury as

well as long-term rehabilitation. Recognition of the exact pathophysiological permutations is paramount in planning appropriate management strategies to improve the standard of care in this cohort of burn patients.

### **Disclosure of conflict of interest**

None.

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