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Review Article

Diabetes mellitus and burns. Part II-outcomes from burn injuries and future directions

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Abstract: Diabetes mellitus is an increasingly prevalent comorbidity in patients presenting to burn facilities. Diabetic patients tend to be older and present in a delayed manner with deeper injuries predominantly affecting the lower limb. Morbidity from burns is higher in this cohort including a longer length of hospital stay, greater need for surgical interventions and increased rate of infective complications. Nevertheless, there seems to be little effect of diabetes on associated mortality. The second part of this review article concentrates on the epidemiological profile of diabetic burn patients and the effect of the disease on morbidity and mortality. In addition, we present a review of therapeutic adjuncts, which may hold promise for the future management of this cohort of burn patients.

Keywords: Diabetes, burn, outcomes, morbidity, mortality

Introduction: epidemiological characteristics of burn injuries in diabetic patients

Diabetic burn patients have a particular epidemiological profile in terms of their age, bodily sites affected by the injury, comorbidities and the timing of presentation to medical facilities. A retrospective review of 73 diabetic admissions to the Baltimore burn centre between 1995-2000 compared to 150 (burn surface area matched) non-diabetic patients revealed a number of findings. The diabetic was older than the control cohort (mean age 60 years vs. 32 years, $p < 0.001$), scalding was the predominant mechanism of injury and the most common bodily sites affected were the lower limbs followed by the head and neck, upper limbs and trunk ($p < 0.05$) [1]. Similar results were derived in another comparative US study of isolated lower extremity/foot burns. The mean age at presentation was 54.6 years for the diabetic vs. 43.7 years for the non-diabetic group ($p < 0.001$) and scalds represented the predominant type of injury [2]. A number of other reports have confirmed that the lower limb/foot is the commonest site for burns in diabetics [3-10].

A variety of 'high risk' activities for sustaining lower limb burn injuries in this cohort of patients have been identified in the literature. These include household activities for women and religious duties for men in Muslim countries (ablution/Friday Mass prayers) [4, 11], as well as foot spas/baths and the use of warming devices [5, 6, 8, 12].

Regarding the timing of presentation to medical facilities, a US retrospective study confirmed that diabetic patients are more likely to present in a delayed manner compared to non-diabetics (45% vs. 23% being admitted to hospital more than 24 hrs. post injury, $p < 0.00001$). In addition, despite similar TBSA in the two cohorts, the percentage of diabetics with full thickness burn was significantly higher (50.5 vs. 31.2%, $p < 0.025$) [13].

The presence of neuropathic complications appears to further influence timing of presentation as indicated in a study of lower extremity burns (mean burn size of 4.2 ± 3.8% TBSA, range 0.5-15%) in diabetic patients treated at a US burn centre. The majority were found to be presenting to medical attention at a mean of 3.5 days after their injury (range 0-25 days). The mean difference between injury and obtaining medical care was 2.1 ± 3.6 days for patients with sensate vs. 9.5 ± 28.3 days for patients with insensate feet [12]. In addition, a consider-

able proportion of patients have poorly controlled blood glucose levels and comorbidities including cardiovascular disease, renal insufficiency and neuropathy [5, 12, 14].

Outcomes of diabetic burn patients: hospital inpatient treatment, length of stay and complications

A ten-year retrospective review assessed outcomes of lower extremity burns in diabetic patients treated at the Fire-fighters Burn Institute, Davis Medical Centre. The mean hospital stay was 5.65 ± 5.8 days per percentage TBSA. A total of 56 out of 68 patients (82%) underwent grafting, 19 needed readmission and 9 had at least one re-grafting procedure. The overall complication rate was 90% with a rate of 44% for local infection/cellulitis, 13% graft loss, 6% osteomyelitis and 4% gangrene. The cohort had a high amputation rate, with 11 patients undergoing procedures including below knee, transmetatarsal, and toe amputations. Two deaths were noted and seventeen others had serious complications including deep vein thrombosis, pulmonary embolus, respiratory and renal failure. Comparison between the insensate and sensate foot patients revealed that the rates of skin grafting (57% vs. 45%), amputation (24.3% vs. 6.5%) and length of stay (LOS) per TBSA (6.8 ± 6.5 vs. 4.3 ± 4.5 days) were statistically higher in the insensate foot subgroup [12].

Similar results were reproduced in a different retrospective US burn centre study with a higher proportion of diabetics needing surgery (72.6% diabetic vs. 32% non-diabetics, $p < 0.01$) despite similar TBSA values. There was also a five-fold higher ratio of fatal to non-fatal burns, longer hospitalization period (17 vs. 9 days, $p < 0.0010$), and higher cost (by 74%) associated with the diabetic group [1].

A comparative report of 181 diabetic and 190 (sex and date of admission matched) non-diabetic adult patients admitted to the William Randolph Hearst Burn Centre, US between January 1996 and May 2000 assessed treatment outcomes. The total burn size was comparable in the two groups but diabetic patients had a higher rate of full thickness burns (51 vs. 32%, $p = 0.025$). The rate of tangential excision/split skin grafting, other burn related procedures (debridement, escharotomy, fasciotomy, amputation) and length of stay was significantly higher in the diabetic cohort (49.5 vs. 28%, $p = 0.01$, 56.7 vs. 32.2%, $p = 0.001$, and 23.3 ± 26.5 vs. 12.2 ± 12.4 days, $p = 0.0001$ respectively). The rate of infection was greater in diabetics (64.9 vs. 50.5%, $p = 0.05$), while rates of ICU admission and ventilator days, despite being higher in the diabetic group, did not reach statistical significance. Mortality rates were virtually identical in the two groups (2.1% vs. 2.2%) [13].

A retrospective review of adult patient encounters at a US metropolitan burn facility investigated infective complications between non-diabetic and diabetic cohorts [14]. Diabetic patients were significantly older (54 ± 13 vs. 27 ± 20 years, $p < 0.0001$) with a larger percentage of TBSA (11 ± 19 vs. 6 ± 11%, $p < 0.001$) and greater cardiovascular comorbidity. Complication rates were higher in the diabetic group, including bacteraemia, chest sepsis and urinary tract infections (UTI). Community-acquired cellulitic wounds in diabetics were caused predominantly by Staphylococcus aureus (SA), Streptococcus, Proteus, Pseudomonas and methicillin resistant staphylococcus aureus (MRSA); on the contrary in non-diabetics, SA and Pseudomonas were the most frequent offending microbes. In terms of nosocomial infections (bacteraemia, sepsis, pneumonias, UTI, burn wound infections) diabetics had a higher frequency of Acinetobacter, Proteus, MRSA and Candida, while in non-diabetics the most likely culprits were Streptococcus, Escherichia coli and Hemophilus Influenza.

Furthermore, the increased susceptibility of diabetics to particular strains of bacteria including Acenitobacter species has been confirmed as an increasingly prevalent problem in burn critical care units [15].

Diabetic patients are also more susceptible to fungal infections. Although Candida represents the most common fungal organism in burn wounds with little morbidity, more uncommon organisms have been reported in diabetic burn victims involving the Zygomycetes class of fungi. This category of mucormycotic infections tend to be situated in deeper tissue planes and have a propensity to cause tissue necrosis and systemic dissemination [16].

A prospective study of 40 (age and burn size matched) patients in a US centre confirmed that time to complete wound closure is significantly longer in diabetics (46.4 ± 44.4 days vs. 19.6 ± 8.8 days, p = 0.01) with a similar trend observed in grafted wounds (42.2 ± 42.3 days vs. 17.6 ± 9.4 days, p = 0.02). Secondary outcomes in this work including intensive care and hospital LOS as well as infections and number of graft procedures were longer/higher in diabetics but did not reach statistical significance [14]. The authors commented that despite grafting undertaken to hasten wound healing, it appears impossible to change the unfavourable/recalcitrant milieu of deranged wound healing in diabetic patients. This is consistent with other studies, which have identified diabetes mellitus as an independent risk factor contributing to decreased skin graft take. The proposed mechanism linking hyperglycaemia and suboptimal graft take may relate to local tissue oedema, inhibiting diffusion of metabolites at the wound site [17, 18].

A ten year retrospective analysis of isolated lower extremity/foot burns in diabetics was conducted, comparing 43 adult diabetic to 164 non diabetic patients admitted to Saint Barnabas Medical Centre, US [2]. The mean age was 54.6 for the diabetic and 43.7 years for the non-diabetic group (p < 0.001) with no significant differences in the mechanism of injury, TBSA, burn depth or the number and type of operative procedures between the two groups. There was a significantly higher number of diabetics receiving intensive care unit (ICU) treatment (16.3 vs. 8.5, p < 0.001) with a longer overall LOS (14.1 ± 10.0 vs. 9.8 ± 9.3, p < 0.01); nevertheless mortality rates were comparable between the two groups. The fact that diabetes mellitus is an independent risk factor for increased hospital stay has been also confirmed in a recent retrospective study of 770 patients undergoing surgical intervention for burns at the Royal Perth Hospital, Australia (increase of LOS by 18% in diabetics, p = 0.05) [19].

Effect of hyperglycaemia chronicity on burn injury outcomes

Critical illness states including burns are associated with stress-induced hyperglycaemia (SIH) as part of the metabolic response. Similarly, hyperglycaemia is the metabolic hallmark of diabetes mellitus (DH). Hence, the question arises as to whether the combined effect of DH and SIH has an additive effect on worsening outcomes/mortality following burn injuries ('second hit' phenomenon).

In the non-burns trauma literature, SIH (as opposed to DH) has been associated with a statistically significant increase in mortality rates [20, 21]. Furthermore, reports in both adult and paediatric burn cohorts indicate that SIH is associated (apart from worse mortality) with increased rates of invasive infection and reduced skin graft take [22], with early tight glycaemic control mitigating these effects as well as improving outcomes [23-25]. It is interesting to investigate the effect of different types of hyperglycaemic states (in terms of pre-injury chronicity) as well as glucose control (for established diabetes) on burn outcomes.

Pre-diabetes

A recent study investigated the effect of pre-diabetes (defined as admission HbA1c between 5.7-6.4%) in 208 adult burn patients compared to control (admission HbA1c < 5.7%) subjects [26]. Patients with pre-diabetes had significantly higher time-weighted glucose levels, albeit similar rates of hypoglycaemia and glycaemic variability. Lower survival rates were seen in pre-diabetics (92.6 vs. 98.7%, p = 0.041), despite similar rates of unplanned readmission, ICU admission, mechanical ventilation, LOS and infection rates. Interpretation of the increased mortality in pre-diabetics needs to be viewed in light of the sub-cohort being older, having larger areas of full-thickness burns as well as differing comorbidity profiles. In addition, suboptimal glucose control during hospital stay may have contributed to this finding.

Chronic hyperglycaemia on admission

A retrospective study assessed outcomes in 258 adult burn patients with euglycaemia on admission (glycosylated haemoglobin (HBA1c) < 6.5%), compared with those with chronic hyperglycaemia (HBA1c > 6.5%, including patients with diagnosed and undiagnosed DM). Patients with chronic hyperglycaemia were significantly older and were more likely to have respiratory disease and hypertension; never-

theless burn related characteristics in terms of TBSA and depth were similar. Despite the hyperglycaemia cohort having significantly higher time-weighted glucose/glucose variability, higher rates of unplanned readmission (18.8 vs. 3.6%, p = 0.001) and longer LOS (13 vs. 9 days, p = 0.038), mortality rates were similar between the two groups [25].

Diabetes mellitus as an established diagnosis at presentation

In patients with an established diagnosis of DM, pre-injury as well as inpatient glycaemic control appears to influence recovery in a variety of ways.

Effect of pre-injury glycaemic control

Analysis of pre-injury HbA1c in a cohort of 40 age and burn size matched diabetics and non-diabetics revealed that patients with levels higher than 8% showed a trend towards delayed wound closure compared to those with lower levels (59.4 ± 54.2 days vs. 27.6 ± 9.6 days) [14].

Effect of inpatient glycaemic control

Comparison of diabetic burn patients with controlled vs. uncontrolled (latter defined as glucose levels higher than 180 mg/dl greater than 50% of times it was checked), showed that the uncontrolled group had higher rates of infection (72 vs 55%, p ≤ 0.025) burn related procedures (68.0 vs. 45.4%, p < 0.025) and longer ICU stays (24.2 ± 23.2 vs. 9.6 ± 9.0 days, p = 0.048) [13].

Diabetes mellitus: an independent contributor towards burns mortality?

A study evaluated the effect of diabetes/glucose control on clinical outcomes in 57 diabetic and 405 non-diabetic burn ICU patients in a US centre. Diabetic patients were older and had higher admission/mean blood glucose levels, greater glucose variability as well as out of range measurements compared to non-diabetics (p < 0.05). Ventilator- and hospital-free days were non statistically significant but diabetic patients appeared to have fewer ICU free days than non-diabetic patients (23 vs. 27 days, p < 0.05). Mortality rates were found to be higher in diabetics (21 vs. 13 patients) but not in a statistically significant manner, a finding confirmed through multivariate linear and logistic regression analyses [27]. Limitations, apart from the retrospective nature of this work, include the lack of stratification of diabetic patients according to HBA1C/pre-admission diabetic control.

A number of other reports have investigated the effect of diabetes on mortality from burn injuries. A review of 31,338 adult burn patients from the American National Burn Repository revealed that diabetes predicted an increased LOS (by 26%) but not increased mortality [28]. This finding has been replicated in other studies already analysed in our work [2, 13]. Furthermore, a review of 265 elderly burn patients (defined as age over 65) did not find diabetes to be predictive of either haemodynamic/respiratory complications, or mortality [29]. Corroborate findings were reached in two further studies in elderly diabetic patients (defined as age over 60 and 80 years respectively) [30, 31]. Similar analyses of diabetes mellitus (categorised under either 'comorbidities' or 'gastrointestinal/urological' disorder) have failed to demonstrate a significant link with post burn mortality [32, 33].

Careful appraisal of the current literature illustrates that a particular trend may exist in terms of the differential effect of hyperglycaemic states (SIH, pre-diabetes, established diabetes at presentation) on burn morbidity and mortality. It appears that SIH, especially if inadequately controlled, as well as a 'pre-diabetic' state are associated with increased mortality from burn injuries. When hyperglycaemia becomes established (undiagnosed and diagnosed diabetics), there is good evidence that morbidity increases (including complications such as infections, surgical interventions, and overall length of stay). Nevertheless the mortality rates are comparable between diabetic and non-diabetic patients [1, 2, 9, 12-14].

A variety of mechanisms have been proposed to explain this phenomenon ('mortality paradox'). One hypothesis is that other clinical factors (such as age, injury severity score, and TBSA) overwhelm the effects of diabetes on final outcomes from burns [27]. Another possible explanation for the lack of increased mortality observed in this subgroup of patients is that the patients who are admitted to burn facilities are those who have the required physiological reserves to survive the acute life

threatening phase of their injury despite their comorbid conditions [34]; in other words the presence of chronic hyperglycaemia renders a 'survival advantage'. It becomes clear that given the small number of studies available and their limitations, the trend regarding the effect of hyperglycaemia chronicity on outcomes is solely a preliminary conclusion; this area clearly warrants further research.

Therapeutic adjuncts in the management of diabetic burn patients

A variety of novel therapeutic approaches have been reported in the literature as adjuncts in the treatment of diabetic burn injuries. Most of them have been appraised in either animal models or small scale clinical studies and clearly need more formal evaluation before they are widely adopted in practice.

Negative pressure wound therapy (NPWT) and hyperbaric oxygen (HBO) therapy

NPWT has the potential to enhance wound healing in diabetics by virtue of a variety of mechanisms acting on intrinsic and extrinsic healing parameters. These include:

a) Enhanced fibroblast mitosis/proliferation.

b) Angiogenesis promotion (contributing to augmented granulation tissue formation).

c) Oedema reduction.

d) Decreased bacterial colonisation.

e) Depression in the expression of matrix metalloprotease proteins 1, 2, 13 mRNA, which aid degradation of collagen and gelatin [35-42].

A potential rationale for the application of NPWT in diabetics is to limit burn wound progression. The impairment of blood flow in the zone of stasis comprises an initial phase of oedema (highest at 1-3 hrs. post burn) followed by neutrophil adherence to the capillary wall, fibrin deposition, vasoconstriction and microthrombus formation (lasting up to 48 hrs post burn) [43]. Most importantly, these changes have been found to be reversible and appropriately-timed interventions may prevent progressive loss of tissue through conversion into a zone of coagulation [44].

A swine model of partial-thickness burns confirmed that early (within 12 hrs. post injury) application of NPWT prevented burn depth progression (i.e. the degree of stasis, the inflammatory cellular response as well as collagen degradation) [45].

A small controlled case series of this modality used on partial thickness upper limb burns has confirmed increased perfusion in NPWT treated wounds as well as a considerable reduction of oedema with decreased need for skin grafting [46]. Application of NPWT related modalities on diabetic burn injuries is a potentially exciting strategy, which needs to be formally evaluated in larger clinical studies.

NPWT has also been used in conjunction with HBO (following surgical debridement) in a single case report of bilateral patellar burns [47]. Perfusion of tissues with 100% oxygen aims to correct the local hypoxia in the burn wound and may be beneficial by improving the function of polymorphonuclear leucocytes, limiting infection (improvement of antibiotic penetration into bacteria) and accelerating healing (enhancement of tissue growth and angiogenesis) [48].

HBO has been recently proposed as an important pre- and post-operative adjunct for the management of grafted diabetic foot burns with a total of 20-30 sessions recommended in treatment responsive patients [49].

Fibrin glue

A retrospective study of 1881 US and Spanish adult patients investigated the value of fibrin glue in restoring graft adherence affected by smoking and type II diabetes mellitus. The cohort included patients who needed skin grafting (for injuries less than 20% TBSA), those with a greater than ten year history of insulin controlled type II DM and patients who smoked more than 20 cigarettes/day. Analysis of age, sex and TBSA-matched patients revealed that fibrin glue resulted in a statistically significant improvement in skin graft take in all groups including controls. Diabetes appeared to decrease stapled-only graft take in comparison with the control non-diabetic group (79% vs. 58%, $p < 0.05$). In type II diabetic patients, fibrin glue, in addition to staples, resulted in 26% improvement in graft take compared to stapled-only grafts (84 ± 4.2% vs. 58 ± 5.3%, p

< 0.05) [50]. These encouraging results have been attributed to the multiple beneficial attributes of fibrin glue, which include the enhancement of haemostasis, graft adherence, as well as its antibacterial action [51].

Light modalities

A study investigating polychromatic light emitting diode (LED) therapy on full thickness burns in diabetic mice suggested its effectiveness in accelerating burn wound healing via an up regulation of nitric oxide (NO) production at the wound level. Phototherapy with polarised light (400-200 nm spectrum) as well as low level visible spectrum (diode) laser have also been shown to accelerate healing of full thickness burns in rats with mechanisms involved including a higher deposition of collagen/increased fibroblast proliferation, a shorter inflammatory phase and improved revascularisation [52-54].

Platelet derived growth factor (PDGF), fibroblast growth factor (FGF)

PDGF is secreted predominantly by platelets and also by other cells involved in wound healing including macrophages, fibroblasts and keratinocytes. It is a powerful chemoattactant/mitogen and via a synergistic effect with other factors like tumour growth factor-β (TGF-β), it plays a pivotal role in wound healing. To date, a recombinant form of PDGF is the only growth factor approved by the US Food and Drug Administration and European authorities for topical use on diabetic foot ulcers with adequate peripheral circulation. Its efficacy has been established in randomized controlled trials showing an improved healing timescale as well as a greater reduction in the surface area of wounds [55].

Diabetic murine full thickness wounds treated with recombinant PDGF and FGF for 5 to 14 days exhibited a greater number of fibroblasts and capillaries in the wound compared to controls and this was was accompanied by accelerated wound closure at 21 days [56]. These cytokines have not been formally studied in burns models or wounds as yet but they are promising theoretical adjuncts awaiting formal evaluation.

L arginine supplementation

A rat study investigated the effect of L arginine administration to streptozocin-induced diabetic animals with 20% TBSA deep dermal burn injury. Arginine supplementation mediated an enhanced inflammatory reaction, shedding of necrotic tissue and improved epithelial cell advancement in the burn wound. Furthermore, supplementation decreased the glucose content of the cells in the skin and increased the hydroxyproline and TGF-beta content compared to the control group [57].

Arginine represents a conditionally essential amino acid, which has not been extensively investigated in clinical studies. Nevertheless, given its early association in the literature with worse mortality rates, it currently has no established role in burn care [58].

Erythropoeitin (EPO)

Erythropoeitin is widely used for the treatment of chronic kidney disease and chemotherapy associated anaemia. There is accumulating evidence supporting a beneficial effect of EPO administration on wound healing in diabetic murine models. The implicated mechanisms involved include a shorter duration of the inflammatory phase, as well as enhancement of fibroplasia, angiogenesis and re-epithelialisation. Results from large-scale studies are eagerly awaited to appraise the efficacy of EPO administration in burns clinical practice [59].

Recommendations for the prevention of burn injuries in diabetic patients

Diabetes mellitus is an increasingly prevalent metabolic disease, which can significantly complicate burns rehabilitation. Preventive measures are crucial for this subgroup of patients including:

a) Patient education about the risk of burns/scalds, especially in areas affected by neuropathy.

b) Visual and tactile inspection of limbs as part of regular foot care.

c) Avoidance of walking barefoot using foot heating devices spas.

d) Tight glucose control to delay diabetic complications and reduce the incidence of tissue injury [2, 6, 10, 60].

Conclusion

Diabetes mellitus represents a worldwide epidemic. Healthcare professionals will be increas-

ingly faced with challenges relating to the management of diabetic burn patients. The host of alterations in key physiological processes seen in this metabolic disease have ramifications, which increase the morbidity of patients with thermal injuries. Interestingly, the associated mortality appears to be unaffected. Appreciation of the individual characteristics of this subpopulation of burn victims will allow better treatment planning and provision, with a view to reducing complications and improving outcomes.

Disclosure of conflict of interest

None.

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