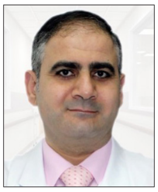
Targeting oxygen free-radicals in diabetic wound healing: three case reports





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The Arabian Gulf region has seen an increasing rise in diabetic foot ulcers (DFUs) with prevalence ranging from 4.7% to 19% in Saudi Arabia (Hu et al, 2014; Mairghani et al, 2017). Current practices for standard of care include wound debridement, wound offloading and dressings. The authors successfully managed diabetic foot ulcers with oxygen free-radical binding technology as an adjuvant therapy for our patients. HemaGel® (VH Pharma), a hydrophilic gel, contains sterically hindered amines that bind with reactive oxygen species (ROS) and thereby accelerates wound healing by showing an anti-inflammatory effect. The three case reports in this article discuss the use of targeted oxygen free radicals to promote wound healing by oxidant/antioxidant disequilibrium methodology in the authors' patients. With supporting diabetes controlling medications and HemaGel, wound healing was achieved successfully in these patients.

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According to the International Diabetes Federation (IDF), the age-adjusted prevalence of diabetes in the Middle East and North Africa (MENA) region is the highest worldwide (IDF, 2019). Diabetic foot and lower-limb complications are common, costly and result in 10–20 times more amputations in people with diabetes than in those without diabetes (IDF, 2017). Skin ulceration usually precedes the need for amputation (Apelqvist and Larsson, 2000). Epidemiological data on diabetic foot ulcers (DFUs) from the Arabian Gulf region are scarce, while published data from Saudi Arabia show a prevalence ranging from 4.7% to 19% (Hu et al, 2014; Mairghani et al, 2017).

In light of how diabetes impairs wound healing through vascular, neuropathic, immune and biochemical abnormalities (Greenhalgh, 2003), wound care is a serious issue in patients with diabetes. Although well-established management principles for diabetic leg and foot ulcers exist, treatment remains challenging (Everett and Mathioudakis, 2018). Adjuvant therapies that target some of the underlying causes of DFUs have been developed and are being used in centers across the Arabian Gulf region. As diabetes is highly prevalent in this region and is a leading cause of non-healing wounds, the authors believe that it is imperative to report clinical cases of efficacious treatment in this patient population.

Case report 1 (Dr. Elhadidi)

A 41-year-old man with a history of diabetes for 10 years and a glycated haemoglobin (HbA_{1C}) of 8% presented to the surgical clinic with an 8-month non-healing ulcer of his right great toe. Initial wound treatment consisted of dressings with antiseptic solutions and topical antibiotics for a period of 8 months without any improvement. Local application of epidermal growth factor over this 8-month period did not yield better results. The patient also underwent monthly wound debridement procedures. Upon the last debridement, the wound culture was negative for bacterial growth and an X-ray of the foot did not show any osteomyelitis.

At that stage, approximately 9 months into wound management without clear progression towards healing, daily dressing with an FDA-approved hydrophilic gel that binds oxygen free-radicals (HemaGel) began. This was followed by fast epithelial growth across the wound gap and from all wound sides. There was no overgrowth of tissue in the wound edges. It took 3 months of HemaGel application for the patient's wound to heal completely. Skin integrity remained very good more than 9 months later. Diabetes management was also part of the overall treatment plan for this patient.

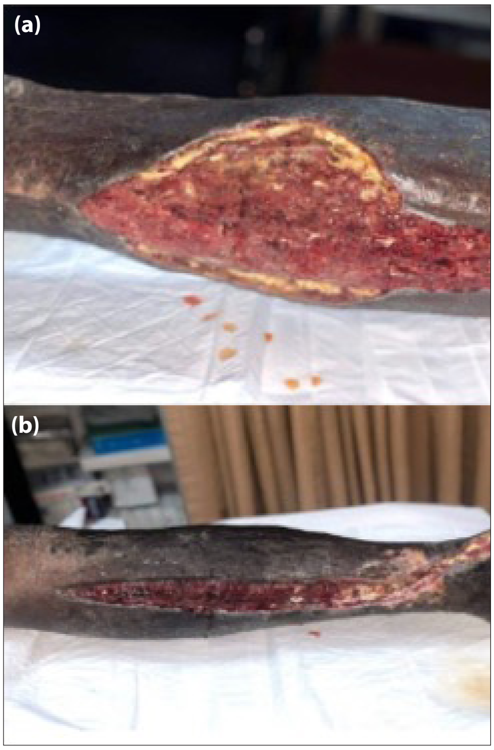

Figure 1 a & b. Wounds following fasciotomy and debridement.

Case report 2 (Dr. Wahdan)

A 41-year-old man was seen in the emergency room for severe pain, oedema and redness of his left lower limb. The patient experienced severe pain in his left foot that would prevent him from walking or simply touching the ground. Physical examination revealed mild oozing due to swelling and the presence of vesicles and superficial ulcerations from the dorsum of the left foot to the patient's knee. Despite normal mobility of the left lower limb, a peripheral pulse could not be felt and sensitivity was reduced. The patient's past medical history was significant only for insulin-dependent diabetes mellitus. Laboratory investigations showed an HbA_{1c} of 10.7%, elevated white blood cell (WBC) count of 35,000, C-reactive protein (CRP) of 276 mg/L and low haemoglobin of 8.5 g/dL. Magnetic resonance imaging (MRI) showed diffuse left leg subcutaneous oedematous changes with swelling and partial dilation of subcutaneous venous channels. There was partial involvement of deep and superficial left leg muscles. No significant enhancement was observed.

The patient was diagnosed with compartment syndrome of the left leg with marked cellulitis and left diabetic foot infection. Intravenous (IV) therapy with ceftriaxone and metronidazole was initiated. This regimen was later changed to piperacillin/tazobactam as per the infectious disease specialist. Pain was controlled with paracetamol and meperidine. Management of the patient's diabetes was achieved using insulin pump therapy for the first week of his hospital stay in addition to oral glucose-lowering drugs.

The patient underwent an urgent fasciotomy of the left leg. A second surgical intervention was performed 48 hours later for further debridement of the open wounds and necrotic tissue and to assess the vascularisation of the leg muscles *[Figure 1a and 1b]*. The patient was discharged from the hospital with two open wounds for which daily dressing was performed in the outpatient clinic using HemaGel® (VH Pharma). This specific hydrophilic gel was selected based on its unique mechanism of action and our past experiences of proven effectiveness in managing infected wounds. One month later, wound debridement was performed to remove the remaining necrotic tissue and the patient was sent home. Frequent dressing changes using the same hydrophilic gel for an additional month were performed. A skin grafting procedure was considered when two consecutive wound cultures were negative for infection.

By then, laboratory inflammatory markers were back within the normal range, and the fasciotomy wounds were a healthy red colour with clean granulation tissue. Skin grafts were performed approximately 2 months after the patient initially presented to the emergency room. The procedure was successful, and the wounds healed completely *[Figure 2a and 2b]*.

Figure 2. Wounds following skin grafts.

Case report 3 (Dr. Ali)

A 55-year-old man with morbid obesity and poorly controlled diabetes, as evidenced by a HbA_{1c} of 11%, presented to the clinic with a non-healing right leg venous ulcer. Past medical and surgical history were significant for diabetes mellitus and right femur fracture with intramedullary nail fixation 7 years earlier. Following this surgery, the patient developed deep vein thrombosis due to prolonged recumbency. Previous treatment approaches

Figure 3. Progression of right leg venous ulcer from treatment initiation (a) to treatment completion (c).

for his right leg venous ulcer proved ineffective or were poorly complied with by the patient. In our clinic, the patient underwent a wound debridement procedure followed by wound dressing with HemaGel for approximately 5 months. Dressing changes were performed daily for the first 2 weeks and every other day thereafter. Compression bandages were also applied. *Figure 3* shows the progression of the wound from treatment initiation to completion.

Discussion

Taking into consideration the regional growth of diabetes (IDF, 2019), the high prevalence of DFUs (Hu et al, 2014; Mairghani et al, 2017) and the increased risk for lower-extremity amputation associated with diabetes (Cancelliere, 2016), it is inherently important to effectively manage DFUs, as described in the cases highlighted in this article.

The current gold standard of care practices for DFUs include surgical wound debridement, wound offloading, dressings that promote a moist wound environment and control exudate, glycaemic control, and vascular assessment (Everett and Mathioudakis, 2018). Despite these measures being taken, approximately 82% of lower-extremity amputations occur among people with diabetes suffering from foot ulceration (Dillingham et al, 2002). This is due, in part, to the inability of traditional interventions to fully address the underlying causes of non-healing diabetic leg and foot ulcers. Diabetic neuropathy, peripheral arterial disease leading to tissue ischaemia and the development of excess free-radicals all contribute to the slow healing of lower-extremity ulcers (Posthauer, 2004; Everett and Mathioudakis, 2018).

Oxygen free-radical binding technology is an adjuvant therapy aimed at supporting the natural physiological process of wound healing. When skin injury occurs, a cascade of events aimed at repairing the damaged tissue is triggered. This complex process can be impaired by oxygen free-radicals, specifically reactive oxygen species (ROS). ROS are highly reactive particles that form at the site of injury and can disturb and destroy healthy cells through oxidative stress, thus slowing or even interrupting wound healing (Schäfer and Werner, 2008; Bryan et al, 2012). The hydrophilic gel used to treat our patients' wounds, contains sterically hindered amines that exert an anti-inflammatory effect by effectively binding ROS (US Patent, 2020). Furthermore, the elastic layer formed at the surface of the wound creates a physical barrier from the environment and promotes moist wound healing while absorbing the exudate.

This specific hydrophilic gel was selected for wound care in the patients described herein because of the gel's unique mechanism of action and the patients' profile. In healthy individuals, the cell damaging effects of ROS released in the initial wound healing cascade would be mitigated by antioxidant defense and scavenging systems (Carrascosa et al, 1998). However, in diabetes, persistent hyperglycaemia causing non-enzymatic protein glycosylation and glucose auto-oxidation has been reported to increase the production of ROS. The result is oxidant/antioxidant disequilibrium that compromises wound healing (Carrascosa et al, 1998). In these three case reports, the authors successfully targeted oxygen free-radicals to support the wound healing capabilities of our patients.

In a recent retrospective study of the economic impact of DFUs on healthcare in Saudi Arabia, Alshammary et al (2020) studied 99 patients with diabetes admitted with foot ulcerations to a single tertiary care centre between 2007 and 2017. The overall cost of managing these patients was approximately SAR661,804.30 (US$176,481.20) annually, which equates to SAR6684.90 per patient/year (US$1,782.60). This cost analysis included drug usage, wound dressings, surgical procedures, admissions and basic investigations with the largest portion of healthcare expenditure allocated to hospital admissions and surgical procedures. This highlights the financial imperative to encourage the early use in the wound management plan of low-cost, effective treatment strategies, such as dressings, that prevent wound deterioration and promote wound healing in patients with diabetes.

Conclusion

In this article, the authors described the successful management of diabetic wounds in three patients using a unique sterically hindered amine-containing hydrophilic gel. To their knowledge, these are the first case reports on the use of this type of wound care technology to be published in a peer-reviewed journal.

Considering the significant medical and financial burden of diabetes and diabetic wounds in the Arabian Gulf region, large, multicentre prospective studies are recommended to further evaluate this oxygen free-radical binding technology. WME

Ethical consent
Informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board.

Disclosures
None of the authors report a conflict of interest related to this article.

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