Case study

Intra-ulcero insulin application in the treatment of a diabetic foot ulcer: A clinical observation

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Foot ulcers are a frequent and complex complication in people with diabetes – over 3 years of observation the cumulative incidence of foot ulcers in people with diabetes (types 1 and 2) was found to be aproximately 6% in a US-based study (Ramsey et al, 1999). Diabetic foot ulcers are often present for long periods of time and have poor healing rates (Zimny et al, 2002).

One method that may potentially improve the healing of diabetic foot ulcers in people with diabetes is intra-ulcero application of insulin. Exogenous insulin could potentially stimulate insulin receptors and growth factor receptors – these have been demonstrated to be impaired in rodent models (Spravchikov et al, 2001). Insulin-like growth factor-1 (IGF-1) expression has been found to be present only in the stratum granulosum and spinosum of uninjured skin of people with diabetes (IGF-1 is found throughout the epidermis of people without diabetes; Blakytny et al, 2000). IGF-1 is also absent from the basal layer of skin at the edge of ulcers of people with diabetes, and from dermal fibroblasts of people with diabetes (Blakytny et al, 2000).

Such use of exogenous insulin is further supported by the findings of an increased insulin-degrading activity in fluid from wounds of people with diabetes, which underscores the idea that local insulinopenia in people with diabetes might be an important factor in delaying wound healing (Duckworth et al, 2004). Furthermore, cultured fibroblasts from chronic diabetic wounds have been shown to have a diminished proliferative capacity and abnormal morphology (Loots et al, 1999), which could be due to a lack of stimulating growth factors.

In this case study the authors report on the use of insulin in a topical fashion on the wound of a man with type 1 diabetes.

Case study details

Mr X is a 59-year-old male (at time of presentation of ulcer: weight, 95 kg; body mass index, 31.0 kg/m^2; HbA_{1c}, 7.3%) who was diagnosed with type 1 diabetes at the age of 9 years. He had a neuro-ischemic diabetic foot ulcer on the plantar surface of his left heel; the ulcer was slow healing. His microvascular complications included proliferative retinopathy and end-stage renal disease – he was scheduled for kidney transplantation but the surgeons were reluctant to perform this due to his foot ulcer. He had other concomitant medical conditions, these were:

- chronic atrial fibrillation
- diastolic heart failure (classified as Class II, as defined by the New York Heart Association)
- hypertension.

His medication consisted of:

- pravastatin 20 mg daily
- allopurinol 100 mg daily
- bumetanid 4 mg daily
- spironolactone 25 mg daily
- lisinopril 40 mg daily
- insulin human isophane 10 international units (IU) in the morning and 8 IU in the evening
- insulin aspart 2–4 units with the evening meal
- warfarin 2.5 mg, 10 times per week.

He presented with the ulcer in mid-July 2004, when its size was approximately 1.2 cm by 3.2 cm and classified, according to the Wagner grading system, as a grade 2.

In early September 2004 the wound size was 0.9 cm by 2.6 cm. At this time he was also on dicloxacillin 250 mg four times daily and ciprofloxacin 250 mg once daily.

By early November 2004 the ulcer area had reduced to 0.7 cm by 2.4 cm. His renal function had worsened by this time.

From 17 November 2004, after giving written informed consent, Mr X received 4IU human insulin weekly within the ulcer cavity in addition to conventional therapy. Conventional therapy consisted of debridement of contaminated and necrotic tissue from within or adjacent to the wound until the surrounding healthy tissue was exposed using mechanical methods. In addition, pressure relief was managed using removable cast walkers.

Results

As shown in the Mr X's foot ulcer gradually healed and within 12 weeks of starting topical insulin treatment it was completely healed with no adverse reactions to the topically applied insulin. He had a succesful kidney transplant operation on 8 February 2005; at the time of writing, the transplant was functioning normally.

Discussion

Mr X's foot ulcers healed within 12 weeks after the intra-ulcero application of human insulin. However, as the ulcer already had recovered to approximately 44% of the initial size (1.2 cm by 3.2 cm [3.84 cm^2] in July 2004) upon the commencement of topical insulin treatment (early

November 2004) we can not conclusively state that healing was achieved due to the topical insulin intervention alone; rather that this treatment increased the healing rate, that is, the expected 16–18 weeks expected for the ulcer to heal according to the rate of the wound's surface area reduction was, with topical insulin treatment, reduced to 12 weeks.

This reduction in time is clinically significant in that it gave Mr X the opportunity to undergo a vital kidney transplantation sooner.

Possible deleterious effects of such topical applications of insulin include 'site reactions'. These could be due to a hypersensitivity or an allergy to the insulin or to one of the insulin formulation components (such as metacresol or phenol) or perhaps to the acidic nature of the formulation. The risk of hypoglycaemia associated with topical insulin treatment, however, is minimal as insulin is poorly absorbed transdermally (Heinemann et al, 2001).

Our finding is in slight contrast to earlier described efforts (Greenway et al, 1999) in that Greenway and colleagues described iatrogenically induced ulcers on the forearms of people with and without diabetes; these ulcers differ greatly from those that occur on diabetic feet. However, as the pathophysiology behind this has become clearer with the discovery of, for example, insulin receptors and growth factor receptors in the epidermis, the findings of an increased insulin degrading activity in wound fluid from people with diabetes and diminished proliferative capacity and abnormal morphology of cultured fibroblasts from diabetic foot ulcers, we believe that topical insulin could play a major role in the treatment of such ulcers. However, formulation, dosage and frequency of the insulin application for this purpose needs further examination. ■

Table 1. Mr X's wound size from presentation to healing.

Week	Wound size in cm (area in cm^2)
-14	1.2x3.2 (3.84)
-8	0.9x2.6 (2.34)
0 (topical insulin treatment started)	0.7x2.4 (1.68)
2	0.6x2.3 (1.38)
4	0.4x1.8 (0.72)
6	0.4x1.6 (0.64)
8	0.3x1.1 (0.33)
10	0.2x0.7 (0.14)
12	0x0 (0)

Note: The wound surface areas were calculated by multiplying the wound size numbers together. This may mean that the actual wound sizes were actually somewhat smaller than the size stated.

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Editor's note

Please note that insulin is not indicated for such topical use on any wounds of any patient in the UK. If any such treatment were to be considered approval would be required.

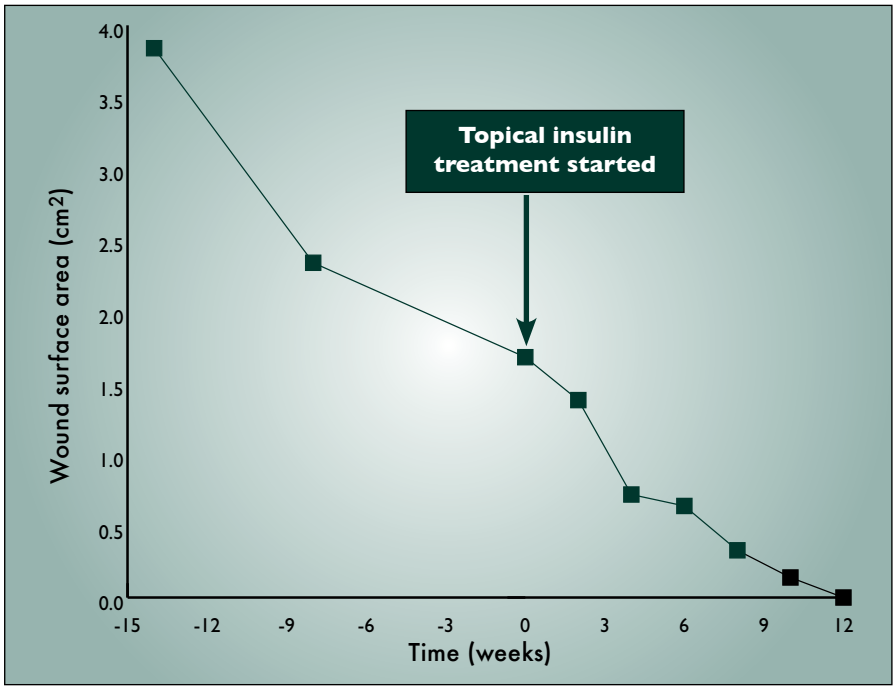

Figure 1. Graph demonstrating reduction of Mr X's wound size over time to full healing.