

# Letters

## Coincidence of hand and foot ulceration in people with diabetes

While diabetic hand infection with the potential threat of upper limb amputation has recently been described from distinct African countries [1–4], contemporary reports on diabetic hand ulceration in diabetic patients from western communities are rare and mostly anecdotal [5]. We therefore appreciated the case report and reminder of hand neuropathy in diabetic ‘at risk patients’ by Coppini and Best in a recent issue of this journal [6].

Owing to the general lack of data, we studied, in an ongoing prospective study, the prevalence of hand ulceration together with acute diabetic foot lesions in patients visiting our diabetic foot clinic.

A total number of 407 diabetic patients have presented to our diabetic foot clinic with active foot ulceration since June 1998. Among them, nine patients (2%) suffered from a foot ulcer and a mostly unrecognized hand lesion concurrently (see Table 1 for clinical characteristics of study patients). Another five patients had a history of previous upper-limb amputation. While four of these patients reported an acute trauma unrelated to diabetes as the causative factor finally leading to amputation, in one patient amputation of two digits became necessary as a result of uncontrolled diabetic hand infection.

The outcome of the nine observed acute hand lesions included conservative healing in five patients (56%), surgical intervention without amputation in one patient, and partial digit amputation in another. Two patients died with unhealed hand lesions, after toe amputation and AKA (above knee amputation) for

their foot lesions were unavoidable despite vascular reconstruction. Diabetes was combined with scleroderma in one patient, and with calciphylaxis and end-stage renal disease in another, which may be potential additive underlying conditions responsible for the development of the observed hand lesions.

In five cases burns were responsible for the observed hand lesions, while progressive infection of superficial skin lesions was observed in two patients. It might be interesting to note that burns as causes for the observed foot lesions were far more common in patients with combined hand and foot lesions (3/9) than in patients with foot lesions alone (4/398). Higher prevalence of active smoking, coexisting renal insufficiency, increased severity of diabetic neuropathy of the lower limb, and predominance of males were additional differences observed between the patients with hand lesions and those without.

We conclude that the staff of institutions dealing with the diabetic foot should be aware of the possible coexistence of hand problems in their patients. Especially male diabetic patients with active or previous foot burns, severe lower limb diabetic neuropathy, co-existing renal insufficiency, and a history of smoking should be considered at risk for hand complications. Those patients should be screened for loss of protective sensation in the upper extremity and receive specific education to avoid hand injuries.

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**Table 1** Clinical characteristics of patients with and without acute diabetic hand lesions

|                                                                                     | With acute hand lesion ( <i>n</i> = 9) | Without hand lesion ( <i>n</i> = 398) |
|-------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------|
| Age (mean ± SD)                                                                     | 57.8 ± 10.3                            | 69.6 ± 10.9                           |
| Diabetes duration (mean ± SD)                                                       | 15.9 ± 9.6                             | 15.0 ± 10.2                           |
| Type 1:Type 2 diabetes ( <i>n</i> )                                                 | 2:7                                    | 32:366                                |
| Female:Male ( <i>n</i> )                                                            | 2:7                                    | 164:235                               |
| Loss of protective sensation<br>(monofilament insensitive and/or tuning fork ≤ 4/8) | 8 (89%)                                | 316 (81%)                             |
| Insensitive to 5.07 monofilament                                                    | 7 (78%)                                | 233 (59%)                             |
| Insensitive to tuning fork (0/8)                                                    | 8 (89%)                                | 197 (49%)                             |
| Peripheral vascular disease<br>(ankle brachial index ≤ 0.8)                         | 5 (56%)                                | 200 (50%)                             |
| Chronic renal insufficiency<br>(creatinine > 1.5 mg/dl)                             | 5 (56%)                                | 85 (21%)                              |
| Proliferative diabetic retinopathy                                                  | 5 (56%)                                | 172 (43%)                             |
| Active smokers                                                                      | 6 (67%)                                | 32 (8%)                               |
| Foot burns                                                                          | 3 (33%)                                | 4 (1%)                                |

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## Localized insulin allergy treated with continuous subcutaneous insulin

Immunological complications of insulin therapy have been evident since the introduction of animal insulin in 1922. Although advances in insulin purity and recombinant DNA technology have reduced their frequency considerably, allergic responses still occur, usually due to additives in the solution rather than the insulin molecule *per se*.

A fully independent 79-year-old man with a 28-year history of Type 2 diabetes complicated by stable ischaemic heart and peripheral vascular disease, presented with symptomatic hyperglycaemia requiring conversion to insulin (HbA<sub>1c</sub> 10.2%, NR < 6.5%). Previously, he had never been exposed to insulin and had no history of anaphylaxis or urticaria. Blood glucose levels and symptoms rapidly improved on twice-daily premixed human insulin (48 U/day). However, 2 months after conversion, glycaemic control deteriorated with further weight loss. The patient also complained that, 2 h after injection, the site became swollen, lasting for up to 48 h. Post-injection examination revealed a 2-cm round firm, non-tender swelling on the anterior abdominal wall. He reported similar reactions at other injection sites. This was assumed to be a local hypersensitivity reaction.

Potential allergens included insulin *per se*, needle lubricant and injection medium. Initially, he was tried on bovine lente insulin (different species, methyl-p-benzoate as preservative, zinc suspension), but subcutaneous injection produced the same allergic response. The patient suffered identical reactions to regular human soluble and isophane insulin, and highly purified pork isophane insulin.

The patient was temporarily converted back to oral hypoglycaemic agents and had a negative allergy test to injection medium and needles suggesting that the insulin molecule was the likely allergen. On oral agents, glycaemic

control quickly deteriorated (HbA<sub>1c</sub> 14%). On admission to hospital adequate glycaemic control was obtained with an insulin infusion with no evidence of a systemic reaction.

Subsequently, the patient was tried on a basal bolus regimen of LisPro (Humalog) and Humulin I but developed subcutaneous swellings with a weal and flare reaction after 2–3 h. However, there was no itching or irritation, as would normally be seen with type 1 cutaneous hypersensitivity. The timing of the allergic response described would be more typical of a type 3 hypersensitivity reaction, which is IgG-mediated.

Investigations supported the diagnosis of type 1-mediated hypersensitivity with a raised eosinophil count  $1.6 \times 10$  (normal 0.0–0.5) and a markedly elevated IgE level of 1227 kU/l (1–180). IgE-specific RAST test confirmed antibodies to Insulin bovine 14.4 kUA/l, Insulin human 33.7 kUA/l and Insulin porcine 24.2 kUA/l. IgG levels were normal.

After discussion with the patient, he opted to add 10 mg soluble hydrocortisone to each injection of insulin. This led to resolution of the allergic response and adequate glycaemic control was obtained with a total of 38 U in 24 h. He was discharged on twice daily premixed pork insulin. This regimen worked initially but the allergic response recurred within 2 months.

As the allergic reactions appeared to be variable in size and duration, possibly reflecting the volume of injected insulin, the patient was commenced on CSII (MiniMed 507) containing LisPro insulin, which delivers a smaller volume of insulin than with standard injection. Three months after starting CSII there has been no sign of an allergic response. HbA<sub>1c</sub> has fallen to 9.3% (normal range to percentage). IgE levels are lower at 342 kU/l (1–180 kU/l).

Generalized and local allergic reactions to the insulin molecule are usually type I immediate hypersensitivity and mediated through IgE insulin antibodies. Type 3 (immune complex-mediated) hypersensitivity can also produce a delayed local reaction that can occur 30 min after injection and last for 12–24 h. These reactions may be responsive to the addition of subcutaneous hydrocortisone [1].

Immunogenicity has been reported more frequently with animal insulins, with beef insulin producing more circulating antibodies and more local allergy than pork insulin [2]. Local allergy to LisPro insulin is extremely rare [3] and this insulin analogue has been used to treat allergy to regular human insulin [4]. Rapid absorption of subcutaneous LisPro insulin, and hence reduced exposure to cutaneous mast cells, may be responsible for these observed differences in immunogenicity.

For this patient, there was marked variation in the size of the allergic reaction presumably related to differences in injection site absorption rates and amount of insulin used.

CSII was effective probably as a consequence of a smaller insulin depot at the infusion site [5].

In summary, this patient appears to have a pan-insulin allergy including an allergy to LisPro insulin. His clinical state dramatically improved with the use of continuous subcutaneous insulin infusion.

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