Progressive and disabling lipoatrophy associated with insulin aspart via a continuous subcutaneous insulin infusion

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Abstract
Since the advent of insulin analogues, the incidence of insulin-induced lipoatrophy has been relatively rare save for a small number of isolated cases. We report a case of severe disfiguring lipoatrophy in an 18-year-old female patient following a change in the mode of administration of insulin aspart from subcutaneous injections to continuous subcutaneous insulin infusion (CSII).
This case highlights the need for further research into the causes of insulin-induced lipoatrophy and the need for caution when starting a patient on a CSII. Copyright © 2015 John Wile y & Sons.

Key words
lipoatrophy; insulin infusion; aspart; insulin allergy; CSII

Introduction
Lipoatrophy is a recognised complication of insulin therapy characterised by a disfiguring loss of subcutaneous fat at the site of insulin injections.1 Prior to the introduction of human insulin, lipoatrophy was relatively common with a recorded incidence varying between 10%2 and 54%.3 However, since the introduction of insulin analogues, lipoatrophy has become comparatively rare. Only a handful of case studies have emerged of lipoatrophy associated with lispro (Humalog),1,5 aspart (Novom ix, Novorapid),6 detemir (Levem ir)6,7 and glargine insulin.8
The mechanism of lipoatrophy is generally poorly understood although an immune pathogenesis seems likely (despite the lack of inflammatory features in lipoatrophic lesions). Deposition of IgM with C3 or fibrin- fibrinogen in the walls of dermal blood vessels in biopsies taken from the edges of atrophy areas lends credence to this hypothesis.9 Similarly, improvements observed in response to corticosteroid therapy are in keeping with immune complex-mediated tissue damage.9

Case history
We report the case of an 18-year-old female patient with a 15-year history of type 1 diabetes (urinary C-peptide: creatinine ratio <0.2 nmol/mm mol) and a BMI of 27 who presented to the diabetes insulin pump clinic with a large area of lipoatrophy in her abdominal wall.
She was diagnosed with type 1 diabetes aged three years and was initially treated with Velosulin and Insulatard. In the first seven years of insulin therapy, she developed urticarial reactions (but no atrophy) at the injection sites and was found to be allergic to insulin additives namely: zinc, protamine and metacresol (by formal skin patch testing). The addition of dexam ethasone to her norm al insulin injections helped ease her cutaneous sympt om s but contributed to significant weight gain and deterioration in glycaemic control. Consequently, she switched to Novorapid and Levem ir at age 13 which led to resolution of the local injection site reactions.
From her early teens she suffered from increasingly severe hypoglycaemia unawareness with frequent major nocturnal hypoglycaemic episodes. At age 16, she was commenced on a continuous subcutaneous insulin infusion (CSI) with an Anim as pump using aspart (Novorapid) insulin. The CSII enabled her to reduce her total daily dose of insulin from 100 units a day to 55 units a day and reduced the frequency of hypoglycaemic events while maintaining her HbA1c (6.7–7.2%). She noticed a small indent in her abdomen a year into her CSII. The patient was advised to vary the site of her CSII cannula. Despite rotation of
the cannula site, the indentation progressed reaching a diameter of 4x8 cm with a depth of 2 cm (Figure 1). A diagnosis of lipoatrophy was confirmed on ultrasound which also located four similar smaller lesions in the abdomen all relating to previous CSII cannulation sites. She declined combining her insulin with dexamethasone due to previous weight gain and deterioration in glycaemic control when administered steroids for her insulin allergy. Similarly, alternative insulin analogues were not tried instead of insulin aspart in this case because of previous insulin allergies. The patient continued to rotate cannula sites while avoiding the area of lipoatrophy and, on follow up a year later, there had been no progression (confirmed on ultrasound – Figure 2) but also no resolution of her lipoatrophy.

**Discussion**

This case is noteworthy for the association between lipoatrophy and insulin aspart administered via CSII. Furthermore, it is unusual in the fact that the patient developed lipoatrophy only after starting CSII despite having taken insulin aspart for over five years beforehand. This would suggest that the mechanism for the development of lipoatrophy in this case may be related to the mode of administration, rather than the form of insulin, given the temporal relationship between lipoatrophy and pump administration, independent of insulin aspart.

This case goes against previous suggestions that CSII *per se* does not have a significant role in the development of lipoatrophy with insulin analogues or that it could provide a viable solution to lipoatrophy caused by injected insulin.

We hypothesise that the pathogenesis of insulin-induced lipoatrophy here could be related to the continuous administration of insulin via CSII. It has been speculated that adipocytes which are chronically exposed to high local insulin concentrations may subsequently develop severe insulin resistance, leading to lipolysis and slimming of adipocytes. This would be in keeping with our findings. Alternatively, lipoatrophy could be associated with a reaction to the pump cannula; however, there is little in the literature to support this hypothesis.

Treatment options for the described patient are limited. Although changing the site of injection or cannulation has been shown to reverse lipoatrophy in some patients, this is not always effective, as shown in our case. In some reports, the progression of lipoatrophy has been halted by swapping between insulin analogues; however, again, there is also evidence to the contrary. Similarly, unlike the case we are presenting here, modifying the mode of administration of insulin from intermittent injections to continuous infusion has been beneficial in reducing the advance of lipoatrophy in two documented cases. Corticosteroids have proved effective when co-administered with insulin (dexamethasone) or given orally (daily low-dose prednisolone); nonetheless, their use needs to be balanced against side effects including weight gain and the risk of deterioration in glycaemic control.

**Conclusion**

We highlight here the need for further research into the causes of insulin-induced atrophy in insulin analogues and its management. This case emphasises the need to consider the risk of lipoatrophy when prescribing CSII in patients who have previously experienced local reactions to, or lipoatrophy with, subcutaneous insulin analogues. Additionally, we would also advise caution in overstating the case for the benefits of pump therapy in the treatment of lipoatrophy.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
Lipoatrophy associated with insulin aspart pump therapy

References