Lipoatrophy: re-emerging with analogue insulins. Is there a link with CSII?

Introduction
Lipoatrophy (LA) was commonly seen with insulin use prior to the 1970s, occurring in 25–55% of patients using conventional bovine or porcine insulin.1 The incidence of LA fell to less than 10% with the introduction of highly purified insulin 1 and it has been largely unreported and hence considered extremely rare since the development of recombinant human insulin and insulin analogues. In the past decade, however, there has been an increase in reports of LA among patients using various rapid- and long-acting analogue insulin preparations. Lipoatrophy is more commonly seen in young people,1 therefore its incidence is particularly relevant in a paediatric setting. The presence of LA is clinically significant because it may lead to impaired insulin absorption and instability of blood glucose control. Furthermore, its adverse cosmetic effects can cause distress to patients and their carers.

Case reports
We retrospectively collected data on patients identified with LA from our clinic population of 328 patients. Over a two-year period, four patients with type 1 diabetes presented with LA (see Table 1). All four patients were female, and receiving treatment with insulin aspart (NovoRapid) via continuous subcutaneous insulin infusion (CSI). Lipoatrophy was detected one to three years after commencing CSII therapy. (Figures 1 and 2.)

No detrimental effect of LA on the glycated haemoglobin (HbA1c) was demonstrated; however, the cosmetic effects were disturbing to patients and carers. All patients were advised to rest the lipoatrophic sites and avoid administering insulin into the areas. In all patients LA persisted at the most recent follow up, albeit with some improvement.

To help elucidate an immunological basis for LA we looked for co-existing autoimmune disorders and noted that patient number two had coeliac disease.

Discussion
Lipoatrophy is a rare and likely under-reported complication of insulin therapy, which appears to be re-emerging. Lipoatrophy represents destruction of subcutaneous fat and presents with well demarcated, depressed areas at sites of insulin administration, typically following 6–24 months of regular insulin treatment. We present four cases of LA: all female, and all on CSII with insulin aspart. This raises a number of interesting points.

Abstract
Over the last decade, there has been an increase in reported cases of lipoatrophy as a complication of treatment with analogue insulin preparations. Lipoatrophy causes undesirable cosmetic appearances and may cause variable glycaemic control.

We report a case series of four female patients from a tertiary paediatric diabetes unit presenting with lipoatrophy while on treatment with insulin aspart via a continuous subcutaneous insulin infusion (CSI) pump for the management of type 1 diabetes. We did not observe any cases of lipoatrophy in patients receiving multiple daily insulin injections. In examining the effect of lipoatrophy on glycaemic control, we found no detrimental effect of lipoatrophy on the patients’ glycaed haemoglobin.

Cases of lipoatrophy should be reported to drug manufacturers and through the appropriate national adverse drug reaction reporting system. This will facilitate observation of trend, and help monitor for associations, informing future research. Copyright © 2014 John Wiley & Sons.

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Key words
diabetes; lipoatrophy; paediatrics; CSII
The precise mechanism of LA is still unknown, although it is considered to be an immunological phenomenon. This theory is supported by the presence of IgM, IgA, C3 and fibrin in LA lesions and a response to steroid therapy in a number of cases. Our case series suggests that the continuous exposure to insulin via CSII may play a role in inducing the immunogenic response. Reports of LA occurring with insulin analogues via injections and pump therapy imply that the mechanism may be independent of the delivery system. However, this observation may not necessarily be applicable to a paediatric population. In theory, infusion of insulin and maintaining the catheter at the same site over a number of days could predispose to the development of LA, since the repeated administration of insulin to a particular area has been identified as a contributing factor. It is conceivable that, in young children, sites for cannula insertion for CSII may be limited, leading to a decrease in the recommended rotation of insertion sites, compared to rotation of injection sites with multiple daily injections. This is supported by our data series where LA presented only in patients on CSII.

In addition, previous studies and reports have described an increased incidence of LA in females, a point highlighted by the demographics of our case series. Further research by Salgin et al. in 2013 showed that Hashimoto’s thyroiditis and coeliac disease – both autoimmune conditions, and with a higher prevalence in females – were more prevalent in patients with LA. Lipoatrophy was also associated with an increased risk of Hashimoto’s thyroiditis and coeliac disease in female patients.

### Table 1. Demographic data in patients identified with lipoatrophy (LA)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of diabetes (years)</th>
<th>Duration of CSII use (years)</th>
<th>Total daily dose (units/kg)</th>
<th>Site of LA</th>
<th>HbA1c (%) 3 months prior to LA diagnosis</th>
<th>HbA1c (%) at LA diagnosis</th>
<th>Follow up (months)</th>
<th>LA resolved (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3</td>
<td>1.5</td>
<td>1.3</td>
<td>0.7</td>
<td>Buttock</td>
<td>7.1</td>
<td>6.9</td>
<td>4</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>7</td>
<td>3.3</td>
<td>3.25</td>
<td>0.8</td>
<td>Abdomen</td>
<td>8.3</td>
<td>7.8</td>
<td>8</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>8</td>
<td>5.6</td>
<td>2.45</td>
<td>0.7</td>
<td>Thigh</td>
<td>8.9</td>
<td>7.7</td>
<td>25</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>10</td>
<td>4.9</td>
<td>1.6</td>
<td>0.4</td>
<td>Abdomen</td>
<td>6.8</td>
<td>7</td>
<td>9</td>
<td>N</td>
</tr>
</tbody>
</table>

The authors concluded that their findings support the hypothesis that an immune complex-mediated inflammatory process may be important in the development of LA. Only one of our four patients currently has a co-existing autoimmune condition. All patients will continue to be monitored for the possible development of Hashimoto’s thyroiditis and/or coeliac disease.

Management of LA presents a serious challenge, particularly in adults where spontaneous resolution is less common than in children. Various management strategies have been employed and postulated. These include rotating away from affected sites, rotating away from CSII catheter sites, and rotating away from affected sites in females.
Conclusions
Understanding the risk factors for developing LA and ultimately understanding the pathogenesis of LA will be useful in modifying the treatment options in the future.

We recommend further research in this area. Cases of LA should also be reported to drug manufacturers and through the appropriate national reporting system for adverse drug effects. This will facilitate observation of trend, and help monitor for associations, informing further research.

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Book review
Managing the diabetic foot

Third edition
By Michael E Edmonds and Alethea VM Foster
Published by Wiley-Blackwell, 2014
246 pages, price £39.99 paperback
ISBN: 0 470 655054
Website: www.wiley.com

like this book. The previous editions were excellent; this third edition is superb.

The introduction is comprehensive, providing a good overview of diabetic foot pathology, and concludes by emphasizing the importance of both the multidisciplinary diabetic foot clinics and the foot protection teams.

This introductory chapter is followed by six chapters on the staging levels, from the ‘normal’ foot to the unsalvageable foot. Each section has good, clear photographs to reinforce the clinical presentation.

There is a mention in chapter three, the high-risk foot, about painful neuropathy, an area often neglected by health professionals. The various drugs, together with their dosages, are documented. The longest chapters, four and five, are concerned with Stage 3, the ulcerated foot, and Stage 4, the infected foot. In the former there is salient, updated information on ischaemic disease with the addition of arterial therapies mentioned such as percutaneous transluminal angioplasty and sub-intimal angioplasty. There is also a good section in chapter four on ‘off loading’ devices.

There is updated information on Charcot’s neuroarthropathy and a welcome mention of surgical procedures that can be done to restore foot architecture. This is an area of controversy, in that surgical intervention may invoke further development of Charcot’s pathology.

In chapter five, there is a very useful table relating to antibiotic prescribing aligned to the micro-organisms involved in the infection. Furthermore, there is a comprehensive table on antibiotic suitability and dosage levels for those diabetic patients who have nephropathy.

The final chapter relates to Stage 6, the unsalvageable foot. It mentions the team approach in dealing with amputation and includes a section on rehabilitation for the amputee.

Finally, there is a useful appendix on differential diagnosis, with key terms, followed by the likely pathology. In addition, there is also a good reading list to allow the reader to delve further.

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