Lipodystrophy: Something to consider in the diabetes clinic

Claire Adams, Lisa Gaff, Audrey Melvin

Lipodystrophy refers to a spectrum of rare conditions characterised by a lack of functional fat in the absence of calorie restriction. Individuals with lipodystrophy are at risk of metabolic complications, such as severe insulin resistance, dyslipidaemia and non-alcoholic fatty liver disease. Although rare, it is most often diagnosed in the diabetes clinic, where patients present with complications of the condition. The focus of this article is to provide an overview of lipodystrophic syndromes and their presentations, and to discuss the management implications of this condition.

Lipodystrophy refers to a spectrum of rare conditions characterised by a lack of functional fat in the absence of calorie restriction (Brown et al, 2016). It has been estimated that worldwide there are 1.3–4.7 cases of lipodystrophy per million people (Chiquette et al, 2017).

Adipose tissue is an important organ and is very effective at storing excess dietary energy within lipid droplets. A reduction in functional adipose tissue means that this excess energy cannot be efficiently stored and leads to the accumulation of fat in organs such as the liver, skeletal muscle and pancreas; this is referred to as ectopic fat deposition (Robbins and Savage, 2015). Ectopic fat places individuals with lipodystrophy at risk of metabolic complications, such as severe insulin resistance with diabetes, ovarian dysfunction and acanthosis nigricans, as well as dyslipidaemia and non-alcoholic fatty liver disease (Garg, 2011).

Although lipodystrophy is rare, it is often first identified in our diabetes clinics. Increasing awareness of the condition is important as it will allow for the prompt diagnosis of those affected with lipodystrophy and the initiation of appropriate treatment. This article briefly outlines the subtypes of lipodystrophy, how they may present and current therapeutic options available to those affected.

Lipodystrophic syndromes

Lipodystrophy is subclassified according to whether the lack of fat is partial or generalised, and whether it is inherited or acquired in nature (Brown et al, 2016). There are broadly four major categories of lipodystrophy (Brown et al, 2016):

- Congenital generalised lipodystrophy.
- Familial partial lipodystrophy.
- Acquired generalised lipodystrophy.
- Acquired partial lipodystrophy.

The most prevalent form of lipodystrophy is caused by highly active antiretroviral therapy for HIV-infected patients. It is partial and acquired. Highly active antiretroviral therapy-related lipodystrophy is readily diagnosed in at-risk individuals and has been extensively reviewed elsewhere (Chen et al, 2002; Domingo et al, 2012).

Generalised lipodystrophy refers to all-over lack of adipose tissue and can be inherited or acquired (Garg, 2011). The severity of the metabolic complications is closely related to the amount of functional adipose tissue present (Huang-Doran et al, 2010).

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Article points

1. Lipodystrophy is subclassified according to whether the lack of fat is partial or generalised, and whether it is inherited or acquired in nature.
2. It is important to take particular notice of legs, arms, hips and buttocks for evidence of fat loss and muscular prominence.
3. Treatment focuses on preventing and managing the metabolic complications, with dietary intervention the cornerstone of management.

Key words

- Adipose tissue
- Fat loss
- Lipodystrophy
- Metabolic complications

Authors

Claire Adams, National Severe Insulin Resistance Service (NSIRS), Addenbrooke's Hospital and Metabolic Research Laboratories, Wellcome Trust–Medical Research Council Institute of Metabolic Science (WT–MRC IMS), University of Cambridge; Lisa Gaff, NSIRS and Wolfson Diabetes Centre, Cambridge University Hospitals NHS Foundation Trust; and Audrey Melvin, NSIRS, Addenbrooke's Hospital and WT–MRC IMS, University of Cambridge.

Page points

1. The severity of metabolic problems is proportional to the amount of reduced adipose tissue; the metabolic effects of generalised lipodystrophy are therefore often worse than partial lipodystrophy.
2. Patients may present with evidence of fat loss or abnormal distribution of fat.
3. Patients may also present with complications of the condition, such as difficult-to-treat diabetes and non-alcoholic fatty liver disease.

Congenital generalised lipodystrophy is inherited. It is generally recognised at birth or soon afterwards due to the lack of fat, with secondary complications such as dyslipidaemia and non-alcoholic fatty liver disease developing in childhood and diabetes developing in the teenage years (Agarwal et al, 2003).

Acquired generalised lipodystrophy is more likely to present in adult services, with patients reporting a progressive loss of body fat over months or years; however, it can also present in childhood (Misra and Garg, 2003). The causes of acquired generalised lipodystrophy are varied, but it is often associated with autoimmune disease. Metabolic complications can be severe and frequently correlate with the extent of adipose tissue failure (Brown et al, 2016).

Partial lipodystrophy refers to a condition where a variable amount of adipose tissue remains, and again can be inherited or acquired. Familial partial lipodystrophies (FPLDs) are characterised by a lack of fat on limbs, buttocks and hips, and often present in puberty (Huang-Doran et al, 2010; Brown et al, 2016). There are a number of different subtypes and several causative genes implicated which, when disrupted, can result in a variety of clinical features and fat loss (Robbins and Savage, 2015). The distribution of the remaining adipose tissue varies depending on the underlying cause. For example, in FPLD type 1, an excess of fat accumulates in the abdomen; whereas in FPLD type 2, excess fat can accumulate in the face, neck and vulva in females (Köbberling and Dunnigan, 1986; Garg et al, 1999). FPLD type 1 is the most common form of lipodystrophy to be found in patients attending the diabetes clinic, and it is often overlooked. Although the condition is not due to a defect in a single gene, it has a dominant pattern of inheritance (Guillín-Amarelle et al, 2016).

Fat loss in acquired partial lipodystrophy is often observed in childhood, affecting the face first and then spreading down the body. This distribution of lipodystrophy is infrequently associated with metabolic derangement (Misra et al, 2004).

Recognising lipodystrophy

People with lipodystrophy may present with evidence of fat loss or an abnormal distribution of fat. It is important to take particular notice of the legs, arms, hips and buttocks for evidence of fat loss and muscular prominence (Garg, 2011). Other aesthetic changes can be due to both the lack of subcutaneous adipose tissue and/or consequences of insulin resistance. They include muscular hypertrophy, acanthosis nigricans and skin tags. Specifically in women, male-pattern hair loss can occur, along with reduced breast tissue and loss of hip contour (Stears and Hames, 2014).

Alternatively, individuals may present with complications of the condition. For example, women may present with features of hyperandrogenism, including hirsutism and/or oligomenorrhoea, difficult-to-treat diabetes, non-alcoholic fatty liver disease and dyslipidaemia (Stears and Hames, 2014). As such, lipodystrophy should be considered in patients with a combination of these conditions. It is not uncommon for patients with lipodystrophy to have previously been investigated for Cushing's syndrome, due to similarities in clinical characteristics between the two conditions.

Women affected by lipodystrophy generally have a more striking phenotype, as healthy men have less adipose tissue than healthy women, in addition to a different distribution of adipose tissue. Women also experience more pronounced metabolic complications (Huang-Doran et al, 2010).

While patients with lipodystrophy may be identified in the diabetes clinic, not all will present this way. Patients may also present in other settings with different symptoms, including endocrine and reproductive clinics with polycystic ovary syndrome, dermatology clinics with acanthosis nigricans and lipid clinics with hypertriglyceridaemia.

A diagnosis of lipodystrophy is based on clinical and biochemical assessment. In certain cases, genetic testing is indicated where a hereditary cause for the lipodystrophy is suspected.

Management

Current therapeutic approaches focus on preventing and managing the metabolic complications of lipodystrophy (Brown et al, 2016). Dietary interventions are the cornerstone of management in all forms of the condition. Although patients may not appear overweight, they benefit from similar dietary advice and treatment as those with severe obesity, as the metabolic complications are similar.

It is important to note that BMI is not an accurate measure of metabolic risk for patients

with lipodystrophy. In particular, patients with generalised lipodystrophy typically have very low BMIs. In such cases, if the condition goes unrecognised, misleading dietary advice – where the emphasis is placed on weight gain – can worsen their metabolic complications.

The evidence base for the dietary management of patients with lipodystrophy is sparse due to the rarity of the condition. Advice is therefore based on the evidence for treating type 2 diabetes, obesity, cardiovascular disease and high triglycerides (Stears and Hames, 2014). Patients are assessed on an individual basis, taking into account their diagnosis, biochemical parameters and dietary history.

The general advice for all patients with lipodystrophy includes calorie and fat restriction (Brown et al, 2016). Fat intake (both saturated and unsaturated) is restricted, with the aim of reducing it to less than 20–30% of total energy intake. An accompanying increase in lean protein is advised to aid satiety. We also encourage the use of low-glycaemic-index carbohydrates to aid glycaemic control.

In general, weight loss is beneficial for all patients, and a 500–1000 kcal deficit in energy intake may be advised. Any increase in physical activity is promoted to maximise insulin sensitivity and aid weight loss. In our practice, we have observed that engaging in dietary management can reduce liver fat, improve metabolic parameters and help to reduce insulin dosing.

In cases where lipodystrophic patients have significantly elevated triglycerides, a strict fat restriction to less than 25 g per day is suggested, followed by a gradual reintroduction as tolerated. The lipase-inhibiting medication orlistat is sometimes useful for reducing the absorption of dietary fat.

Patients may also benefit from specialist weight loss services for support; however, access to such resources can be restricted to individuals above a certain BMI. Roux-en-Y gastric bypass surgery has been successfully utilised in a number of patients with lipodystrophy; in addition to weight loss, improvements have been observed in glycaemic control, non-alcoholic fatty liver disease and dyslipidaemia (Melvin et al, 2017). However, as with other weight management programmes, access to metabolic surgery is often restricted to individuals of a certain BMI.

A lack of adipose tissue for people with lipodystrophy can result in low levels of the adipose tissue-derived hormone leptin, which in turn can cause an increase in appetite and food intake (hyperphagia). This can greatly complicate dietary interventions. In certain cases, treatment with recombinant leptin therapy can reduce hyperphagia, allowing for improved metabolic control (Oral et al, 2002; Brown et al, 2016). The role of leptin in congenital generalised lipodystrophy is well established, with improvements seen in glycaemic control, hepatic steatosis and hypertriglyceridaemia (Brown et al, 2018). The role of leptin is less well established in patients with partial lipodystrophy and mild disease; however, for those with partial lipodystrophy and severe metabolic abnormalities, leptin has been shown to be an effective treatment (Diker-Cohen et al, 2015).

Pharmacotherapy in parallel with dietary intervention is also important in the management of diabetes and dyslipidaemia (Brown et al, 2016). Many patients who have severe insulin resistance associated with their lipodystrophy have very high exogenous insulin requirements. Both concentrated injectable insulins and continuous subcutaneous insulin infusion therapy have successfully been used to target hyperglycaemia in these patients.

For couples planning a pregnancy with a confirmed genetic cause of lipodystrophy, genetic counselling should be considered. This gives couples the opportunity to discuss the estimated risk to their unborn child of developing the disorder, and the options and indications for prenatal diagnosis (Harper, 2010).

For some people, the effects of lipodystrophy on appearance can lead to negative body image, so psychological support should be considered (Adams et al, 2018).

Conclusion

Although lipodystrophy is a rare disease, it should be considered in non-obese patients with difficult-to-control diabetes, fatty liver disease and raised triglyceride levels. Physical examination is a crucial part of diagnosis, so particular care should be given to examining the patient's fat distribution. Advice from and referral to specialists will aid diagnosis and provide access to appropriate treatments. ■

Page points

1. BMI is not an accurate measure of metabolic risk for patients with lipodystrophy, as they typically have low BMIs.
2. Dietary advice is based on the evidence for treating type 2 diabetes; a low-fat, low-glycaemic-index diet is advised, along with weight loss where appropriate and increased physical activity.
3. Specialist weight loss services or bariatric surgery may be helpful; however, these are often restricted to patients with higher BMIs.
4. Treatment with recombinant leptin therapy may help certain subtypes of lipodystrophy, and patients with severe insulin resistance may have very high exogenous insulin requirements.

"Although lipodystrophy is a rare disease, it should be considered in non-obese patients with difficult-to-control diabetes, fatty liver disease and raised triglyceride levels."

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