Clinical Lipidology

Diagnosis and management of lipodystrophy: a practical update

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Lipodystrophy is a group of rare conditions characterized by partial or complete loss of subcutaneous adipose tissue. Lipodystrophy is associated with metabolic derangements including severe insulin resistance, diabetes, hypertriglyceridemia, pancreatitis, nonalcoholic fatty liver disease and, in females, hyperandrogenism, polycystic ovarian syndrome and subfertility. The underlying cause may be genetic or acquired. Patients may present in childhood or adulthood. The diagnosis is frequently delayed, especially in partial lipodystrophy. Avoidance of excess dietary energy intake, despite the often lean appearance of the patient, is the current mainstay of treatment, aiming to avoid short- and long-term complications, while allowing normal growth in children. Early involvement of a specialized multidisciplinary team in the diagnosis and management of patients with lipodystrophy may enable evidence-based management guidelines to be developed. The timely diagnosis of lipodystrophy is becoming more important as novel treatment options such as recombinant methionyl human leptin therapy has recently been approved for use in some patients.

Keywords: adipose tissue • diabetes • diet • insulin resistance • lipodystrophy • metreleptin • multidisciplinary team • triglycerides

Lipodystrophy is a rare group of conditions characterized by partial or complete loss of subcutaneous adipose tissue. Although a minority of patients with lipodystrophy first present in infancy, the majority present in many other clinical settings. The aim of this review is to enable practicing clinicians in the diabetes, lipid, hepatology, dermatology and gynecology clinics, or in general practice, to recognize that a patient may have lipodystrophy, and to better understand the current clinical management options for these patients. The review will focus on the management of the metabolic sequelae in adult patients, but it is important to note that many of these patients present in childhood or adolescence and that the support needed by these patients goes beyond the problems caused by abnormal metabolism due to the cosmetic, psychological and reproductive implications of these rare conditions.

What is lipodystrophy?

Lipodystrophy is a rare group of conditions characterized by partial or complete loss of subcutaneous adipose tissue. The underlying cause may be genetic or acquired. Lipodystrophy is commonly but not always associated with metabolic derangements including severe insulin resistance, secondary diabetes, hypertriglyceridemia, pancreatitis, nonalcoholic fatty liver disease and, in females, hyperandrogenism, polycystic ovarian syndrome and subfertility. There is also an increased risk of premature cardiovascular disease. In addition to loss/absence of adipose tissue, patients are also affected by cosmetic manifestations of severe insulin resistance including acanthosis nigricans (Figure 1), skin tags, and, in females, features of hyperandrogenism including hirsutism and male-pattern hair loss. Some patients, especially those with generalized

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Figure 1. Examples of acanthosis nigricans (A & B) in the axilla and (C) on the nape of the neck.
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lipodystrophy, may also have musculoskeletal symptoms due to reduced intra-articular fat in joints. In some patients the underlying cause of lipodystrophy may cause other problems, for example cardiomyopathy in patients with a lamin mutation or renal disease in patients with acquired lipodystrophy. In the last 10–15 years much progress has been made identifying the molecular basis of the inherited lipodystrophies and this is the subject of previous reviews [1,2]; however the molecular basis of lipodystrophy in many patients remains to be discovered, especially in the group of patients with familial partial lipodystrophy type 1 (FPLD1) [3,4]. This current review will concentrate on the clinical recognition and management of patients with lipodystrophy rather than reviewing the underlying pathophysiology [2].

How is lipodystrophy classified?

Lipodystrophy is classified by the extent of fat loss (generalized or partial) and whether it is genetic or acquired. Further subcategorization may be made for the genetic lipodystrophies depending on the gene affected (Table 1). This general classification is a useful framework, but some patients do not fit as new genetic causes of lipodystrophy have recently been discovered, for example a mutation in the *c-fos* gene has been found in a single patient with congenital generalized lipodystrophy (CGL) who does not have any of the previously identified mutations for CGL [5], and in some patients, especially those with FPLD1, a syndrome that is likely to be relatively common [3,4], the genetic cause of lipodystrophy is yet to be identified. Lipodystrophy (partial or generalized) may also be present as a feature of a complex syndrome (Table 2). These very rare syndromes are associated with DNA repair defects and/or progeria (early aging) and include Werner syndrome, Hutchinson–Gilford progeria syndrome, mandibuloacral dysplasia (types A and B), SHORT syndrome (short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly and teething delay) and Bloom syndrome. It is also important to note that there is heterogeneity of fat loss in individuals with lipodystrophy, especially at initial presentation. An example is patients with *LMNA* mutations, who tend to lose subcutaneous peripheral fat at puberty. Also, the lipodystrophic phenotype may be less marked in males than females. Human immunodeficiency virus-associated lipodystrophy is categorized as an acquired partial lipodystrophy, but has a distinct clinical management approach.

How does a patient with lipodystrophy present clinically?

The most common first presentation of a patient with lipodystrophy depends on the subtype of lipodystrophy. While generalized lipodystrophy may be identified easily in neonates, the diagnosis of acquired lipodystrophy and familial partial lipodystrophy may be overlooked for many years, especially in men. A common presentation of women with partial lipodystrophy is young women presenting with hirsutism

and/or oligomenorrhea, or women presenting with difficult-to-control diabetes in pregnancy. Many of these patients have been attending diabetes clinics for a number of years before their lipodystrophy is identified. The American Association of Clinical Endocrinologists (AACE) recently developed consensus recommendations for the detection of lipodystrophy with the aim to improve the detection of all types of lipodystrophy [6]. They have developed a group of core characteristics that should alert a clinician to the possibility of a diagnosis of lipodystrophy (Box 1).

Congenital generalized lipodystrophy

Congenital generalized lipodystrophy (CGL) is a very rare autosomal recessive condition secondary to a mutation in the *AGPAT2*, *BSCL2*, caveolin 1 (*CAV1*) or polymerase-I-and-transcript release factor (*PTRF*) genes. Berardinelli [7] and Seip [8] first described CGL in 1954 and 1959, respectively, in patients now known to have a mutation in *BSCL2*. This form of CGL (Berardinelli–Seip syndrome), is now known as type 2 CGL, and CGL due to a mutation in *AGPAT2* is now known as type 1 CGL [9]. Individuals with CGL usually present at birth or in infancy with a near-total absence of body fat and prominent muscularity. The infant will often also have acanthosis nigricans, hepatomegaly and an umbilical hernia. The parents may describe that the child has a voracious appetite and may have abnormal 'food-seeking' behavior [10,11]. They may have accelerated growth and/or precocious puberty. They may have acanthosis nigricans at birth, or this may develop later. Secondary diabetes usually develops in childhood or adolescence. Hypertriglyceridemia is also common. Hepatic steatosis is usually present, which can progress to cirrhosis. Girls may have premature pubarche and menarche and may later develop clinical features of hyperandrogenism including hirsutism and clitoromegaly, and may have oligomenorrhea. Associated clinical features are hypertrophic cardiomyopathy, which may be severe [12], renal hypertrophy and mental retardation. Patients with type 2 CGL have the most severe form of lipodystrophy as they also have a lack of mechanical fat, for example, in joints, leading to musculoskeletal symptoms. Occasionally, boys with CGL may be diagnosed in early adulthood as boys sometimes have a less severe metabolic phenotype and their muscular appearance is thought to be normal.

Table 1. Classification of lipodystrophy with the eponymous name.

Classification	Inherited	Acquired
Generalized	CGL:	AGL:
	• CGL1, *AGPAT2* (AR)	• 'Lawrence'
	• CGL2/'Berardinelli–Seip', *BSCL2* (AR)	• Autoimmune (low C4)
	• CGL3, *CAV-1* (AR)	• Membranoproliferative glomerulonephritis (low C3-nephritic factor)
	• CGL4, *PTRF* (AR)	• Infections/panniculitis
Partial	FPL:	APL:
	• 'Dunnigan–Kobberling'	• 'Barraquer–Simons'
	• FPLD1/'Kobberling', genetic basis unknown	• Autoimmune (low C4)
	• FPLD2/'Dunnigan', *LMNA* (AD)	• Mesangioproliferative glomerulonephritis (low C3-nephritic factor)
	• FPLD3, *PPARγ* (AD)	• Infections/panniculitis
	• FPLD4, *PLIN1* (AD)	• HAART associated
	• FPLD5, *CIDEC* (AR)	• Autoinflammation, lipodystrophy and dermatosis syndrome *PSMB8* (AR)
	• *AKT2* (AD)	• Mutations in *LMNB2* have been associated with APL
	• *ZMPSTE24* (AR; with mandibuloacral dysplasia)	

The associated genetic mutation is stated where known. The pattern of inheritance is in parenthesis.
AD: Autosomal dominant; AGL: Acquired generalized lipodystrophy; APL: Acquired partial lipodystrophy; AR: Autosomal recessive; CGL: Congenital generalized lipodystrophy; FPLD: Familial partial lipodystrophy; HAART: Highly active antiretroviral therapy.

Table 2. Lipodystrophy as a feature of complex syndromes.

Syndrome	Gene	Clinical features
Werner syndrome	*RECQL2* (AR)	Variable partial loss of subcutaneous fat, premature aging, progeroid features, short stature, scleroderma-like skin changes, cataracts, premature greying of hair
Hutchinson–Gilford progeria syndrome	*LMNA* (AD)	Variable loss of subcutaneous fat progeroid features, short stature, low body weight, decreased joint mobility, osteolysis
Mandibuloacral dysplasia (type A)	*LMNA* (AR)	Loss of subcutaneous fat from extremities with normal or increased fat on neck and trunk, progeroid features in some patients, growth retardation, mandibular hypoplasia, osteolysis of the distal phalanges and clavicles, skin pigmentation
Mandibuloacral dysplasia (type B)	*ZMPSTE24* (AR)	Generalized lipodystrophy, progeroid features in some patients, growth retardation, mandibular hypoplasia, osteolysis of the distal phalanges and clavicles, skin pigmentation
Weidemann–Rautenstauch syndrome (neonatal progeroid)	Unknown (AR)	Generalized loss of body fat and muscle mass and progeroid appearance at birth
SHORT syndrome	*PIK3R1* (AD)	Variable partial loss of subcutaneous fat short stature, hyerextensibility, ocular depression, Rieger anomaly, teething delay
Bloom syndrome	*RECQ2* (AR)	Variable partial loss of subcutaneous fat, growth retardation, skin abnormalities (sun sensitivity, telangiectasia, hypo- and hyper-pigmentation), predisposition to malignancy

AD: Autosomal dominant; AR: Autosomal recessive; SHORT: Short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly and teething delay.

Acquired generalized lipodystrophy

Acquired generalized lipodystrophy (AGL; Lawrence syndrome) may present in childhood or adulthood. Patients with AGL have normal fat distribution at birth but progressively lose fat over a period of months to years, usually from the face and upper limbs first (Figure 2). In some patients the loss of fat is preceded by the development of a panniculitis, an inf ammation of the subcutaneous fat with nodule development, and is then followed by a generalized loss of subcutaneous fat. AGL may be associated with autoimmune conditions such as dermatomyositis, autoimmune hepatitis and mesangiocapillary glomerulonephritis, or malignancy such as lymphoma, and so an underlying cause should be suspected in patients with AGL [13]. It is sometimes difficult to distinguish AGL from cachexia due to another illness such as malignancy or uncontrolled diabetes. AGL should be considered in patients with difficult-to-manage diabetes and weight loss, where there is coexistent insulin resistance, severe hypertriglyceridemia and/or pancreatitis, especially when compliance with insulin therapy is good. Intraabdominal fat stores are usually maintained/increased in AGL, but reduced in undernutrition [14].

Familial partial lipodystrophy

Familial partial lipodystrophy (FPLD) usually has an autosomal dominant pattern of inheritance. A number of mutations have been found to be causative, including in the *LMNA*, *PPARγ*, cell-death-inducing DNA fragmentation factor a-like effector c (*CIDEC*) and *PLIN1* genes. Current clinical classification categorizes FPLD into one of five main types of FPLD (types 1–5) based on the genetic cause (Table 1). The classical pattern of fat loss also tends to vary according to the genetic diagnosis (Figure 3). Patients with FPLD1 (Kobberling syndrome; genetic basis unknown) classically present with a loss of gluteal and limb fat, but increased subcutaneous abdominal fat (Figure 3A). FPLD1 is likely to be relatively common and the diagnosis in patients attending diabetes clinics is probably frequently overlooked, as it is only by examining the patient in their underwear that the paucity of subcutaneous fat on the buttocks and legs is noticed. These patients often have severe insulin resistance and poorly controlled diabetes and triglycerides, yet the therapeutic options for them are currently limited in general diabetes clinics as most FPLD1 patients do not qualify for therapies such as GLP-1 agonists and weight loss programs.

Patients do not qualify as their body mass index (BMI) often only falls into the 'overweight' or 'obese' (25–35 kg/m^2) rather than the 'morbidly obese' (>40 kg/m^2) range [3,4]. Patients with FPLD2 (Dunnigan syndrome), which is secondary to a mutation in *LMNA*, usually present in early adulthood with loss of gluteal, abdominal and limb fat and an increase in facial, labial and neck fat (Figure 3B). Patients with FPLD1 and FPLD2 usually have normal fat distribution in childhood, but at around the time of puberty start to lose subcutaneous adipose tissue from the legs and arms. This fat loss is often very apparent in the gluteal region. Some patients accumulate fat on the face and neck and therefore have a 'cushingoid' appearance. Patients with FPLD2 usually have loss of subcutaneous abdominal adipose tissue, but abdominal distension due to accumulation of intra-abdominal fat, whereas patients with FPLD1 have accumulation of both subcutaneous and intra-abdominal abdominal adipose tissue. Male patients with FPLD2 often remain undiagnosed except through family screening as the clinical phenotype can be very subtle. Patients with FPLD3 secondary to mutation in *PPARγ* often have a very subtle phenotype of lipodystrophy, even in adulthood, with some loss of gluteal and lower limb fat (Figure 3C). These patients are more likely to present with metabolic problems, for example, severe hypertriglyceridemia with eruptive xanthomata. Young women with FPLD may present with symptoms of hyperandrogenism, including hirsutism and oligomenorrhea or with difficult-to-manage gestational diabetes, but the diagnosis may be overlooked for many years, especially in men. This is partly because a muscular appearance is normal in men and also because some, but not all, forms of lipodystrophy have less marked physical and metabolic effects in men [15]. Most, but not all, patients also have acanthosis nigricans (Figure 3A–C). It is extremely important to fully undress and examine all patients first presenting to lipid and diabetes clinics otherwise the opportunity to diagnose FPLD may be missed. Some patients with FPLD2 may develop cardiac consequences including cardiomyopathy and cardiac rhythm disturbances, thus a full physical examination is important, and echocardiography and a baseline electrocardiogram are recommended [16].

Acquired partial lipodystrophy

Acquired partial lipodystrophy (APL; Barraquer–Simons syndrome) is characterized by a progressive loss of adipose tissue – usually in a cephalocaudal fashion – with loss of fat from the face, neck and arms and usually with sparing of the lower trunk and legs. This usually presents in childhood or adolescence, but may present in adulthood. There may be excess fat accu-

Box 1. Clinical characteristics in patients that increase the suspicion of lipodystrophy.

Core clinical characteristic for lipodystrophy
- Loss or absence of subcutaneous body fat in a partial or generalized fashion

Core clinical characteristic for familial partial lipodystrophy
- Loss of subcutaneous body fat, typically occurring around or shortly after puberty, occurring in the extremities and/or gluteal region with sparing of fat loss or accumulation of excess fat in the face and neck or intra-abdominal area.

Presence of diabetes with evidence of severe insulin resistance
- Diabetes mellitus with requirement for high doses of insulin; for example, requiring ≥200 units/day, ≥2 units/kg/day, or currently taking U-500 insulin
- Ketosis-resistant diabetes

Other evidence of severe insulin resistance
- Acanthosis nigricans
- Polycystic ovaries syndrome (PCOS) or PCOS-like symptoms (hyperandrogenism, oligomenorrhea and/or polycystic ovaries)

Presence of hypertriglyceridemia
- Severe hypertriglyceridemia (>6.0 mmol/l)
- Triglyceride levels that are nonresponsive to therapy and/or modifications of diet (≥3.0 mmol/l)
- History of pancreatitis associated with hypertriglyceridemia

Evidence of hepatic steatosis or steatohepatitis
- Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease
- Radiographic evidence of hepatic steatosis (e.g., on ultrasound or CT)

Other
- Family history of similar physical appearance and/or history of fat loss
- Prominent muscularity and enlarged veins in the extremities
- Disproportionate hyperphagia (cannot stop eating, waking up to eat, fighting for food)
- Secondary hypogonadism in a male, or primary/secondary amenorrhea in a female patient

Adapted with permission from [6].

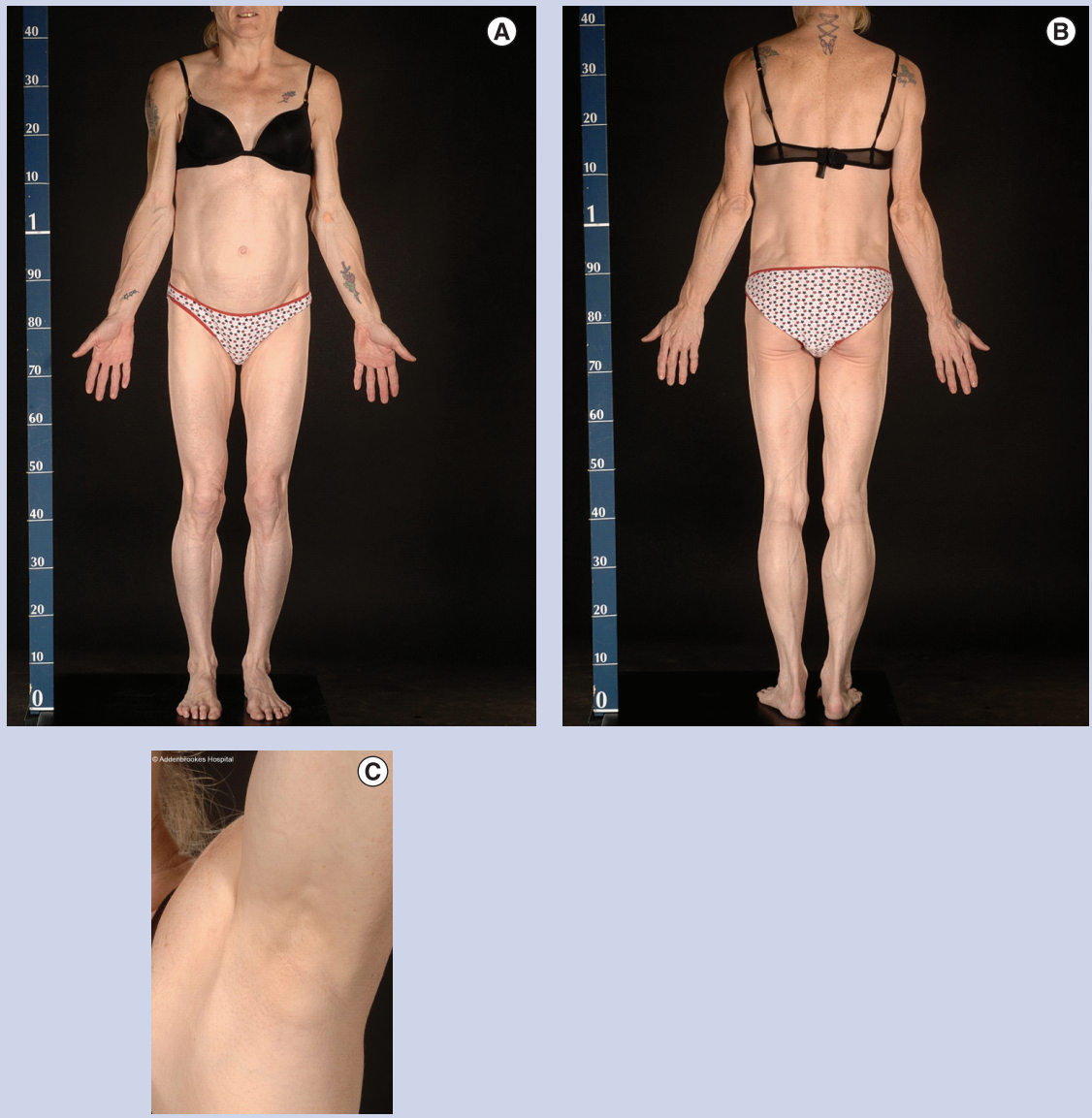

Figure 2. Female patient with acquired generalized lipodystrophy (A & B); note the absence of acanthosis nigricans (C). This patient has pancreatic beta cell failure and a low insulin concentration secondary to recurrent hypertriglyceridemia induced pancreatitis.
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mulation in the legs, gluteal region and lower abdomen. These patients often have a normal metabolic phenotype. APL is sometimes associated with mesangiocapillary glomerulonephritis, autoimmune diseases such as systemic lupus erythematosis and dermatomyositis, and autoimmune hepatic disease, and many patients have abnormalities in complement levels (low C3 and/or C4) and may have a positive C3 nephritic factor [13,17]. APL can also occur in association with an inf ammatory panniculitis as part of an inf ammatory or connective tissue disorder [18,19], or can be the presenting feature of lymphoma [20], and it is important that appropriate clinical history, examination and investigations are performed to exclude these diagnoses in patients presenting with APL.

HIV-associated lipodystrophy

HIV-associated lipodystrophy usually develops in patients receiving highly active antiretroviral therapy (HAART)-containing protease inhibitor or nucleoside reverse transcriptase inhibitors. Patients usually lose adipose tissue from their face, arms and legs and accumulate subcutaneous fat on their neck (buffalo hump) and abdomen. Most patients develop hypertriglyceridemia but not all develop diabetes [1,21,22]. HIV-associated lipodystrophy is discussed in more detail later in this review.

Localized lipodystrophy

Small local areas of lipodystrophy, or lipoatrophy, can develop as a consequence of a localized panniculitis or following the injection of drugs, most commonly insulin. If these sites are avoided for any future injections, and there is no progression of the lipoatrophy with time, this is not associated with any systemic metabolic sequelae and patients can be reassured.

What is the optimum approach to metabolic management in patients with lipodystrophy?

Management of patients with lipodystrophy is complex and should ideally be performed by a multidisciplinary team with specialist expertise in adult and pediatric lipodystrophy and diabetes/lipid management, and with good access to support from other services

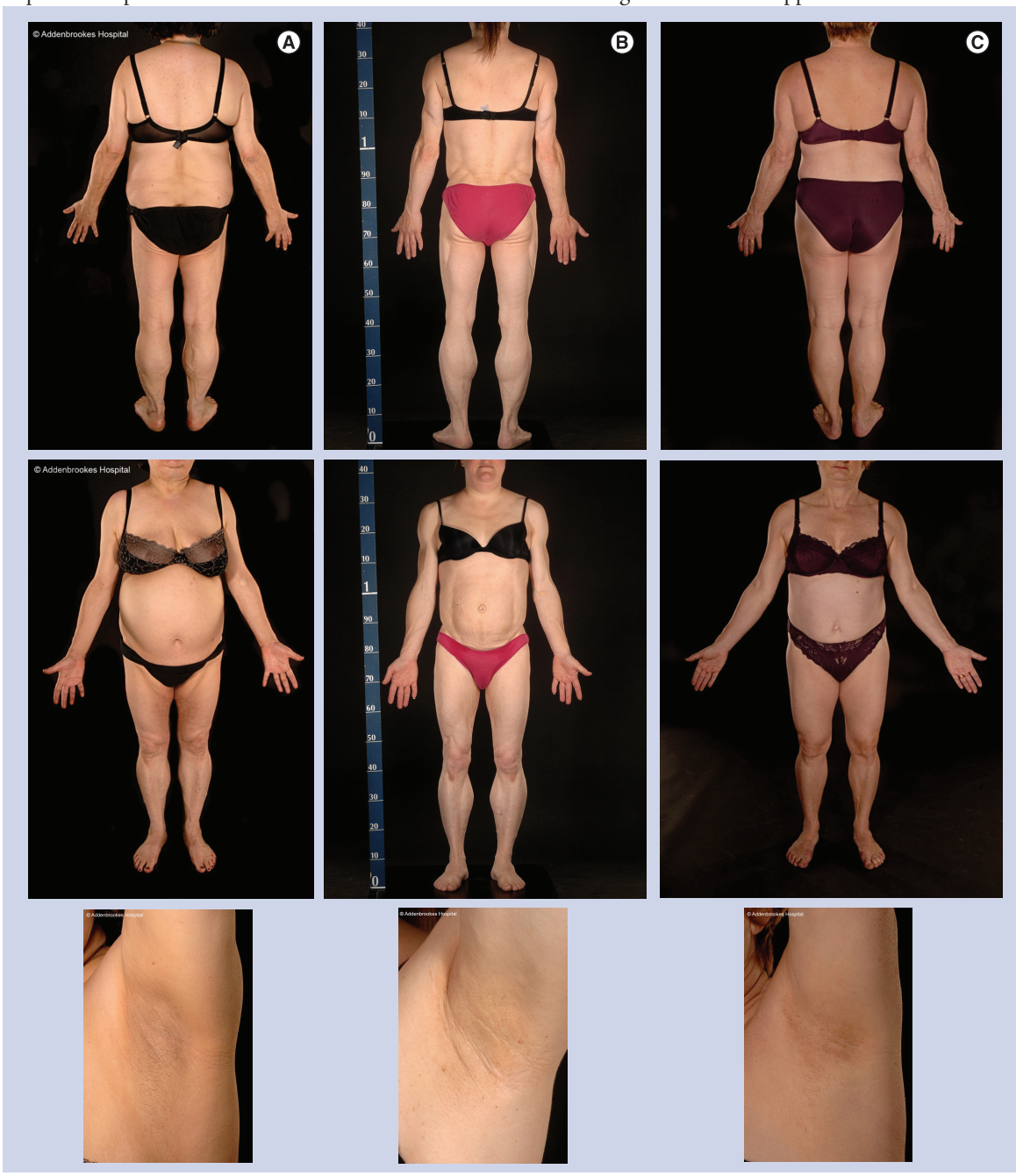

Figure 3. Female patients with different subtypes of familial partial lipodystrophy. Shows the typical phenotypes of **(A)** familial partial lipodystrophy (FPLD) type 1, genetic cause unknown, **(B)** FPLD type 2, secondary to a mutation in *LMNA* and **(C)** FPLD type 3, secondary to a mutation in *PPARG*. All three patients have axillary acanthosis nigricans as shown in the bottom panel.
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including genetics, hepatology, plastic surgery, dermatology, psychology, gynecology/fertility, obstetrics and bariatric surgery. This review will concentrate on management of the metabolic consequences of lipodystrophy, but this should not undermine the importance of the other aspects of management, especially the psychological impact of the cosmetic appearance of lipodystrophy.

Restriction of dietary energy intake in the treatment of lipodystrophy

Many patients with lipodystrophy have reduced capacity to store excess dietary fat in the peripheral limb/gluteal subcutaneous adipose tissue stores and, therefore, store excess dietary fat ectopically in liver and muscle. This both exacerbates insulin resistance and can lead to local tissue abnormalities including steatohepatitis, cirrhosis and hepatocellular carcinoma. Elevated circulating triglycerides can also cause pancreatitis. Savage *et al.* [23] showed that in patients with lipodystrophy who were fed a high-fat load, there was a significant increase in the blood glucose concentration compared with controls and an increase in mean triglycerides from 2.9 to 6.8 mmol/l, accounted for mainly by a rise of 4.5 to 30.8 mmol/l in one subject with a *PPARγ* mutation. There was no change in triglyceride concentration seen in the control subjects. The basal metabolic rate was not different between lipodystrophy patients and control subjects when adjusted for lean mass, similar to previous studies [24]; however, in the patients with lipodystrophy the total daily energy expenditure increased after the fat load, mainly due to increased fat oxidation, compared with control subjects. These findings support the view that diets high in fat should be avoided in patients with lipodystrophy due to possible acute and chronic metabolic sequelae. Many patients, especially those with generalized lipodystrophy, encounter difficulties adhering to dietary guidance due to hyperphagia secondary to leptin deficiency [25,26]. Data from patients with generalized lipodystrophy treated for 12 months with recombinant methionyl human leptin (metreleptin) therapy showed that the patients reported a dramatic reduction in appetite with associated reductions in weight, percentage body fat, significant improvement in triglyceride and glucose concentrations and reduction in liver volume [27]. Metreleptin therapy is discussed in more detail later in this review. These data further indirectly suggests that a reduction in dietary energy content, or at least limiting energy intake only to that which is needed on a daily basis (allowing for growth in children), appears to be a logical intervention that is likely to be beneficial in patients with lipodystrophy. However, there are no published dietary guidelines available for patients with lipodystrophy and very little published literature on the outcomes of dietary manipulation in patients with lipodystrophy. It is also unclear whether the same dietary intervention should be advised in patients with different types of lipodystrophy. More research is also needed into the optimum dietary composition in these patients, especially in children.

Dietary manipulation: using other metabolic diagnoses as a model for treating patients with lipodystrophy

Low-fat diet in patients with familial hyperchylomicronemia

Dietary fat content usually varies between 20 and 200 g/day. If a bolus of fat of 85 g is eaten, with complete absorption, the increase in plasma triglyceride concentration will be 33 mmol/l if no clearance occurs [28]. There are no published data in patients with lipodystrophy on the clinical outcomes of diets containing different fat content, however, in the case of familial chylomicronemia, in which hypertriglyceridemia-induced pancreatitis causes failure to thrive due to exocrine and endocrine failure of the pancreas, there is a significant response to a low-fat diet that usually consists of a maximum of 10–15% of the daily caloric intake from fat, with reductions in saturated and trans fats. For an adult with lipoprotein lipase deficiency, restricting the intake of dietary fat to 25 g daily will usually prevent recurrent pancreatitis. Infants and children who are advised a very low fat diet need input from a specialist dietitian to ensure optimal energy supply for growth, as well as complete fulfilment of essential fatty acid requirements.

Low calorie diets in patients with Type 2 diabetes

Despite the relative paucity of data regarding dietary intervention in patients with lipodystrophy, there is a growing body of evidence that in patients with Type 2 diabetes, caloric restriction by various approaches, including bariatric surgery, diet and pharmaceutical intervention, improves glycemic control, reduces ectopic lipid deposition and improves insulin sensitivity. Some of these data are important in the proof-of-principle that these interventions may be of benefit in patients with lipodystrophy, and are therefore reviewed below. A recent 8-week pilot study of the metabolic effects of a 600 kcal/day liquid diet in 11 patients with Type 2 diabetes, reported that within 7 days of starting the diet, plasma glucose normalized and liver fat decreased by 30%. There was also an improvement in the first phase of the insulin response and a decrease in pancreatic fat. There was a mean weight loss of 15 kg [29]. The Diabetes Remission Clin-

ical Trial (DIRECT) will have a similar protocol in 240 patients over a 2-year period to investigate whether these metabolic improvements and adherence to the liquid diet are sustainable [30]. In an earlier study, eight obese patients with Type 2 diabetes were studied before and after weight stabilization on a moderately hypocaloric 3% fat (very low-fat) diet. There was a weight loss of 8 kg, normalization of fasting plasma glucose and rate of hepatic basal glucose production, and an 81% reduction in intrahepatic lipid [31]. Finally, a study of low calorie diet in patients with Type 2 diabetes pre-bariatric surgery showed that in 29 out of 51 patients there was a ≥50% reduction in total insulin dosage within 10 days of beginning the low-calorie diet, and that this response predicted early remission of diabetes post-operatively [32]. In addition to its affect on blood glucose, reduction in dietary energy intake also affects the circulating triglyceride concentration and triglyceride content in liver and muscle.

Bariatric surgery

Evidence of the effectiveness of bariatric surgery as a treatment for Type 2 diabetes was first provided by a 14-year study of 608 morbidly obese patients who underwent Roux-en-Y gastric bypass (RYGB). 82.9% of patients with Type 2 diabetes maintained normal levels of plasma glucose, HbA1c, and insulin over the follow-up period [33]. The RYGB operation restricts caloric intake by reducing the stomach capacity to around 30 ml, delays gastric emptying with a narrowed gastric outlet, and bypasses the foregut with a Roux-en-Y gastrojejunostomy. The mechanism underlying improvement in glycemic control remains controversial and may include caloric reduction, an effect on incretin hormones, or a combination of both [34]. There are now several different bariatric surgical techniques in use. The most common procedures are RYGB, adjustable gastric banding and sleeve gastrectomy. These procedures can all be performed laparoscopically and the complication rates are low [35]. The majority of patients with lipodystrophy have a BMI in the normal range, with few reaching the current UK referral criteria for access to obesity services or for bariatric surgical services [36]. However, studies in patients with diabetes and a BMI <35 kg/m^2 have shown metabolic benefit. In a study of 62 patients with Type 2 diabetes and a BMI <35 kg/m^2, at 12 months post-gastric bypass mean BMI had fallen from 30.1 to 22.6 kg/m^2, mean HbA1c from 9.7 to 5.8%, and there was remission of diabetes in 57% of the patients [37]. A recent meta-analysis of 13 trials involving 357 patients looking at the metabolic effects of bariatric surgery in Type 2 diabetic patients with a BMI <35 kg/m^2, showed that post-operatively 80.0% of the patients achieved good glycemic control (HbA1c <7%) without glucose-lowering medication. The surgery also had a low incidence of major complications (3.2%) and no mortality [38]. There are no controlled trials examining bariatric surgery outcomes in patients with lipodystrophy, but there are several case reports with positive outcomes. All cases describe the outcomes of RYGB in female patients with partial lipodystrophy (Table 3) [39–41]. All patients had a BMI <35 kg/m^2, and all had secondary diabetes. One patient had a *LMNA* mutation (*FPLD2*) and two were without a genetic diagnosis (probably FPLD1). All cases were able to markedly reduce diabetes therapy after RYGB surgery. In our own service a 44 year old female patient with FPLD1 had successful RYGB surgery 11 months ago and has now been able to stop all insulin therapy and has well-controlled diabetes and a normal lipid profile. Her weight reduced from 81.9 to 63.5 kg, and her BMI reduced from 33.2 to 25.0 kg/m^2 with a reduction in HbA1c from 114 (12.6%) to 50 mmol/mol (7.0%). There was also a reduction in percent body fat from 37.0 to 24.6% (Figure 4). In the UK, access to bariatric surgery for patients with Type 2 diabetes remains limited, especially in patients with BMI <35 kg/m^2, due to cost, the limited supply of surgical specialists and the perceived problems with complications despite good evidence of safety and efficacy [42]. The current National Institute for Clinical Excellence (NICE) criteria for bariatric surgery stipulate that "*Bariatric surgery is recommended as a treatment option for people with obesity if they have a BMI of >40 kg/m^2, or 35–40 kg/m^{2}and other significant disease that could be improved if they lost weight*" [36].

Physical activity

Physical activity is also central to improving insulin sensitivity and metabolic control in patients with Type 2 diabetes, but there are no controlled trial data in patients with lipodystrophy, except for some limited data showing benefit in individuals with HIV-related lipodystrophy [43,44].

An approach to dietary management

There is no established evidence base for the dietary management of patients with lipodystrophy and our clinical service continues to develop and collect evidence over time. A specialist adult dietitian is therefore a key member of our multidisciplinary team. Within our clinic adult patients are all seen individually by a specialist diabetes dietitian at each clinic appointment. The advice given by the dietitian will vary dependent on the diagnosis of the patient. Children should only be managed by an appropriately trained pediatric dietitian. Weight, BMI and waist and hip circumference are measured at each appointment. All

Table 3. Outcomes of Roux-en-Y gastric bypass surgery in female patients with partial lipodystrophy.

Study (year)	Patient	Pre-op		Post-op	
		BMI (kg/m^2)	Metabolic status	BMI (kg/m^2)	Metabolic status
McGrath (2006); Obesity Surgery [39]	41-year-old female, partial LD (cause unknown)	29.0	500 units insulin, ↑↑Tg, pancreatitis, PCOS, infertility	26.6	At 8 months post-op, HbA1c 7.0%, off insulin, then successful pregnancy
Utzschneider (2006); Diabetes Care [40]	55-year-old female, partial LD	33.1	300 units insulin, ↑↑Tg (39 mmol/l), recurrent pancreatitis	23.2	At 16 months post-op diabetes and lipids well controlled off all medication
Ciudin A (2011); Clinical Endocrinology [41]	28-year-old female, FPLD2 (*LMNA* mutation)	31.7	Metformin, rosiglitazone, fenofibrate, ↑Tg	20.2	At 12 months post-op diabetes and lipids well controlled off all medication
Patient attending National Severe Insulin Resistance Service, Cambridge [Stears A, Unpublished Data]	44-year-old female, FPLD1	33.2	Levemir 60 units bd, liraglutide, simvastatin 1.2 mg od, very poor glycemic control, HbA1c 114 mmol/mol (12.6%)	25.0	At 11 months post-op, HbA1c 50 mmol/mol (7.0%) on metformin alone

FPLD: Familial partial lipodystrophy; LD: Lipodystrophy; op: Operative; PCOS: Polycystic ovary syndrome; Tg: Triglyceride concentration.

patients have an initial assessment to gain insight into their knowledge of dietary treatments/current dietary habits. Patients are then asked to complete a food and activity diary. We encourage a 7-day detailed diary, including where possible weights of foods alongside any other specific nutritional information available. Hunger levels are recorded on a scale of 1–5 (1 = low and 5 = high) and mood is also recorded. We may also request blood glucose readings and insulin doses for those patients who may benefit from carbohydrate counting. The completed diary is then assessed by the dietitian. Nutritional requirements are usually calculated for individual patients using the Henry Equation [45]. A calorie reduction of 500–1000 Kcals a day will be suggested to aid weight/fat loss if required. When applying this dietary approach to patients with lipodystrophy, it is important to note that patients with lipodystrophy have an increased energy expenditure when based on their bodyweight, for which an increased muscle mass is likely to be a key, but perhaps not the sole contributor, and this needs to be taken into account when estimating energy requirements [23,24,46]. Some patients have problems with fasting and postprandial hypoglycemia due to hyperinsulinemia, and may benefit from advice encouraging ingestion of food containing low glycemic index carbohydrates [47]. The patients are followed-up regularly in the clinic with repeat anthropometry and biochemistry. For all patients and families of children with lipodystrophy, regular dietetic follow-up by email and/or telephone is offered to promote motivation.

Generalized lipodystrophy

Patients with generalized lipodystrophy are generally the most difficult patients to manage from a dietary perspective. Patients appear lean due to their complete absence of fat, and leptin-deficiency promotes hyperphagia and food-seeking behavior, especially in children [10,11,25]. They may be considered to appear 'malnourished' by a dietitian or other healthcare professional. For example, two patients with generalized lipodystrophy who attend our clinic have BMIs of 13.0 and 16.0 kg/m^2, respectively (healthy adult range 18.5–25.0 kg/m^2). These patients are often keen to gain weight due to their cosmetic appearance. A number of our patients have been previously provided with advice regarding weight gain/nutritional (high-energy) supplement drinks on prescription by dietitians or other healthcare professionals. This is inappropriate advice as due to inability to store fat these patients will all require a diet very low in fat irrespective of their weight. Excess calorie intake especially with dietary fat will raise triglycerides and therefore increase risk of pancreatitis. Dietary input will is individualized depending on the patient's current metabolic control and also the age of the patient. In adults, if a patient is found to have raised triglycerides, a daily restriction of 25 g fat is recommended until levels have reduced. Written guidance is provided. Otherwise, we aim to reduce fat (of any source, unsaturated and saturated fat) along with carbohydrate intake (specifically refined carbohydrate). Increasing lean protein intake to provide 20–25% of daily intake, for

example with skinless chicken, white fish, beans and pulses, aids satiety. We encourage low glycemic index carbohydrate, for example sweet potato, boiled potatoes, basmati rice, granary bread and lentils, to help avoid postprandial hyper- or hypo-glycemia. If the patient has diabetes then they will be advised appropriate carbohydrate restrictions, which are dependent upon their weight and blood sugar control. We do not use specific targets for fat intake, but lowering dietary fat as much as possible while ensuring the diet is palatable and patients are able to adhere. If patients are able to tolerate a very low fat diet (less than 15% of total calories) then we would encourage an essential fatty acid supplement, such as walnut oil. It is important to also ensure a small amount of oily fish in the diet, or supplements for fat-soluble vitamins. Many patients are unable to sustain this low level of dietary fat intake long term and ongoing support and advice is

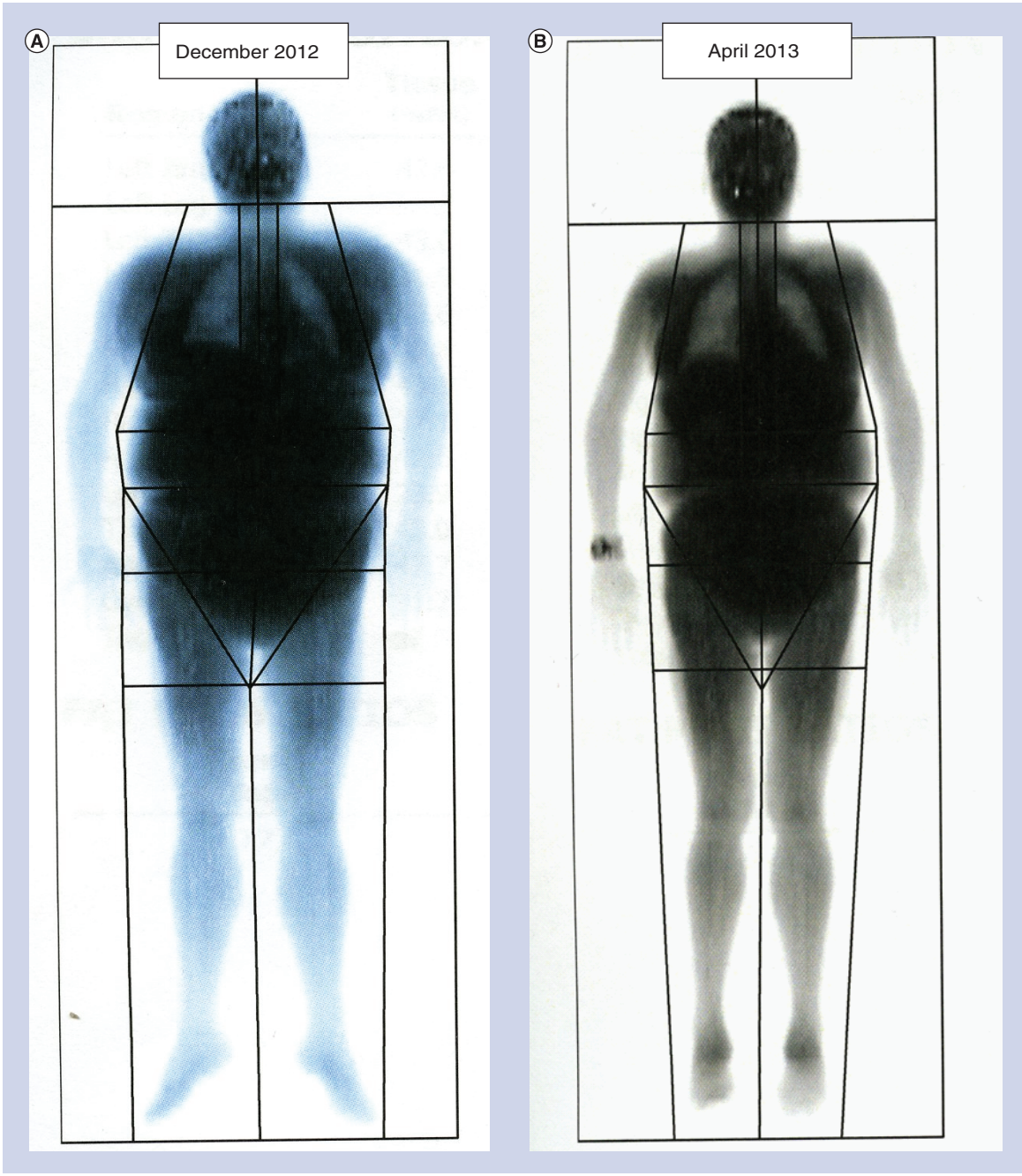

Figure 4. Dual-energy x-ray absorptiometry scan: body fat distribution in a patient with familial partial lipodystrophy type 1 (A) pre and (B) 4 months post Roux en-Y gastric bypass surgery. Note marked reduction of abdominal fat post surgery.

essential [48]. A micronutrient profile can be completed on patients if there is a concern over the nutritional adequacy of the diet. Practical tools include written material on reading food labels, lists of snack and meal ideas, carbohydrate counting, recipes and online food and activity diaries and/or apps. In children, dietary restriction needs to be carefully balanced with energy requirements for growth and regular follow-up with repeated anthropometry is required.

Partial lipodystrophy

The approach to dietary management in adult patients with partial lipodystrophy is similar to that used for patients with generalized lipodystrophy. Many patients with partial lipodystrophy have central obesity and they therefore often tend to be more motivated to lose weight. Again, the aim of treatment is to keep as lean as possible to aid blood glucose and lipid control. In our clinic partial or complete meal replacements have been used to aid weight loss, similar to those used successfully in obese patients. Patients are referred to obesity clinics in their local area if required. Exceptional funding may be required as often referral criteria specify a BMI of greater than 35 kg/m^2. As patients are often centrally obese, waist and hip measurements are often more useful than BMI as many patients will have a BMI within normal ranges but a high waist to hip ratio. Abdominal obesity is defined as a waist–hip ratio above 0.90 for males and above 0.85 for females. In children, once again dietary restriction needs to be carefully balanced with energy requirements for growth and regular follow-up with repeated anthropometry is required.

Pharmaceutical therapies used to lower energy intake

Leptin

Leptin (from the Greek word leptos, meaning thin) is a 16 kDa 167 amino acid secreted protein. It was first described in 1995, following the identification of the mouse leptin (ob) gene in 1994 [49–52]. Leptin is mainly produced by adipose tissue, but is also expressed in the mammary gland, testes, ovary, endometrium, stomach, hypothalamus, pituitary and placenta. Leptin signals the status of body energy reserves in adipose tissue to the brain and other tissues so that changes in food intake and energy expenditure can occur in order to regulate energy balance. Circulating leptin levels are directly proportional to the amount of body fat [53]. Subcutaneous fat expresses more leptin mRNA than visceral fat. Leptin levels fall with restriction of food intake and with weight loss, and this fall is associated with increased appetite and decreased energy expenditure. Women have higher leptin concentrations than men, independent of BMI. This is likely to be is secondary to differences in fat mass, body fat distribution and sex hormones. Leptin expression and secretion are increased by insulin and glucocorticoids, and decreased by beta 3-adrenergic activity, androgens, free fatty acids, growth hormone and peroxisome proliferator-activated receptor-γ (PPARγ) agonists. In both rodent models and in humans, leptin deficiency is associated with hyperphagia and obesity.Treatment with recombinant leptin has been successful in obese children with leptin deficiency [54]. In patients with lipodystrophy, low circulating leptin concentrations are common due to reduced fat mass.

Clinical trials of recombinant methionyl human leptin therapy in patients with lipodystrophy

There are data from several open-label trials demonstrating metabolic benefits from the administration of recombinant methionyl human leptin (metreleptin) therapy in both generalized and partial lipodystrophy, and limited data on the treatment of HAART-induced lipodystrophy in HIV-positive patients [55–57]. The most convincing benefit from metreleptin therapy is in patients with generalized lipodystrophy. An open-label pilot study in nine female patients with lipodystrophy (three with AGL, five with CGL and one with FPL) with severe metabolic abnormalities conducted at the NIH showed that administration of metreleptin subcutaneously twice a day for 4 months resulted in marked improvements in hypertriglyceridemia and/or hyperglycemia. There was a 60% decrease in mean triglyceride concentration ($p < 0.001$) and an absolute decrease in HbA1c of 1.9% ($p = 0.001$) in the eight patients with diabetes. There was also a significant reduction in liver volume [58]. On the basis of these initial results, an open-ended, open-label study of leptin treatment in patients with lipodystrophy was initiated in August 2000 at the NIH to examine the long-term safety and clinical effects of metreleptin treatment in patients over 5 years of age with lipodystrophy (excluding patients with HIV-associated lipodystrophy). The study population consisted of patients with acquired or inherited lipodystrophy who had at least one of diabetes mellitus, insulin resistance (fasting insulin level >30 μIU/ml), and hypertri-glyceridemia, and a fasting leptin level of <8.0 ng/ml (males) and <12.0 ng/ml (females). A recent publication presents data for the first 3 years of metreleptin treat-ment in this population [55]. Some of the patients had received treatment for over 3 years (maximum of 9 years). In the overall population metreleptin treatment led to reductions in HbA1c of -2.1% ± 0.5% (95% CI: -3.2 to -1.1%) and a mean percentage reduction in serum triglyceride of -36.7% ± 6.4% (95% CI: -49.7 to -23.7%) at 3 years.

There was also a significant reduction in liver transaminases with the change from baseline ALT concentrations of -45 ± 19 U/l (95% CI: -86 to -4 U/l) after 3 years of metreleptin treat-ment (n = 19). No subgroup ana-lysis was reported for different types of lipodystrophy. Adverse events related to metreleptin were reported in 31% of patients included fatigue, hypoglycemia, alopecia and weight decrease. Injection-site adverse events were observed in two patients. Other adverse events of included T-cell lymphoma, which was reported in two patients with acquired lipodystrophy, both of whom had immu-nodeficiency and abnormal bone marrow biopsy specimens at baseline.

Efficacy of metreleptin therapy in different types of lipodystrophy

An earlier ana-lysis of the above NIH study reported responses in 48 patients treated with metreleptin who were grouped according to lipodystrophy type (12 acquired, 13 AGPAT2, seven siepin, nine LMNA, two PPARγ, four unknown) [59]. The metabolic response to metreleptin was compared between patients with different types of lipodystrophy in the 35 patients with data at baseline and at 12 months. All patients with acquired lipodystrophy had a large reduction in serum triglyceride and all had a reduction in HbA1c from baseline. In the patients with CGL, patients with a *SEIPIN* mutation were found to have lower levels of serum triglyceride at baseline compared with *AGPAT* mutation patients. 11 out of 12 patients with an *AGPAT2* mutation had a decrease in serum triglyceride, and four out of six*SEIPIN* patients had a decrease in their serum triglyceride with 12 months metreleptin therapy. HbA1c values in the *SEIPIN* patients at baseline had a distribution similar to that of *AGPAT2* patients. Eleven out of 12 *AGPAT2* patients had a decrease in HbA1c after 12 months of metreleptin treatment and four out of six*SEIPIN* patients had a decrease in HbA1c. In the patients with partial lipodystrophy, a reduction in serum triglyceride was seen in all *LMNA* (FPLD2) patients after 12 months of metreleptin therapy and five out of six*LMNA* patients showed a decrease in HbA1c over 12 months. In the two *PPARγ* (FPLD3) patients, one had a 53% decrease and the other had a 32% increase in serum triglyceride and both showed a decrease in HbA1c over 12 months [59]. Another smaller open-label study did not find any significant reduction in HbA1c in FPLD2 patients, although there was a reduction in triglycerides [57]. In another open-label study their was a response to metreleptin in studies over 6 months in 24 FPLD2 patients according to their baseline leptin concentration. This study showed that metreleptin therapy was equally effective in reducing circulating and hepatic triglyceride in FPLD2 patients with both severe and moderate hypoleptinemia, but did not improve hyperglycemia in either group [60].

Leptin therapy & nonalcoholic fatty liver disease

Another area of potential benefit of metreleptin therapy is in the treatment of nonalcoholic fatty liver disease. This was studied as part of the above open-label, prospective NIH study of leptin therapy in patients with inherited and acquired lipodystrophy [55,58]. Liver biopsies were performed at baseline and after about 6 months of leptin (n = 27). NASH activity was assessed using the NASH Clinical Research Network (CRN) scoring system. 86% of patients had NASH at baseline, falling to 33% (p = 0.0003) with leptin therapy. There were significant improvements in steatosis grade, ballooning injury scores and mean NAFLD activity score (p < 0.0001). Patients with established hepatic fibrosis remained stable on metreleptin therapy [61].

Potential mechanisms of action underlying the metabolic effects of leptin in patients with lipodystrophy

The most likely key mechanism of action of leptin is reduction in the hyperphagia that is widely believed to occur due to leptin deficiency. A recent study using functional magnetic resonance imaging ana-lysis of food-related brain activity demonstrated insufficiency of postprandial suppression of food-related satiety in patients with lipodystrophy compared with healthy control subjects, which was restored by leptin therapy [25]. Another study evaluated 14 patients with lipodystrophy at baseline and after 4 and 12 months of leptin therapy. All patients reported a decrease in appetite on therapy. After 4 months, both daily caloric intake and resting energy expenditure decreased and dual energy x-ray absorptiometry (DXA) demonstrated significant decreases in fat mass and lean body mass. The changes were sustained at 12 months follow-up [62]. A further study also demonstrated that leptin therapy improved both satiety time and satiation in patients with lipodystrophy [26]. In human studies, leptin has been shown to improve insulin suppression of glucose production by the liver and to increase insulin-stimulated uptake of glucose by skeletal muscle in patients with lipodystrophy [63]. A study in rodents showed that leptin stimulates fatty acid oxidation by activating AMP-activated protein kinase (AMPK) [64] and a study of a leptin infusion in eight healthy human males showed increased activation of changes in signal transducers and activators of transcription-5'AMPK (STAT-AMPK) signaling, and an increase in skeletal

muscle palmitate oxidation after a 1 h leptin infusion [65]. These and other studies suggest that an increase in fat oxidation associated with leptin therapy could suggest a mechanism by which leptin therapy reduces hepatic steatosis in individuals with lipodystrophy [61,66].

Access to leptin therapy now & in the future

Metreleptin has been available for patients in the USA and Europe from Amylin Pharmaceuticals (CA, USA), on a compassionate basis for patients with lipodystrophy through a named patient program at a limited number of centres. In March 2013, metreleptin was approved in Japan for the treatment of lipodystrophy (in-licensed by Shionogi from Amylin Pharmaceuticals, a subsidiary of Bristol-Myers Squibb). In February 2014, the US FDA, approved metreleptin (Myalept®), in addition to diet, for leptin-deficient patients with congenital generalized or acquired generalized lipodystrophy. Further clinical trials may be required before approval for partial lipodystrophy is considered in the USA. Metreleptin is not currently licenced in Europe. AstraZeneca, who recently acquired metreleptin, has recently stated that the compassionate use programs in Europe and the USA will continue for patients with both partial and generalized lipodystrophy for the near future, but this is subject to review. There is no current evidence to suggest that metreleptin therapy would be beneficial in patients with FPLD1 who have central obesity and a relatively high leptin concentration, and further studies are needed in this patient group.

GLP-1 agonists

The GLP-1 agonist class of drugs, including exenatide and liraglutide, are incretin mimetics. This class of drugs are currently licenced for the treatment of hyperglycemia in patients with Type 2 diabetes usually in combination with a sulfonylurea, a thiazolidinedione, metformin, basal insulin or a combination of the above. GLP-1 agonists lower blood glucose levels by stimulating glucose-dependent insulin secretion, inhibiting glucagon secretion, slowing gastric emptying, and increasing satiety. Therapy with GLP-1 agonists often results in weight loss, but these drugs are not currently licensed for weight loss *per se* [67,68]. In the UK, use of GLP-1 agonists is 'rationed' for use mainly in patients with Type 2 diabetes and a BMI >35 kg/m^2. However GLP-1 agonists are an attractive therapeutic option in patients with lipodystrophy as they reduce appetite resulting in a negative energy balance, and have also been shown to have a favorable effect on the blood lipid profile, including serum triglycerides, possibly by reducing absorption of intestinal lipoproteins [69,70]. There are no published studies of treatment of patients with lipodystrophy with GLP-1 agonists, but there are some case reports of benefit in patients with HIV-associated lipodystrophy where both weight loss and improvement in metabolic control were reported [71]. In our service we have been piloting the use of GLP-1 agonist therapy (mainly once-daily liragutide) in approximately seven patients with FPLD1, with positive results to date and no patients stopping treatment due to side effects [Stears A, Hames C, Unpublished Data]. We may extend the patient population to other types of lipodystrophy if the initial patients demonstrate sustained benefit. Our main reservation in the use of these drugs is the possible rare association with pancreatitis, clearly a concern in patients at risk of severe hypertriglyceridemia and pancreatitis [72]. To date, we have avoided use of GLP-1 agonists in patients with a previous history of pancreatitis.

Orlistat

Orlistat inactivates gastric and pancreatic lipases in the lumen of the stomach and small intestine. The inactivated enzymes are unavailable to hydrolyze dietary triglycerides into absorbable free fatty acids and monoglycerides, and therefore absorption of approximately 30% of dietary triglycerides is inhibited. There are no published studies on the use of orlistat in patients with lipodystrophy, but we frequently use orlistat as an adjunct to dietary advice to reduce weight and fat absorption. Improvements in metabolic parameters have been demonstrated in patients with Type 2 diabetes. Clinical trials in obese patients with Type 2 diabetes demonstrated a mean difference with placebo versus orlistat in weight loss of 1.83 versus 3.06 kg, and a mean difference from placebo in HbA1c reduction of 0.18 versus 0.55%. The effect on HbA1c was not independent of weight reduction. Orlistat use has also been associated with a reduction in serum cholesterol, triglycerides and hepatic steatosis, but it is unclear if these effects on these metabolic parameters are independent of weight loss [73,74].

Insulin sensitizers

Metformin

Metformin hydrochloride is a biguanide that lowers both basal and postprandial plasma glucose. Metformin has several mechanisms by which it reduces the blood glucose concentration. First, reduction of hepatic glucose production by inhibition of gluconeogenesis and glycogenolysis. Second, increase in muscle insulin sensitivity, improving peripheral glucose uptake and utilization. Third, delay of intestinal glucose absorption. Fourth, stimulation of intracellu-

lar glycogen synthesis by acting on glycogen synthase. And, lastly, an increase in the transport capacity of membrane glucose transporters. Metformin does not stimulate insulin secretion and, therefore, does not produce hypoglycemia. There are no randomized studies of the use of metformin therapy in patients with inherited forms of lipodystrophy, but improvement in insulin sensitivity has been shown in small studies of patients with HIV- associated lipodystrophy [75]. In our clinical practice we recommend metformin therapy in most patients with lipodystrophy who tolerate it, due to its insulin-sensitizing action, and because data from studies in patients with Type 2 diabetes suggest significant benefits for both microvascular and macrovascular outcomes [76,77]. Metformin also has favorable effects on lipid metabolism and reduces total cholesterol, LDL cholesterol and triglyceride levels, although its affects on hepatic steatosis are unclear [78].

Thiazolidenediones

Thiazolidenediones (TZDs) activate the nuclear receptor-PPARγ, which leads to increased insulin sensitivity of liver, fat and skeletal muscle. Treatment with TZDs reduces hepatic glucose output and increases peripheral glucose disposal. Pioglitazone is the only currently available TZD as rosiglitazone was withdrawn due to concerns regarding its cardiovascular safety. There was no excess cardiovascular risk with pioglitazone reported in the ProActive study [79], but pioglitazone has a number of adverse effects including weight gain, fluid retention/overload, osteoporosis and possibly bladder cancer that limit its clinical use. Despite this, there is evidence that pioglitazone is an effective glucose-lowering therapy, and also that it has a positive effect on triglyceride metabolism and fat distribution. In most clinical trials there has been reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels compared with placebo, with small increases in LDL-cholesterol levels. A meta-ana-lysis of seven trials in patients with HIV-related lipodystrophy showed that rosiglitazone modestly improved fasting insulin, but worsened triglycerides LDL- and HDL-cholesterol when compared with placebo or no treatment. Pioglitazone had no impact on fasting insulin, triglycerides or LDL-cholesterol, but improved HDL-cholesterol when compared with placebo in two trials. Neither drug favorably impacted measures of fat redistribution in this patient cohort. The authors concluded that rosiglitazone should be avoided and that pioglitazone has a limited benefit in HIV-related lipodystrophy [80]. A case series of five patients with FPLD2 treated with rosiglitazone over 12 months showed that hip circumference increased significantly and there was a reduction in fasting glucose levels and liver transaminases [81]. A case report of pioglitazone use in a 25 year old female with FPLD2 showed that after 18 months, glycemia and triglycerides levels normalized, and hepatic enzymes and liver ultrasound appearances improved [82]. Another case report describes how use of pioglitazone in a 54-year female with FPLD2 resulted in sustained improvements in metabolic control and insulin sensitivity [83]. However, in our own practice, several patients with FPLD2 have not tolerated pioglitazone due to the increase in facial and neck adipose tissue. An apparently logical patient population in which to use TZDs is in patients with FPLD3 secondary to a mutation in *PPARγ*. Savage *et al.* [84] reported three patients with dominant-negative mutations in the nuclear hormone receptor PPARγ and a syndrome of severe hyperinsulinemia and early-onset hypertension.The metabolic response to 6 months treatment with rosiglitazone was reported in two affected patients. With rosiglitazone treatment, total body fat was increased in both patients with the fat increase more marked in the limb/gluteal fat depots than in the trunk region. Insulin sensitivity and HbA1c normalized in one patient, but the other remained severely insulin resistant and showed little change in HbA1c. There was little effect on fasting glucose in either patient. Treatment with TZD therefore remains an option for patients with FPLD3 and other forms of lipodystrophy, but this must be decided on an individual patient basis with a discussion regarding potential weight gain and the relative absence of long-term outcome or safety data.

High-strength insulin

Humulin® R U-500 insulin

Patients with lipodystrophy and secondary diabetes often require very high insulin doses (several hundred units per day) due to severe insulin resistance. The high volumes of insulin require split injections for each insulin dose, and when combined with the paucity of injection sites in patients with reduced subcutaneous fat this can lead to discomfort, reduced compliance and sub-optimal glycemic control. There are several high-strength insulin formulations available or in development. The most commonly used is Humulin R U-500 insulin (Eli Lilly and Co), which is concentrated fivefold, so that each 1 ml of Humulin R U-500 insulin contains the equivalent of 500 units of insulin. This insulin became commercially available in the USA in 1997, but is not licensed in the UK and thus needs to be imported. There are no pen devices available and the insulin is only available in a 20 ml vial and needs to be given with an insulin syringe and needle or via a continuous subcutaneous infusion device (CSII). The use of Humulin R U-500

is becoming more widespread in the USA and is the subject of an excellent recent review and meta-analysis [85]. A study performed in severely insulin-resistant patients with Type 2 diabetes administered 100 units of Humulin R U-500 subcutaneously showed that serum insulin concentration rose within 30 min and remained elevated for at least 7 h. In a meta-ana-lysis of nine studies (eight retrospective) reporting use of Humulin R U-500 with a total of 310 patients, there was a significant HbA1c reduction in all studies, from 1.0 to 3.29%, with an overall reduction of 1.59%. Weight gain was commonly reported with Humulin R U-500 use and there was an increase in minor, but not major hypoglycemia. Humulin R U-500 dosing is similar to that of other diabetes patients and depends on the total daily dose of insulin required, and Humulin R U-500 can also be given in combination with short- or long-acting U-100 insulin [86]. Delivery via CSII is advised if the total daily dose is more than 2000 units. The main safety concern with the use of Humulin R U-500 is the safe storage and administration of this insulin if a patient is admitted to hospital, to avoid inadvertent administration to patients taking U-100 insulin and avoidance of intravenous administration. We and others have developed safety packages, including alerts on the patient record and storage in a labeled box, to help prevent medication errors [86,87].

High-strength basal insulin

Insulin degludec is a new ultra-long acting insulin analogue that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation. This provides prolonged, f at blood glucose lowering with a duration of action of >42 h after a once-daily injection. Insulin degludec is available in two formulations – 100 and 200 units/ml – in a prefilled pen device. The 200 units/ml formulation allows administration of up to 160 units of insulin in a single injection.The U-200 formulation is potentially beneficial for patients requiring high doses of basal insulin as it enables lower volume, single injections to be given. This is likely to improve compliance and glycemic control [88–90]. Glargine U-300 is a new formulation of glargine insulin resulting in a f atter and more prolonged time–action profile than the U-100 formulation. Phase III study results from the EDITION trials were presented at the American Diabetes Association meeting in June 2013. Glargine U-300 is not yet available on the UK market [88,91]. These new insulin formulations have the advantage over U500R of being available in a pen device, but have the disadvantage of not fulfilling bolus/mealtime insulin requirements, and thus are only useful as basal (background) insulin (Box 1).

Lipid lowering

There are no randomized trials of short- or long-term outcomes for lipid-lowering therapy in patients with inherited forms of lipodystrophy, but there is evidence from patients with HIV-related lipodystrophy that combination therapy with diet/exercise and lipid-lowering drugs is effective at improving the characteristic dyslipidemia of elevated triglycerides and non-HDL-cholesterol and low HDL-cholesterol [92].

Triglycerides & pancreatitis risk

In our practice if patients have triglycerides >10 mmol/l despite dietary modification, triglyceride-lowering therapy usually starting with a fibrate is commenced to reduce the risk of pancreatitis. If the triglycerides remain >10 mmol/l then omega 3 fatty acids; for example, Omacor and/or niacin can be added, however, despite effective triglyceride lowering there is also a reported increase in insulin resistance with omega 3 fatty acids [93] and with niacin [94]. In practice we generally aim for a fasting triglyceride concentration of <1.7 mmol/l for cardiovascular risk reduction (see below). This is well below the triglyceride concentration at which pancreatitis is at increased risk [95].

Cardiovascular risk reduction

There is no published evidence base for long-term effects of lipid lowering on cardiovascular risk reduction in patients with lipodystrophy. In our service we follow international guidance for cardiovascular risk reduction for lipid-lowering therapy [95,96]. Newly published guidelines are moving away from aiming for a target lipid concentration and instead recommend an assessment of the likely risk of cardiovascular disease in an individual patient [96]. In patients with lipodystrophy this risk is usually high and lipid-lowering therapy should be with at least moderate intensity statin therapy first-line, with fibrates and other lipid-lowering treatment added in if necessary. It is important to note that statin concentrations are increased by protease inhibitors used in HAART. Recently, there has been concern regarding an increased risk of diabetes onset with statins. One current consensus is that the potential benefit outweighs the risks [97]. For triglycerides again we follow international guidelines that suggest treating a fasting triglyceride concentration >1.7 mmo/l [95]. Whether cardiovascular risk reduction exists with triglyceride lowering with fibrate therapy remains controversial [95], and recent data suggest lack of cardiovascular benefit with niacin [98,99]. In practice, for adequate triglyceride lowering, combination therapy of lifestyle changes and drug therapy is often required. In a randomized,

double-blind, placebo-controlled, 24-week trial of lifestyle modification, fenofibrate, and niacin in 191 (nonlipodystrophic) patients, subjects were randomized into five treatment groups: usual care, low-saturated-fat diet and exercise, fenofibrate and diet and exercise, niacin and diet and exercise, and fenofibrate and niacin and diet and exercise. Fenofibrate significantly improved triglycerides total cholesterol and non-HDL-C whereas niacin improved HDL-C. The combination of fenofibrate and niacin with diet and exercise provided maximal benefit, reducing triglycerides by 52% compared with usual care, increasing HDL-C by 12%, and decreasing non-HDL-C [92].

Management of patients with HIV-HAART-related lipodystrophy

Since HAART therapy for HIV infection was introduced in the 1990s, life expectancy in patients with HIV infection has improved significantly, but the drug regimes have a great deal of toxicity. Up to 50% of individuals receiving combination antiretroviral therapy develop a lipodystrophy syndrome after about 2 years of therapy [22,100]. Patients gradually accumulate subcutaneous fat around the abdomen and the upper back and lose fat from the face and the limbs. The facial fat loss can be severe and the patient may appear emaciated. There may also be associated hypertriglyceridemia and diabetes, which increases cardiovascular risk. The thymidine analogue nucleoside reverse transcriptase inhibitors stavudine and zidovudine and the protease inhibitors, for example lopinavir, are the most strongly associated with the onset of lipodystrophy. The potential benefit of non-nucleoside reverse transcriptase inhibitors remains unclear [21,101]. Changes in lipoprotein concentrations are associated with all HAART drug classes, including protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors [102]. There have been numerous trials investigating which HAART drug–drug combinations have the least effect on adipose tissue distribution and metabolic parameters while retaining efficacy against HIV, but unfortunately lipodystrophy is still a common consequence of these treatment regimes. It is advised that a metabolic profile and family history of cardiovascular disease and diabetes is assessed before starting HAART treatment. If this suggests that the patient is at high risk for metabolic side effects, or already has dyslipidemia, then protease inhibitors should be avoided if possible. Once treatment is established patients should be monitored regularly for metabolic changes and/or changes in fat distribution. There have been many studies investigating the optimum medical and surgical treatment of established HIV-associated lipodystrophy. The lipodystrophy may not resolve once the drug regime is changed, and may remain severe, especially on the face, and cosmetic surgery with cosmetic 'fillers' may be the only beneficial intervention. Liposuction may be helpful for excess fat accumulation on the dorso-cervical fat pad and abdomen, but the effect is not maintained in the long term. Tesamorelin, a growth-hormone-releasing factor analogue, has been approved in the USA for reduction of excess visceral fat in HIV-associated lipodystrophy patients, but fat loss is unaltered [103]. Two, small, open-label studies of metreleptin therapy in HIV-associated lipodystroph ypatients with low leptin concentrations found an improvement in dyslipidemia, improvement in hepatic insulin sensitivity and decrease in visceral fat, but no change in peripheral fat. Efficacy of leptin in HIV-associated lipodystrophy patients with normal leptin concentrations is not clear. Metreleptin is not licenced in the USA or UK for HIV-associated lipodystrophy [56,104,105].

Other management issues

Cosmetic management of lipodystrophy

Many patients with lipodystrophy have ongoing concerns regarding the cosmetic consequences of lipodystrophy. This can affect both men and women with the reduction/absence in subcutaneous facial fat giving a cachectic appearance in both and reduction/absence of subcutaneous, breast, hip and buttock tissue, and muscular hypertrophy of the limbs resulting in a masculine body appearance in women. Excess abdominal fat in patients with FPLD1 and excess facial/neck and vulval fat in patients with FPLD2 also cause problems with body image. While leptin therapy may aid weight loss due to reduction in appetite, treatment with leptin does not replenish fat stores. Concerns regarding too little/too much subcutaneous adipose tissue are best managed by referral to a specialist cosmetic surgeon with experience of managing patients with lipodystrophy. There is published literature on the use of autologous fat grafting and injectable dermal fillers for facial lipodystrophy [106], labioplasty in women with FPLD2 and HIV-related lipodystrophy and breast augmentation in women with FPLD2 and other forms of lipodystrophy [107–109]. Liposuction and/or lipectomy can be used if there is excess subcutaneous fat, for example around the neck or abdomen, but this does not result in changes to metabolic status [110–112]. Many patients in the UK have problems with gaining funding for cosmetic procedures through the NHS, the consequence being that many patients then seek private treatment that may be expensive and unregulated.

Hyperandrogenism

Women with lipodystrophy are also often affected by consequences such as hyperandrogenism, including hirsutism, male pattern hair loss and clitoromegaly. Hirsutism can be treated with limited success with cosmetic approaches and access to laser therapy is becoming more widespread [113]. Medical treatment of hyperandrogenism is usually along conventional lines with anti-androgen therapy [114,115], but some patents with lipodystrophy may respond well to leptin therapy and/or insulin sensitizers [116,117].

Acanthosis nigricans

Acanthosis nigricans affects both male and female patients with lipodystrophy, especially during puberty when insulin concentrations are at their highest. The lesions are typically dark-brown thickened plaques that most commonly affect skin flexures including the neck and axillae, but which may be widespread and severe (Figure 1). Acanthosis nigricans is characterized histologically by the proliferation of epidermal keratinocytes and fibroblasts. There may be some improvement as the patient reaches their twenties and if insulin concentrations fall due to beta cell dysfunction or due to weight loss. Topical and oral retinoids such as topical tretinoin and oral isotretinoin have been reported to improve acanthosis nigricans. Analogues of cholecalciferol, such as topical calcipotriol cream, oral fish oils and ocreotide, have also been used with limited success. Other options include laser and surgical excision [118,119]. It is important to note that nicotinic acid used to treat hypertriglyceridemia can cause acanthosis nigricans [120]. Acanthosis nigricans may be associated with widespread skin tags [121]. For treatment of severe acanthosis nigricans and or skin tags referral to a dermatologist is recommended.

Management of children with lipodystrophy

The focus of this article has been identification and treatment of lipodystrophy in adults. However, many patients, especially those with generalized lipodystrophy, present in childhood or adolescence, and increasingly adult patients with autosomal dominant partial lipodystrophy attending our clinical service have young children who are also affected. In our service we run a separate pediatric clinic that adjoins the adult clinic and is staffed by a consultant pediatrician and pediatric nurse. Pediatric patients are discussed at a combined multidisciplinary meeting. In practice, the clinical approach to treatment of children with lipodystrophy is similar to that in adults, but careful monitoring of growth is required with all dietary interventions that limit energy intake and care is necessary to ensure adequate intake of essential fatty acids. There is less experience of the use of pharmaceutical interventions for secondary/Type 2 diabetes in children, although over recent years incidence of Type 2 diabetes in children has risen, mainly in the context of obesity. This has been the subject of an excellent recent review [122]. There is also increasing experience in the management of children with HAART–HIV-related lipodystrophy [123]. Most pharmaceutical interventions for lipodystrophy used in adults have also been tried in children. There is open-label trial evidence of efficacy of leptin therapy in children with generalized lipodystrophy as young as 2 years of age, with a 63% reduction in fasting triglyceride concentration, 30% increase in insulin sensitivity and 20% reduction liver volume after 4 months of treatment [124]. Metformin has been used with some success in children with Type 2 diabetes [125]. Experience of thiazolidenedione use in children is limited since the withdrawal of rosiglitazone due to concerns regarding increased cardiovascular risk [84,125]. Treatment with pioglitazone has been tried in our service with limited success in a 14 year old boy with severe insulin resistance and secondary diabetes [Stears A *et al.*, Unpublished Data]. The use of GLP-1 agonists in children and adolescents to date is limited, but there is emerging evidence of the potential use of these agents in childhood obesity and as an adjunct to treatment in children with diabetes [126,127]. As with all these pharmaceutical interventions it is important to consider the possible as yet unknown adverse consequences of long-term use and assess the child regularly. Bariatric surgery in children is becoming more widespread, but there are no data on its use in children with lipodystrophy and long-term outcomes in obese children remain unclear [128]. One of the challenges of managing children with lipodystrophy is at what age to intervene with intensive drug therapies and diet, whether to do this before the child has any metabolic abnormalities or whether to wait until metabolic derangements are established. A similar dilemma applies in counseling parents, especially those with autosomal dominant partial lipodystrophy, if and when the best age is to go ahead with genetic screening of their children. There is no established guidance on this at the present time, but more evidence should emerge from ongoing longitudinal observation of outcomes in children with lipodystrophy by specialized teams.

Management of lipodystrophy in pregnancy

Women with lipodystrophy often have problems with subfertility and some, but not all, require referral to fertility services. Women with confirmed genetic causes of lipodytrophy may choose to attend pre-

conception genetic counseling with their partner to discuss the inheritance risks to their offspring and options for pre-natal/ante-natal diagnosis. Medication and diet should be reviewed carefully before conception and leptin therapy should be stopped due to lack of teratogenicity data. Metformin can usually be continued. Insulin therapy, sometimes high-strength insulin, is often required. Dietary education should be rehearsed as careful dietary fat and carbohydrate restrictions are essential in pregnancy to avoid metabolic decompensation.

Conclusion

Lipodystrophy is a group of rare conditions characterized by complete or partial loss of adipose tissue. The underlying cause may be genetic or acquired, and in some patients, remains unknown. Many patients with lipodystrophy have severe metabolic consequences and the mainstay of treatment is restriction of excess calorie intake despite an often lean appearance. This approach can be challenging to institute for the patient, their carers and policy makers. Diagnosis is often delayed, especially in men and commonly in women with partial lipodystrophy. Patients may present initially to a broad range of healthcare providers. Thorough clinical examination of the patient in their underwear is required to avoid the diagnosis being missed. Due to the rarity of this disorder, there are no current evidence-based management guidelines available. Management support by specialized teams may enable accurate and timely diagnosis, access to novel treatment options and expert dietary advice, collection of long-term outcome data, and the development of gold standard treatment algorithms with the aim of reduction in early mortality and high morbidity in patients with lipodystrophy.

Future perspective

Evidence-based management guidance is currently lacking in all aspects of management of patients with lipodystrophy due to the rarity of these patients. Establishment of an evidence-base should be aided by close follow-up of patients with lipodystrophy by specialized teams and systematic collection of longitudinal data. This may be helped by the development of patient registries, which are currently in development. One area of particular interest is collecting data to help decide when it is best to intervene with diet and drug therapy in children with partial lipodystrophy.

Recombinant human leptin (metreleptin) has recently been evaluated as a treatment for lipodystrophy by the FDA and approved only for patients with congenital or acquired generalized lipodystrophy. This may be followed by evaluation in Europe by the EMEA. It is currently unclear if other subgroups of patients will be approved in the future and this decision is likely to be based on further trial data. Other possible future drug therapies include growth hormone, growth hormone-releasing hormone analogues and recombinant IGF-I/IGF-binding protein-3 (mecaserminrinfabate) [103,129,130].

Adipose tissue or stem cell transplant may be another possible future intervention for treatment of lipodystrophy. Studies in mice have shown that transplantation of either white adipose tissue or brown adipose tissue intraperitoneally improved glucose tolerance and increased insulin sensitivity. Human-induced pluripotent stem cells may potentially be a source for autologous cell replacement in patients with lipodystrophy [131].

Any new drug intervention will need to be accompanied by education of patients and their carers and policy makers into the pathophysiology of lipodystrophy and the consequential ectopic fat deposition so that they understand that dietary restriction and avoidance of weight gain is of key importance. With greater understanding then access to interventions such as GLP-1 agonists and bariatric surgery for patients who have lower BMI than the current guidance stipulates may be improved.

As treatment options for patients with lipodystrophy improve, it will become more important that clinical and genetic diagnosis is performed in a timely manner. There are many patients in whom a genetic diagnosis remains elusive and establishing the causal mechanisms in these patients may enlighten development of new treatment options in the future.

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Executive summary

What is lipodystrophy?

- A rare group of conditions characterized by partial or complete loss of subcutaneous adipose tissue.
- Commonly, but not always, associated with metabolic derangements and an increased risk of premature cardiovascular disease.

How is lipodystrophy classified?

- Categorized into four subtypes by the extent of fat loss and whether the lipodystrophy is genetic or acquired: 1. Congenital generalized lipodystrophy (CGL); 2. Acquired generalized lipodystrophy (AGL); 3. Familial partial lipodystrophy (FPLD); and 4. Acquired partial lipodystrophy (APL).
- Further subcategorization is made for the genetic lipodystrophies depending on the gene affected. The genetic cause for many patients is yet to be elucidated.

How does a patient with lipodystrophy present clinically?

- Initial presentation usually dependent on the subtype of lipodystrophy.
- CGL usually identified in neonates or infants.
- Diagnosis of AGL/APL or FPLD may be overlooked, especially in men.
- Women with FPLD may first present with hirsutism, oligomenorrhea or gestational diabetes.
- Full clinical examination of body fat distribution and for acanthosis nigricans is mandatory in patients presenting with diabetes, hypertriglyceridia, hepatic steatosis and/or hyperandrogenism.
- American Association of Clinical Endocrinologists (AACE) have recently published consensus recommendations for detection of lipodystrophy.

What is the optimum approach to metabolic management of patients with lipodystrophy?

- Restriction of dietary energy intake to avoid excess calorie intake is the current mainstay of management, while carefully allowing for growth in children. Bariatric surgery may be helpful in selected patients.
- Specialist therapies including recombinant human leptin (metreleptin; most useful in generalized lipodystrophy) and/or GLP-1 agonists may be needed in selected patients.
- Insulin sensitizers and high-strength insulin can be useful to optimize blood-glucose control, but this can remain challenging.
- Management of patients with HIV–highly active antiretroviral therapy (HAART)-related lipodystrophy should be performed in conjunction with the infectious diseases team.
- Patients often require extensive support with the management of the cosmetic appearance of abnormal adipose tissue distribution, hirsutism and acanthosis nigricans.
- Women may have problems with subfertility. Careful preconception and intrapartum care is needed with amendment of drug treatment and extra dietary support. Preconception genetic counseling may be required.
- Individualized management of patients/families with lipodystrophy is complex and is aided by support from a specialist multidisciplinary team, which should include a dietitian, pediatrician and genetic counselor.

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