

## REVIEW

# Lipodystrophy: metabolic insights from a rare disorder

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### Abstract

Obesity, insulin resistance and their attendant complications are among the leading causes of morbidity and premature mortality today, yet we are only in the early stages of understanding the molecular pathogenesis of these aberrant phenotypes. A powerful approach has been the study of rare patients with monogenic syndromes that manifest as extreme phenotypes. For example, there are striking similarities between the biochemical and clinical profiles of individuals with excess fat (obesity) and those with an abnormal paucity of fat (lipodystrophy), including severe insulin resistance, dyslipidaemia, hepatic steatosis and

features of hyperandrogenism. Rare lipodystrophy patients therefore provide a tractable genetically defined model for the study of a prevalent human disease phenotype. Indeed, as we review herein, detailed study of these syndromes is beginning to yield valuable insights into the molecular genetics underlying different forms of lipodystrophy, the essential components of normal adipose tissue development and the mechanisms by which disturbances in adipose tissue function can lead to almost all the features of the metabolic syndrome.

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### Introduction

Insulin resistance is implicated in a vast burden of premature morbidity and mortality. Through its consistent association at the population level with diabetes mellitus and its complications, fatty liver disease and the polycystic ovarian syndrome (PCOS; with its attendant effects on female fertility), insulin resistance is arguably one of the greatest current threats to human health today. Intensive efforts are therefore underway to understand the genetic and molecular mechanisms underlying this prevalent phenotype. It is well established that obesity is a key player in the pathogenesis of most forms of insulin resistance, interacting with a polygenic diathesis. Despite intensive efforts, however, the molecular mechanisms underlying the relationship between obesity, insulin resistance and metabolic disease are incompletely understood, and the contributory genes are poorly defined.

A powerful approach to this daunting problem – and one that is potentially applicable to any complex trait – is to identify and study the most extreme end of the phenotypic spectrum; that is, in our case, patients with severe insulin resistance. Such patients typically have either profound compensatory hyperinsulinaemia (with fasting levels above 150 pM and post-prandial levels above 1500 pM) or diabetes

that requires high levels (over 200 units per day) of exogenous insulin for glycaemic control. Other clinical features that are characteristic of severe insulin resistance include acanthosis nigricans, the dark velvety thickening of the skin typically most obvious in body flexures and features of hyperandrogenism in girls. These syndromes are largely attributable to rare, inherited mutations in single genes, leading either to defects in canonical insulin signalling (either the insulin receptor itself or to lipodystrophy, where the primary defect is a paucity of adipose tissue (Savage *et al.* 2007b, Semple *et al.* 2010).

Owing to the severity of insulin resistance in these rare syndromes, their attendant physiological perturbations and pathological consequences are particularly overt. Moreover, their monogenic aetiology enables inference of firmer cause–effect relationships. In recent years, the study of patients with severe insulin resistance – particularly those with lipodystrophy – in combination with murine and *in vitro* cellular models has highlighted the potential insights to be gained from patients with rare syndromes. Here, we briefly summarise the lipodystrophy syndromes, their presentation and their classification, then we review recent work into the causes and effects of lipodystrophy, and how the insights they provide may be applicable to prevalent metabolic disease.

## Clinical features of the lipodystrophy syndromes

The lipodystrophy syndromes are a heterogeneous group of disorders in which the primary defect is a generalised or partial absence of adipose tissue, which may be congenital or acquired in origin (summarised in Table 1). Lipodystrophy should be considered in all patients manifesting the combination of insulin resistance (with or without overt diabetes), significant dyslipidaemia and fatty liver. Exceptions do exist such that not all patients with partial lipodystrophy will manifest this triad and not all patients with these biochemical abnormalities will be lipodystrophic. Nevertheless, this triad should at least trigger consideration of the possibility of lipodystrophy. The initial diagnosis hinges on awareness of this constellation followed by careful clinical assessment of fat distribution. Lipodystrophies are traditionally classified according to the anatomical distribution of fat tissue, although genetic classification is becoming increasingly tractable as more causative genes are identified (below). The severity of the metabolic phenotype is approximately proportional to the degree of adipose tissue loss and therefore tends to be worse in generalised lipodystrophy. Because healthy women have more adipose tissue than men, they are more profoundly affected by lipodystrophy, with more

obvious aesthetic effects and greater metabolic dysregulation. Along with the effects of hyperandrogenism, these factors make lipodystrophy more readily detectable in females.

Congenital generalised lipodystrophy (CGL), also known as Berardinelli–Seip congenital lipodystrophy (BSCL), is characterised by a generalised loss of adipose tissue that is generally clinically apparent from birth, affecting the limbs, trunk, face and neck (Garg *et al.* 1992, 1999). During childhood, bone age is advanced, with accelerated linear growth and prominence of skeletal muscle, peripheral veins and the thyroid gland due to paucity of fat. More rarely, there may be organomegaly and, in adulthood, acromegaloïd features (so-called ‘pseudoacromegaly’), including slight enlargement of the mandible, hands and feet. Hyperphagia results from low leptin levels, which correlate with the amount of residual fat. Severe insulin resistance is ubiquitous and inevitably accompanied by compensatory hyperinsulinaemia or the onset of frank diabetes by the second decade. Acanthosis nigricans is present in the neck, axilla, groin and trunk, and at puberty, hyperandrogenism (including oligo- or amenorrhoea, acne, hirsutism and polycystic ovaries on ultrasound) becomes prominent in girls. Severe dyslipidaemia, hepatomegaly and non-alcoholic steatohepatitis are almost universal and may lead to cirrhosis. The dyslipidaemia

**Table 1** Classification and clinical features of lipodystrophies

### Congenital lipodystrophy

#### *Congenital generalised lipodystrophy*

Severe IR; T2DM; severe dyslipidaemia; fatty liver; pseudoacromegaly; PCOS

Gene	Inheritance	Specific clinical features	Refs
AGPAT2	AR		Garg (2004)
BSCL2	AR		Garg (2004)
CAV1	AR (single case)	Short stature	Kim <i>et al.</i> (2008)
PTRF	AR	Muscular dystrophy; modest metabolic disturbance	Hayashi <i>et al.</i> (2009)

#### *Familial partial lipodystrophy*

Femorogluteal and limb lipodystrophy; IR; T2DM; dyslipidaemia; fatty liver; PCOS

Gene	Inheritance	Specific clinical features	Refs
LMNA	AD	Preserved or excess facial and neck fat	Garg (2004)
PPARG	AD	Preserved abdominal fat; hypertension	Savage <i>et al.</i> (2003)
ZMPSTE24	AR	Mandibuloacral dysplasia (MAD)	Agarwal <i>et al.</i> (2003)
AKT2	AD (single family)		George <i>et al.</i> (2004)
CIDEA	AR (single case)	White adipocytes with multilocular lipid droplets	Rubio-Cabezas <i>et al.</i> (2009)

### Acquired lipodystrophy

#### *Acquired generalised lipodystrophy*

Severe IR; T2DM; severe dyslipidaemia; fatty liver; PCOS

##### Associations

May be associated with other autoimmune disorders including juvenile dermatomyositis, SLE, autoimmune haemolytic anaemia, autoimmune hepatitis, low C4 complement levels

Refs  
Misra & Garg (2003)  
Savage *et al.* (2009)

#### *Acquired partial lipodystrophy*

##### Associations

HIV-associated

C3 nephritic factor-associated

##### Specific clinical features

IR (not severe), dyslipidaemia, fatty liver

Cephalocaudal pattern of fat loss, low C3 complement levels, MPGN. IR is rare unless overweight

Refs  
Koutkia *et al.* (2005)  
Misra *et al.* (2004)

AD, autosomal dominant; AR, autosomal recessive; IR, insulin resistance; MPGN, membranoproliferative glomerulonephritis; PCOS, polycystic ovarian syndrome; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus.

is frequently bad enough to lead to eruptive xanthomata and pancreatitis. Splenomegaly is common. Serum adiponectin, sex hormone-binding globulin and insulin-like growth factor binding protein 1 are typically suppressed and can be useful in discriminating lipodystrophy syndromes from those resulting from insulin receptor defects, which can also feature a paucity of fat tissue (Semple *et al.* 2006, 2007, 2008).

Partial lipodystrophies are characterised by abnormal fat topography along with an overall reduction in fat mass, although occasionally total adipose tissue levels are normal. The familial partial lipodystrophy (FPLD) syndromes are milder, autosomal dominant syndromes that may not be prominent until puberty (Garg 2004). The predominant effect is usually on the limb and gluteal fat depots with variable truncal involvement and normal or excess fat on the face and neck. FPLD is more obvious in women as a result of the fact that women normally have significantly more femorogluteal fat than men, and women are also typically more severely affected, often presenting with features of hyperandrogenism. Partial lipodystrophy is particularly difficult to recognise clinically in lean men. Acanthosis nigricans is common, and metabolic features range from asymptomatic impaired glucose tolerance with mild dyslipidaemia to severe insulin resistance, diabetes and profound dyslipidaemia, depending on the extent of fat tissue loss. Non-alcoholic steatohepatitis is a common complication, as is cardiovascular disease. The most common form of partial lipodystrophy is associated with the use of antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection (Tershakovec *et al.* 2004); acquired lipodystrophy may also occur as a component of autoimmune syndromes, involving immune-mediated premature destruction of adipocytes (Seip & Trygstad 1996, Misra *et al.* 2004).

## Molecular genetics of lipodystrophy

Over the past two decades, a combination of linkage analysis and candidate gene screening has led to the identification of nine genes associated with congenital lipodystrophy, either generalised or partial (summarised in Table 1). The observation that the loss of function of these genes leads to lipodystrophy is in itself powerful, illustrating that the encoded protein is essential for normal fat tissue development and/or function in humans and, more distally, for human metabolic health. Such a statement could not be made so convincingly from *in vitro* studies or mouse models alone, although identification of these proteins as essential mediators of adipose tissue function lends further support to the studies of their actions in appropriate model systems. Conversely, our understanding of adipocyte biology has informed candidate gene screens in patients with lipodystrophy of unknown cause, and has in some cases led to the identification of genes that would not otherwise have emerged. Despite this progress, many patients with clinical diagnoses of lipodystrophy carry no mutations in known genes, suggesting that other causative

genes are at play, which have yet to be identified. Thus, based on what is currently known, it is possible to functionally categorise genes implicated in the pathogenesis of lipodystrophy as being primarily involved in i) the transcriptional regulation of adipocyte differentiation, ii) substrate (particularly fatty acid) uptake by adipocytes, iii) triacylglycerol (TAG) synthesis or iv) lipid droplet formation.

### Induction of adipogenic gene expression

Adipocytes are believed to originate from pluripotent mesenchymal stem cells via committed precursors known as pre-adipocytes (Lane & Tang 2005). The differentiation of fibroblast-like pre-adipocytes into mature adipocytes in which a large unilocular lipid droplet occupies most of the cell volume is referred to as adipogenesis. The studies of *in vitro* models of adipogenesis reveal a precise pattern of gene up- and/or down-regulation leading ultimately to the expression of mature adipocyte genes (Rosen *et al.* 2000). Defects in certain key genes would therefore be expected to disrupt adipogenesis and lead to a lipodystrophic phenotype. To date, the clearest example of this mechanism is the form of FPLD associated with dominant loss-of-function mutations in *PPARG* (referred to as FPLD3) (Savage *et al.* 2003, Agostini *et al.* 2006). *PPAR $\gamma$*  is a member of the nuclear hormone receptor superfamily and is highly expressed in adipose tissue, monocytes/macrophages, colon and at lower levels in multiple other tissues (Desvergne & Wahli 1999). It plays a critical role in adipocyte differentiation and is often dubbed the 'master regulator' (Spiegelman 1998). In spite of its established role in adipogenesis however, which is to an extent confirmed by its association with lipodystrophy, defects in *PPAR $\gamma$*  cause only a partial form of the disease. It remains to be explained why the pattern of fat loss is regional, and why some depots are spared and not others.

Mutations in *BSCL2*, encoding the protein BSCL2 or seipin, account for many cases of CGL (Magre *et al.* 2001). *BSCL2* was originally identified as a lipodystrophy gene through a linkage analysis approach. *BSCL2* is a protein of unknown function that localises to the endoplasmic reticulum (ER; Agarwal & Garg 2004, Szymanski *et al.* 2007). Although initially reported to be most highly expressed in the brain, it is also highly expressed in adipocytes (Magre *et al.* 2001, Payne *et al.* 2008). Several studies have suggested that *BSCL2* may be involved in lipid droplet formation and is localised at points of contact between nascent lipid droplets and the ER membrane; however, its precise involvement in this process remains to be elucidated (Szymanski *et al.* 2007, Fei *et al.* 2008, Boutet *et al.* 2009). Patients with lipodystrophy resulting from *BSCL2* mutations are difficult to reliably distinguish from *AGPAT2* mutations (below) on clinical grounds alone, although the loss of adipose tissue from mechanical fat pads such as the palms, soles, orbits, scalp and periarticular regions may be specific to *BSCL2* mutations and may indicate a distinct pathological mechanism (Simha & Garg 2003). Recent data also suggest that adiponectin levels are higher in CGL patients with *BSCL2* mutations than in those with *AGPAT2* mutations

(Antuna Puente *et al.* 2010). Whatever its action within the adipocyte, *BSCL2* clearly plays a pivotal role in adipose tissue function, one that would have been far more elusive without the striking phenotypes of CGL patients.

Autosomal dominant mutations in *LMNA*, encoding lamin A/C, cause Dunnigan-type familial partial lipodystrophy (FPLD2; Cao & Hegele 2000, Shackleton *et al.* 2000, Speckman *et al.* 2000). This is the most commonly identified mutation in lipodystrophic patients. Children are born with an apparently normal fat distribution but typically manifest clinically discernible limb and truncal lipodystrophy with the onset of puberty (when fat depots normally expand). Fat around the head and neck, and visceral fat are typically spared. Lamin A/C is a nuclear envelope protein expressed in all cell types (Dechat *et al.* 2008). Initial studies suggest that *LMNA* mutations are associated with impaired adipogenesis, and molecular studies have implicated the key adipogenic transcription factor SREBP1c (Kim & Spiegelman 1996, Lloyd *et al.* 2002, Wojtanik *et al.* 2009). SREBP1c was found to bind lamin A/C, and *LMNA* mutations have been variously reported to cause the loss of SREBP1c binding or the sequestration, inhibition or mislocalisation of SREBP1c depending on the mutation or experimental system involved (Lloyd *et al.* 2002, Capanni *et al.* 2003, 2005, Boguslavsky *et al.* 2006). Overall, the molecular mechanism underlying the loss of adipose tissue in these individuals is unclear. Similarly, why only selective adipose depots are consistently affected remains unexplained. It is now clear that lamin proteins have many cellular roles including chromatin and transcription factor binding and organisation of the nuclear membrane and cytoskeleton (Dechat *et al.* 2008). This suggests that lamin A/C mutations will affect multiple pathways in developing adipocytes, and this may underlie the varied influences in different adipose depots and other tissues. Interestingly, mutations of the gene *ZMPSTE24*, encoding a metalloproteinase essential for the processing of prelamin A to the mature lamin A protein, can also cause a syndrome of partial lipodystrophy with mandibuloacral dysplasia (MAD; Agarwal *et al.* 2003). While it is currently unclear, the molecular mechanisms involved are evidently likely to significantly overlap those of *LMNA* mutations. Also of note is the association of *LMNA* mutations with a further set of rare familial syndromes including cardiac conduction disease syndrome, some forms of muscular dystrophy and Werner syndrome, MAD, various progeroid syndromes and Charcot–Marie–Tooth syndrome (Worman & Bonne 2007). Some mutations in the *LMNA* gene are consistently associated with tissue-specific phenotypes, whereas others appear to cause ‘overlap syndromes’ in which patients manifest ‘dystrophies’ of more than one tissue type.

Finally, mutations in *AKT2* cause severe insulin resistance in association with lipodystrophy, highlighting the importance of post-receptor insulin signalling in adipose tissue formation (George *et al.* 2004). Insulin is a key component of the cocktail used to induce adipogenesis in almost all cellular adipocyte models (e.g. 3T3-L1 adipocytes) and is also involved in stimulating glucose uptake into adipocytes, so

impaired insulin signalling could conceivably lead to lipodystrophy as a result of impaired adipogenesis and/or limited substrate availability (Saltiel & Kahn 2001).

#### Substrate availability

A single patient with generalised lipodystrophy and short stature has been identified with a homozygous loss-of-function mutation in *CAV1*, encoding caveolin-1, one of a number of proteins mediating caveola formation (Cao *et al.* 2008, Kim *et al.* 2008). Caveolae are specialised plasma membrane microdomains involved in fatty acid uptake, insulin receptor recycling and GLUT4 organisation in adipocytes (Schlegel *et al.* 1998). It is therefore to be expected that the loss of this protein should disrupt adipose tissue function, both through impairments in fatty acid uptake, and thus TAG synthesis, and (more speculatively) through the loss of insulin signalling into the cell (Cohen *et al.* 2003, Saltiel & Pessin 2003). In addition, mutations in *PTRF* (encoding polymerase 1 and transcript release factor, also known as cavin-1) have recently been identified in several kindreds with an autosomal recessive disorder characterised by generalised lipodystrophy and muscular dystrophy (Liu *et al.* 2008, Hayashi *et al.* 2009). Unlike *BSCL2* and *AGPAT2* mutations, in which somatic overgrowth is a common feature, *CAV1* defects were associated with short stature (albeit in a single kindred so far). *PTRF* is another abundant caveolar protein, which appears to stabilise the expression of caveolin, a previous finding that led to its ultimate identification as a causative gene in lipodystrophy (Hill *et al.* 2008, Liu & Pilch 2008). These findings indicate that specialised machinery for efficient uptake of fatty acid substrates into adipocytes is essential for normal metabolic health.

#### TAG synthesis

A large subset of patients with congenial generalised lipodystrophy harbour biallelic mutations in *AGPAT2*, encoding the enzyme acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) initially identified as a cause of generalised lipodystrophy by positional cloning (Agarwal *et al.* 2002). Indeed, collectively, mutations in *AGPAT2* and *BSCL2* account for over 95% of cases of CGL. This acyltransferase enzyme, located in the ER, catalyses the conversion of lysophosphatidic acid to phosphatidic acid, a key step in the synthesis of triglycerides and glycerophospholipids from glycerol-3-phosphate. *In vitro* enzyme assays have confirmed that the majority of known human *AGPAT2* mutants were associated with a marked reduction in enzymatic activity (Haque *et al.* 2005). The failure of TAG synthesis therefore provides a very plausible explanation for lipodystrophy in patients with genetic defects in the *AGPAT2* gene. However, cellular studies have also demonstrated that disruption of *AGPAT2* or *BSCL2* inhibits not only lipid synthesis but also the normal induction of adipogenic gene expression during fat cell development (Gale *et al.* 2006, Payne *et al.* 2008). This may reflect the tight

co-regulation of gene expression and lipid droplet formation in developing adipocytes or indicate that these proteins possess functions in addition to their proposed roles in lipogenesis.

### Lipid droplet assembly

Central to the adipocyte's role as a fat storage organ is the ability to store lipid species in an inert form within the cell as a large, unilocular lipid droplet. Recently, a homozygous mutation in *CIDEA*, encoding a lipid droplet-associated protein, was identified in a patient with partial lipodystrophy, insulin resistance and diabetes (Puri *et al.* 2007, Rubio-Cabezas *et al.* 2009). Histological assessment of biopsies of residual fat depots indicated the presence of multilocular lipid droplets. A particularly striking element of the patient's phenotype was recurrent diabetic ketoacidosis, which is very unusual in patients with acanthosis nigricans and elevated C-peptide levels. The fact that both plasma fatty acid and urinary glycerol levels were elevated suggests that this may have been a consequence of impaired lipolytic regulation. *Cidec* null mice manifest similar reductions in overall fat mass, white adipocytes with multilocular lipid droplets and apparently accelerated lipolysis (Nishino *et al.* 2008). Interestingly, however, the lipolytically released fatty acids appear to be preferentially oxidised within the adipocytes, so plasma fatty acid levels were not elevated in these mice and insulin sensitivity was preserved or even improved. Further work will be required to resolve these intriguing interspecies differences.

### Adipose tissue and metabolic health

In addition to lending insights into the molecular requirements of adipose tissue development, the study of lipodystrophy has also informed our understanding of the role of fat in human metabolic health, both by clearly illustrating in an unambiguous way the profound consequences of lack of adipose tissue, and by providing human models in which to study the mechanisms by which they arise.

#### *Adipose tissue as a key mediator of metabolic health*

Although cautions are rife as to the dangers of excess adipose tissue, the metabolic ill health suffered by patients who wholly or partially lack adipose tissue clearly illustrates that possession of healthy fat depots is an essential requirement for the maintenance of metabolic homeostasis. More than merely storing excess lipid, adipose tissue crucially stores energy in a metabolically 'safe' form. In addition, adipose tissue acts as a dynamic buffer for post-prandial lipid fluxes (Frayn 2002) and is also a key endocrine organ, synthesising and secreting hormones and adipokines, most notably leptin and adiponectin (Kershaw & Flier 2004). As such, lipodystrophy patients have contributed to a shift in the current thinking about metabolic disease from a 'glucocentric' towards a more 'lipocentric' view, with fat perceived as an organ essential for

the maintenance of metabolic homeostasis in the context of a tide of excess calories.

Despite the obvious detrimental effects of excess adiposity on metabolic health, the striking resemblance in biochemical and clinical features of lipodystrophic patients to the morbidly obese illustrates that the relationship between metabolic health and fat mass is a complex one. Consistently, a subset of patients with extremely high body mass index appear nonetheless protected from metabolic disease, the so-called 'metabolically healthy obese' (Bluher 2009). Based on these observations of both common and rare, extreme human disease, an 'adipose expandability' model of metabolic disease has been proposed (Virtue & Vidal-Puig 2008). Here, the underlying assumption is that human adipose tissue has a limited capacity to expand, through a combination of adipocyte hyperplasia (although this is limited in adults) and hypertrophy (Spalding *et al.* 2008). States of positive energy balance are associated with expansion of fat depots to accommodate the excess energy intake, while in states of negative energy balance, the energy stored within fat is mobilised, with subsequent shrinkage in adipose fat mass. However, this expandability is finite and can only occur up to a particular set point which varies on an individual-to-individual basis and which may be genetically determined. Beyond this set point, additional excess energy cannot be accommodated in an appropriate way and, with sustained positive energy balance, adipocytes become hypertrophic and begin to fail. Oxidative and ER stress within the adipocyte, infiltration of macrophages, release of inflammatory cytokines and dysregulation of adipose tissue's normal endocrine role, with impaired production of leptin and adiponectin, follow (de Ferranti & Mozaffarian 2008). This represents unhealthy, stressed adipose tissue. In such states, altered lipolytic regulation, along with the dysregulated hormone and cytokine production, leads to 'lipotoxicity' in other peripheral tissues. As a consequence of the inability of adipose tissue to accommodate surplus energy as fat, fat tends to accumulate in other organs, where it is frequently termed 'ectopic fat'. This ectopic fat accumulation probably affects many organs in the body but is most clearly associated with metabolic abnormalities in the liver, skeletal muscle and more recently the pancreas. Through various molecular mechanisms that are only beginning to be elucidated, insulin resistance is then induced in these tissues (Savage *et al.* 2007a, Poitout & Robertson 2008, Erion & Shulman 2010, Samuel *et al.* 2010).

Based on this model, then, is the proposition that metabolic health is determined by adipocyte expandability (i.e. position of the set point) rather than absolute fat mass (Danforth 2000, Virtue & Vidal-Puig 2008). Individuals with morbid obesity have a normal or high capacity for fat expandability, but, due to the persistently high caloric loads, this capacity is ultimately exceeded and adipose tissue dysfunction ensues. In contrast, individuals with lipodystrophy have a very low set point, which is exceeded in virtually all circumstances, leading to metabolic dysregulation that occurs sooner, earlier and more

severely. In many cases, residual adipose tissue in patients with lipodystrophy is likely to be dysfunctional. This is a very different state from lean individuals who possess numerous, healthy but 'empty' adipocytes that can be readily filled if necessary without compromising adipocyte function. Consistently, mouse strains in which this set point is deliberately lowered show a very similar metabolic picture. An example is the A-ZIP/F-1 transgenic mouse model in which mice express a dominant negative protein that heterodimerises with and inactivates members of the C/EBP and JUN families of B-ZIP transcription factors leading to generalised lipodystrophy (Moitra *et al.* 1998). More direct evidence for the need to be able to expand adipose tissue depots in response to sustained positive energy balance comes from the PPAR $\gamma$  P465L mouse model. The equivalent human variant is associated with partial lipodystrophy (FPLD3) and severe insulin resistance, but the P465L knockin mice do not manifest insulin resistance unless crossed with severely hyperphagic leptin-deficient *ob/ob* mice (Gray *et al.* 2006). In the latter context, namely persistent hyperphagia due to the absence of an essential appetite-regulating hormone (leptin), the defect in adipogenesis and adipocyte function induced by the mutation leads to profound metabolic disturbances and severe early onset diabetes. This model is further supported by transgenic mice overexpressing adiponectin, another adipocyte-derived protein (adipokine) with a putative insulin-sensitising action. When crossed with *ob/ob* mice, these mice become even more obese than standard *ob/ob* mice and yet manifest significantly improved metabolic homeostasis, suggesting that if adipose tissue can expand to accommodate surplus calories, insulin resistance can be ameliorated (Kim *et al.* 2007).

Despite a growing list of genes underlying a predisposition to adiposity (i.e. absolute fat mass), the determinants of this set point (i.e. adipose expandability) are unclear, although it is reasonable to suspect that those genes underlying monogenic lipodystrophy, or other related ones, may be contributory. Focused examination of lipodystrophy and 'metabolically healthy obese' patients may soon reveal insights into this important issue.

Multiple further lines of evidence, both in humans and in murine models, lend support to the adipose expandability hypothesis. One of the most effective and important components of management of lipodystrophy is caloric restriction, in order to minimise the stress imparted on limited or absent fat depots that are already sick and failing (Robbins *et al.* 1979). The low levels of leptin production worsen the situation by precipitating hyperphagia, which is often extreme. Leptin replacement should therefore always be considered in patients with generalised lipodystrophy, and has been shown to have sustained beneficial metabolic effects (Chong *et al.* 2009).

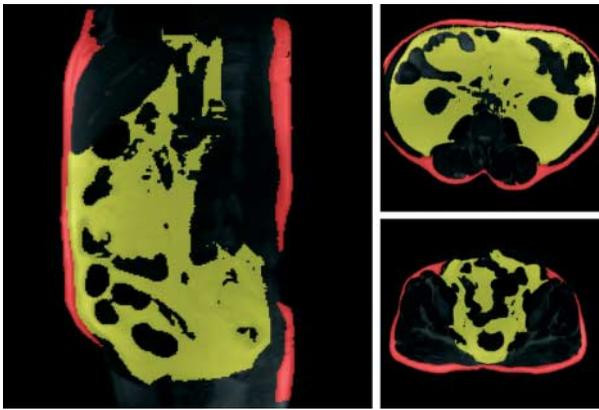
An alternative strategy to relieving metabolic stress on diseased adipose tissue would be to provide extra fat depots. Clearly in humans, the prospect of fat transplantation is still a distant one; nevertheless, transplantation of fat depots into

mouse models of lipodystrophy (e.g. AZIP), which also show the characteristic signature of metabolic disease (hypertriglyceridaemia, low high-density lipoprotein (HDL), fatty liver, etc.), caused a significant amelioration of metabolic health (Gavrilova *et al.* 2000). Subsequent studies, however, have suggested that transplantation of adipose tissue lacking leptin was unable to reverse the metabolic phenotype associated with lipodystrophy, emphasising the need for both increased 'adipose storage capacity' and a brake on ongoing excess energy intake (Colombo *et al.* 2002, Sennello *et al.* 2006).

A more conservative alternative to fat transplantation in humans is the use of thiazolidinediones (PPAR $\gamma$  agonists), commonly used as insulin-sensitising agents in the treatment of diabetes. Insulin sensitisation occurs despite consistent and substantial weight gain associated with use of thiazolidinediones, probably due at least in part to the stimulation of adipogenesis (although fluid retention also contributes to weight gain in this setting). Curiously, these drugs appear to worsen hepatic steatosis in murine lipodystrophy models (Kim *et al.* 2003), raising concerns about their utility in this scenario.

#### *Visceral versus subcutaneous fat*

A striking feature of the lipodystrophy syndromes is the clinical heterogeneity, particularly with respect to the size and site of adipose tissue loss, yet the consistency of the metabolic defect. Whereas adipose tissue is globally absent in patients with generalised lipodystrophy, this loss is more restricted in partial lipodystrophy and, importantly, often associated with compensatory increases in the size of other fat depots, with an increase in overall adiposity in some cases (Fig. 1). With very few exceptions, however, lipodystrophy is associated with impaired insulin sensitivity and dyslipidaemia. One such exception is the form of acquired partial lipodystrophy commonly associated with the presence of an IgG autoantibody which stabilises C3 (complement component C3) convertase leading to low C3 complement levels (Sissons *et al.* 1976). This so-called 'nephritic factor' is also associated with glomerular disease (typically mesangiocapillary glomerulonephritis type II (Williams 1997)). The lipodystrophy associated with C3 nephritic factor almost always develops in a cephalocaudal direction with the loss of facial and upper limb fat preceding variable trunk fat loss. In our experience, people with this form of lipodystrophy only become insulin resistant and manifest other features of the metabolic syndrome when upper body fat loss becomes more extensive and/or when the patient develops relative lower body adiposity. Presumably, either or both of these states lead to lipid stores exceeding the bodies' capacity to accommodate them in healthy adipose depots. These observations highlight the fact that all fat depots are not equal and that some are more strongly associated with metabolic health than others. Specifically, the accumulation of fat around abdominal viscera and inside intra-abdominal organs is strongly associated with obesity-related complications including type 2 diabetes



**Figure 1** Fat distribution in a patient with familial partial lipodystrophy (FPLD) due to a heterozygous R482W *LMNA* mutation. Note the striking paucity of subcutaneous fat (highlighted in red) and abundant visceral fat (highlighted in yellow). The image on the left is a sagittal T1-weighted MRI image, whereas those on the right are transverse abdominal (upper right panel) and gluteal (lower right panel) images.

mellitus and accelerated coronary artery disease (Snijder *et al.* 2004), and indeed it is the subcutaneous fat depots in the limbs and gluteal regions that are invariably lost in congenital lipodystrophy syndromes, often with compensatory up-regulation of the metabolically more ‘dangerous’ visceral fat.

The reason for differences in adipose depots is unclear, but at least one contributing element may be the fact that venous blood from visceral adipose tissue drains into the portal vein and then directly into the liver. Non-esterified fatty acids (NEFAs) and adipokines released into the circulation from visceral adipocytes tend to have a more dramatic impact on hepatic metabolism as a consequence of this intimate anatomical association. However, there is also evidence for cell-intrinsic differences between the different fat depots (Gesta *et al.* 2006), with different patterns of gene expression in fat sampled from different regions. Visceral depots produce more proinflammatory cytokines including  $\text{TNF}\alpha$  and IL6, and less adiponectin. Indeed, transplantation of subcutaneous fat into the abdominal cavity improved the metabolic profile of mice, while visceral-to-visceral or visceral-to-subcutaneous transplantation had little effect, providing further evidence in favour of subcutaneous fat depots being essential for metabolic homeostasis (Tran *et al.* 2008).

#### Free fatty acid turnover/flux

Early severe insulin resistance in children with *PPARG* mutation-associated lipodystrophy highlights the essential role of  $\text{PPAR}\gamma$  in insulin action. This is probably primarily through effects on adipogenesis, but also through a major functional defect in residual adipose tissue. In addition to its role as an ‘energy storage depot’, adipose tissue also plays a vital dynamic role in buffering the post-prandial nutrient/lipid influx. Detailed *in vivo* functional studies of abdominal

subcutaneous adipose tissue in a patient with a dominant negative *PPARG* mutation involving the measurement of arteriovenous fluxes across this fat depot revealed dramatic defects in adipose tissue metabolic flux control (Savage *et al.* 2003, Tan *et al.* 2008). For example, the usual increase in post-prandial triglyceride clearance was essentially absent in this patient, and dynamic changes in adipose tissue lipolysis appeared to be absent. NEFA output was thus low during an overnight fast but sustained following meal ingestion. This inability to trap and store NEFAs post-prandially is likely to expose skeletal muscle and liver to NEFAs in an unregulated manner, with consequent effects on insulin sensitivity.

#### Pathogenesis of hepatic steatosis

Insulin resistance is causally associated with some of the leading worldwide causes of morbidity, but it remains to be determined precisely how it leads to diseases as seemingly diverse as fatty liver, atherosclerosis and PCOS. At the simplest level, it is unclear whether insulin resistance is inherently damaging (and if so how), whether it is the compensatory hyperinsulinaemia that is pathogenic or whether there is some independent factor that causes both insulin resistance and these other effects. Detailed evaluation of patients with different sorts of severe insulin resistance has recently shed light on this matter. Fatty liver is a component of the common metabolic syndrome and a ubiquitous feature of lipodystrophy syndromes, and in both cases, it is strongly associated with high circulating TAG and low HDL-cholesterol levels. This dyslipidaemic signature is extremely important because it is correlated with atherosclerosis risk and premature mortality (DeFronzo 2010). Recently published data from patients with severe insulin resistance due to lipodystrophy or the loss of function mutations in the insulin receptor gene itself (*INSR*) suggest that metabolic dyslipidaemia is due in part to increased hepatic lipogenesis driven by hyperinsulinaemia. This also appears to be true in obese patients with fatty liver (Donnelly *et al.* 2005) and in diabetic offspring (Petersen *et al.* 2007). After binding to the insulin receptor, insulin action is mediated by a complex, incompletely understood branching signalling network. The concept of partial or pathway-selective insulin resistance invokes the potential for insults to selectively inhibit only a subset of insulin’s pleiotropic effects. Moreover, these defects might also be tissue selective, i.e. they might impair insulin action in different insulin target tissues to differing extents. This idea suggests that the hyperinsulinaemia associated with insulin resistance states could drive excess signalling via certain arms of the insulin-signalling network (with consequent hyperstimulation of some pathways), whereas signalling via other pathways might be clearly reduced. Evidence from murine studies suggests that fatty liver is typically associated with impaired insulin-stimulated suppression of hepatic gluconeogenesis, leading to the failure of insulin to suppress hepatic glucose output – the most ‘traditional’ definition of hepatic insulin resistance (resistance to insulin’s glucose lowering

actions) – but enhanced insulin-stimulated lipogenesis. Specifically, the canonical insulin signalling pathway through insulin receptor substrate 1 (IRS1), phosphoinositide 3-kinase (PI3K), protein kinase B (AKT) and FoxO1 is down-regulated, but a parallel pathway in which insulin receptor activation leads to up-regulation of the lipogenic transcription factor SREBP1c (known to be a key mediator of hepatic lipogenesis) is intact, thus mediating increased hepatic lipogenesis in the presence of hyperinsulinaemia. A study of 41 patients with severe insulin resistance due to insulin receptor abnormalities (congenital or acquired) compared to 13 patients with lipodystrophy and 42 patients with undefined molecular pathology showed an extreme form of the prevalent metabolic dyslipidaemia in the latter two groups but an apparently normal lipid profile in patients with *INSR* mutations in spite of high insulin and glucose levels and very modestly elevated free fatty acid levels. *De novo* hepatic lipogenesis and liver fat content were significantly increased in lipodystrophic patients, whereas they were within normal limits in patients with *INSR* mutations (Semple *et al.* 2009).

These data suggest that ‘regular’ obese insulin-resistant patients with fatty liver associated with increased hepatic lipogenesis have a post-receptor defect in insulin action. This is probably a unifying theme in insulin resistance. For example, it has been proposed that thecal cell proliferation in PCOS reflects preserved mitogenic (mitogen-activated protein kinase, or MAPK) signalling in the face of resistance to the glucose-lowering effect of insulin, largely mediated through the PI3K/AKT pathway. Moreover, the idea of partial insulin resistance is consistent with the clinical observation of pseudoacromegaly, a state characterised by acromegaloïd features in the absence of excess GH, in at least some patients with severe insulin resistance (Flier *et al.* 1993, Dib *et al.* 1998).

## Conclusions

The identification and evaluation of patients with rare syndromes of congenital lipodystrophy are not only crucial to their clinical management, but also yields biological insights whose value is disproportionate to their prevalence. As described herein, the study of the molecular genetics of lipodystrophy has identified some of the key players in adipose tissue development and function. Given that a subset of lipodystrophy patients still lack a genetic diagnosis, these existing components are essential but not necessarily sufficient, and it is probable that novel lipodystrophy genes will be identified in the near future. Moreover, the study of patients with lipodystrophy has provided unique insights into the role of adipose tissue in human health, and has in particular contributed to a dramatic shift in the perception of adipose tissue as an essential component of metabolic homeostasis whose dysfunction, as with other tissues, greatly increases the risk of morbidity.

Together with other syndromes of severe insulin resistance (Semple *et al.* 2010), lipodystrophy has started to facilitate the dissection of the molecular mechanisms underlying the complications associated with insulin resistance. More generally, the study of patients with any monogenic disease can provide insights that are highly relevant to common human disease and which are very often unavailable from other models (*in vitro* or *in vivo*). In the case of lipodystrophy, the yields have been threefold: first, improved treatment strategies for patients; second, a greater understanding of adipose biology; and third, insights into the mechanism of a hugely prevalent phenotype that may one day enable us to combat it more effectively.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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