What lipodystrophies teach us about the metabolic syndrome

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Abstract

Lipodystrophies are the result of a range of inherited and acquired causes, but all are characterized by perturbations in white adipose tissue function and, in many instances, its mass or distribution. Though patients are often non-obese, they typically manifest a severe form of the metabolic syndrome, highlighting the importance of white fat in the 'safe' storage of surplus energy. Understanding the molecular pathophysiology of congenital lipodystrophies has yielded useful insights into the biology of adipocytes and informed therapeutic strategies. More recently, genome-wide association studies focused on insulin resistance have linked common variants to genes implicated in adipose biology and suggested that subtle forms of lipodystrophy contribute to cardio-metabolic disease risk at a population level. These observations underpin the use of aligned treatment strategies in insulin-resistant obese and lipodystrophic patients, the major goal being to alleviate the energetic burden on adipose tissue.

Introduction

Lipodystrophies are a heterogeneous group of conditions characterized by a lack of and/or dysfunctional white adipose tissue. They may be genetic (inherited) or acquired in origin and localized, partial, or generalized in distribution; however, despite the aetiological heterogeneity, other than localized forms and most cases of Barraquer-Simons acquired partial lipodystrophy, they almost all cause insulin resistance, non-alcoholic fatty liver disease (NAFLD), and dyslipidemia (characterized by high triglyceride and low HDL cholesterol concentrations) (1). Therefore, despite patients often (though not always) being non-obese or lean, they clinically and biochemically mirror the metabolic syndrome associated with obesity.

Although lipodystrophies are relatively rare, studying these patients has advanced understanding of adipose biology and the pathophysiology of the metabolic syndrome. They act as very informative models of inadequate adipose storage capacity in the face of excess energy intake, resulting in ectopic fat accumulation and insulin resistance. Accumulating evidence suggests that similar mechanisms of adipose overload are responsible for insulin resistance in patients with obesity (2, 3), and therefore treatment of lipodystrophies and obesity are conceptually similar; for example, limited data in patients with familial partial lipodystrophy suggests that bariatric surgery is highly effective in alleviating the metabolic consequences of lipodystrophy (4–6), as has been widely reported in obesity (7).

White adipose tissue is the primary site for physiological energy storage in humans (8) (Figure 1). Surplus energy can only really be stored as glycogen (carbohydrate) or triglyceride (neutral lipid), and the latter represents a more concentrated/energy dense (9 versus 4 kcal/g) and 'lighter' reserve, so it is not surprising that a lean adult human stores approximately 100-fold more energy as triglyceride compared to glycogen (9). In healthy adult humans almost all triglyceride is stored within white adipose tissue, which regulates the uptake of substrates (e.g. glucose and non-esterified fatty

acids), the synthesis of neutral lipid for storage, and release of stored triglycerides through lipolysis. These processes are under nervous, hormonal, and nutritional regulation to facilitate homeostatic energy balance but can be perturbed by chronic overnutrition (resulting in obesity) or inherited disorders of white adipose tissue (lipodystrophies). Adipocytes signal the status of their energy reserves by secreting leptin, which in turn acts centrally to influence energy balance and reproductive capacity. They also secrete a host of other proteins (collectively known as adipokines) with a range of purported functions (10, 11). Clearly, in addition to perturbing energy storage, lipodystrophies may well alter adipokine secretion and/or interactions with stromovascular cells present in adipose tissue. These changes could also contribute to the physiological changes associated with lipodystrophy but have, for the most part, not been extensively studied and so are not considered in detail here.

White fat is distributed in several characteristic sites (or 'depots', Figure 1), which differ substantially between humans and mice. For example, humans do not have a large gonadal fat pad, which is a commonly isolated and studied fat depot in mice. Importantly, the physiological regulation of adipogenesis, lipogenesis, and lipolysis vary in these depots (12–14). For example, human studies have suggested that lipolysis is higher in visceral (intra-abdominal) than in subcutaneous white adipose tissue (15). In this review, we highlight examples of inherited lipodystrophies where selective loss of gluteofemoral fat can recapitulate features of the metabolic syndrome, even if upper body fat depots are unaffected. In other cases, where fat loss is restricted to the face, upper truck and arms, patients do not typically manifest metabolic disease.

Insights from inherited lipodystrophy syndromes with well-defined mechanisms

Clearly defined monogenic diseases can provide unique insights into the biological function of specific genes and the proteins they encode, somewhat akin to observations made in knockout or hypomorphic mouse models. In several cases (for example, *PPARG*, encoding peroxisome proliferator-activated receptor gamma [PPARγ]), the link between specific genes implicated in causing lipodystrophy and adipose dysfunction is clear, whereas in others (such as *LMNA*, encoding lamin A/C) the mechanism is yet to be fully understood. Below, we briefly review selected situations where the link between particular genes and adipose dysfunction is relatively clear; these include examples involving genes implicated in the transcriptional regulation of adipogenesis, triglyceride synthesis, lipid droplet morphology, and lipolysis (Figure 2).

***PPARG*:**

PPARs (peroxisome-proliferator activated receptors α,δ,γ) were identified nearly 30 years ago (16). They all have a DNA-binding domain (DBD) as well as a ligand-binding domain (LBD) that is believed to bind, somewhat promiscuously, a range of putative fatty acid ligands (17–20). Seminal in vitro studies undertaken in the 1990s established that PPARγ is essential for adipocyte differentiation, (21–24) and it is now generally considered to be the 'master regulator' of both adipogenesis, the process through which fibroblast-like precursors are converted into mature adipocytes, and of mature adipocyte function (21, 23). It is, therefore not surprising that *PPARG* mutations cause lipodystrophy, but why these mutations are usually associated with a stereotypical pattern of partial lipodystrophy remains an unresolved puzzle.

Heterozygous, dominant-negative mutations in *PPARG* are associated with autosomal dominant familial partial lipodystrophy type 3 (FPLD3). Several case studies have reported patients with severe insulin resistance, dyslipidaemia in which hypertriglyceridemia appears to be exquisitely sensitive to high fat intake (25), type 2 diabetes mellitus, reduced subcutaneous femorogluteal and leg fat, and

hypertension (26–35). Affected women frequently manifest features of polycystic ovary syndrome (PCOS) (26, 36, 37) and premature onset cardiovascular disease (26), and cirrhosis has been reported (28, 38). The majority of patients with FPLD3 are diagnosed with lipodystrophy in early adulthood, though affected children have been identified through family screening studies (35) and men typically present later than women.

Heterozygous autosomal dominant mutations in either the DBD or LBD of PPARγ have been associated with lipodystrophy (27, 39), though debate continues about whether or not these mutations truly do manifest dominant negative properties (40). LBD variants can bind to DNA response elements but manifest impaired transcriptional responses to agonists or co-activators (35). DBD mutants impair DNA binding, but they can also inhibit wild-type function, possibly via sequestration of co-activators (36). Heterozygous PPARγ missense variants are present in as many as 1:500 people, though prospective functional classification of all possible missense variants in PPARγ suggests that many of these are benign and that gene-environment interactions are important (17, 41).

Some human evidence supports the notion that the degree of loss of PPARγ function correlates with the severity of lipodystrophy. A child harbouring biallelic *PPARG* mutants, a frameshift mutation and a DBD mutation that were predicted to result in near-complete loss of PPARγ function, presented with a congenital generalized lipodystrophy phenotype (42). In contrast, the most common PPARγ variant, p.Pro12Ala (rs1801282, minor allele frequency 0.11), which is thought to only mildly modify PPARγ function, reduces the risk of developing type 2 diabetes without obviously causing a lipodystrophic phenotype (43).

In addition to the in vitro data referred to above, mouse studies strongly support observations that varying levels of PPARγ function produce a spectrum of phenotypes. Complete *Pparg* knockout is

lethal for mice due to its requirement in placental and cardiac development (44). However, embryonal-only *Pparg* knockout(45), heterozygous *Pparg* knockout, *Pparg* hypomorphs (46), and adipose-specific *Pparg* knockout mice all have a lipodystrophic phenotype (including insulin resistance and elevated triglycerides) (47). Several of these models also manifested abnormalities in blood pressure: hypotension in embryonal-only knockout, and hypertension in P465L knock-in mice (consistent with the human condition), though this model did not demonstrate insulin resistance or hypertriglyceridemia (48).

Therefore, impairment in the transcriptional control of adipogenesis results in a reproducible white adipose tissue-mediated partial lipodystrophy associated with all the characteristic features of the metabolic syndrome, the severity of which correlates, at least broadly, with residual PPARγ activity.

***AGPAT2*:**

The most severe form of lipodystrophy is congenital generalized lipodystrophy (CGL), which is inherited in an autosomal recessive manner (49). Mutations in *AGPAT2* (encoding 1-acylglycerol-3-phosphate O-acyltransferase 2) are responsible for a substantial proportion of these patients (50). AGPAT2 is a lysophosphatidic acid acyltransferase that plays a key role in the synthesis of triglycerides from glycerol-3-phosphate (51).

Affected patients present from infancy with an almost complete lack of adipose tissue, extreme insulin resistance, hypertriglyceridemia (potentially leading to pancreatitis), and severe hepatic steatosis (52). Many have acanthosis nigricans, a condition characterized by dark discoloration and velvety thickening of flexural skin, and children may have a progeroid-like appearance due to the lack of facial adipose tissue. Patients are essentially aleptinemic and leptin replacement therapy is now a mainstay of therapy, as discussed below.

Biallelic *AGPAT2* mutations associated with CGL are predicted to profoundly disrupt the protein product. Many are splice site mutations that result in a frameshift with premature stop codons or exon skipping (53). Only a few missense variants have been identified in patients with *AGPAT2*-associated CGL, including p.Glu172Lys, which is thought to prevent the binding of substrate and catalytic activity (54). Functional studies have consistently demonstrated that mutants linked to CGL result in almost complete loss of AGPAT2 enzymatic activity (55).

AGPAT2 demonstrates tissue-selective expression in both visceral and subcutaneous adipose tissue, unlike AGPAT1, which is widely expressed (56). Homozygous loss-of-function variants appear to cause a failure of early adipogenesis due to several proposed interlinked mechanisms: perturbation of phospholipids, inhibition of PPARγ, and adipocyte apoptosis (57–59). There is a profound alteration of the lipidome, including reduced phosphatidylinositol and elevated lysophosphosphatidyl choline (LPC), in *AGPAT2* knockdown 3T3-L1 adipocytes (60), the result of which is reduced activity in the PI3K/Akt pathway and inhibition of PPARγ activity. The lack of Akt signalling results in adipocyte apoptosis and, though PPARγ over-expression may partially restore the adipogenic potential in *AGPAT2* knockout cells, they still undergo apoptosis (61). These conclusions are supported by a lipodystrophic phenotype in *Agpat2*-null mice (62).

These findings highlight the devastating metabolic consequences of near-total fat loss due to a major impairment in the ability of adipocytes to synthesize triglyceride. This defect in neutral lipid synthesis is compounded by sustained hyperphagia due to severe leptin deficiency in CGL.

***PLIN1*:**

The perilipins are a group of proteins that were originally identified as highly abundant proteins covering the surface of lipid droplets (63–65). Since then they have been found to be critical for the regulation of lipolysis from lipid droplets (66–69); specifically, PLIN1 regulates the first two steps in

triglyceride hydrolysis, namely those catalysed by adipose tissue triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL (encoded by *LIPE*)), the major diglyceride lipase.

Gandotra et al. identified the first three families affected with heterozygous loss-of-function *PLIN1* mutations, all of which were inherited in an autosomal dominant fashion (70). They presented with partial lipodystrophy, particularly manifesting a lack of subcutaneous lower limb and gluteofemoral fat. Biochemically, they had hypoadiponectinaemia, hyperinsulinemia, NAFLD, and profound hypertriglyceridemia. Two different frameshift mutations were reported, both of which were shown to be expressed and to be targeted to the surface of lipid droplets (70). The mutant *PLIN1* reported in these cohorts increased basal lipolysis in an in vitro model (67) by failing to effectively bind ABHD5, a key activator of ATGL (71–73). PLIN1 is almost exclusively expressed in white and brown adipocytes, where it is very specifically involved in stabilising lipid droplets and in regulating lipolysis, thus the phenotype described in patients with *PLIN1* mutations highlights the fact that a highly specific defect affecting energy storage in adipocytes is sufficient to produce almost all the features of the metabolic syndrome.

***CIDEC*:**

Cell death-inducing DFFA-like effector C (CIDEC; also known as the murine form, Fsp27) is another lipid droplet-associated protein that is expressed in white adipose tissue (74, 75) where it is required for the formation of large unilocular lipid droplets (76). Mice lacking Fsp27 uniformly manifest reduced fat mass with multilocular lipid droplets in all white adipocytes (77, 78), and over-expression of Fsp27/CIDEC in a range of cell types consistently increases lipid droplet size (75, 79–81). Many human cell types can contain lipid droplets, including myocytes, hepatocytes, and pancreatic islet cells. However, these lipid droplets always adopt a multilocular form, whereas the ability to form a single massive lipid droplet is a unique property of the white adipocyte (82). This high volume-to-surface area ratio facilitates very precise regulation of lipolysis, which is clearly

important in a cell type responsible for bulk storage (and release) of surplus energy as neutral lipid for the whole organism.

In 2009, a single patient was identified with a partial lipodystrophy phenotype caused by a homozygous nonsense mutation in *CIDEC* (83). Clinically, the patient had absent lower limb and gluteofemoral adipose tissue with reduced total body fat mass. The proband had poorly controlled diabetes mellitus with a propensity for ketoacidosis despite elevated C-peptide and negative anti-islet and anti-glutamic acid decarboxylase antibodies. She also had severe hypertriglyceridemia (resulting in acute pancreatitis), acanthosis nigricans, hepatic steatosis, and hypertension. Fat biopsy demonstrated a mixed population of white adipocytes with many, though not all, containing multilocular lipid droplets. This unusual phenotype was recapitulated in an adipocyte-specific *Fsp27* knockout mouse (84), which similarly demonstrated multilocular white adipocytes, in addition to insulin resistance. When fed a chow diet, *Fsp27*-null mice are lean and insulin sensitive; however, when challenged over many weeks with a high fat diet, or when crossed with obesity-prone *ob/ob* mice or mice lacking brown adipose tissue, these mice do manifest NAFLD and severe insulin resistance (78).

Though apparently a very rare condition in humans, these data further demonstrate that disruption of the ability of white adipocytes to form unilocular lipid droplets is sufficient to cause partial lipodystrophy and features of the metabolic syndrome.

Other genetic lipodystrophies

Several other human genetic lipodystrophies have been recognised, though exactly how these cause lipodystrophy is less clear. Biallelic loss-of-function mutations in *BSCL2* (encoding seipin) on chromosome 11 are a major cause of congenital generalized lipodystrophy (52). Affected patients have almost complete absence of body fat from birth, severe insulin resistance, and

hypertriglyceridemia (85). The syndrome is also associated with cardiomyopathy and intellectual disability. *BSCL2* is clearly critical for the development and function of cultured white adipocytes (86, 87), and both whole-body and adipose-specific *Bscl2* knockout mice manifest a lipodystrophic phenotype (88). Recent cryogenic electron microscopy-derived structural models suggest that both the Drosphila orthologue (89) and human seipin (90) oligomerize to form a ring-like structure in the ER membrane. These data are consistent with seipin's proposed involvement in the early formation of lipid droplets from the ER, a model supported by a series of yeast (91) and other cell-based experiments (92, 93).

Heterozygous mutations in lamin A/C are probably the most common cause of monogenic partial lipodystrophy (94–96). Lamin A/C is a well-established component of the nuclear lamina network expressed in almost all cells. Different *LMNA* mutations have also been linked to cardiomyopathy and muscular dystrophy, and some patients with *LMNA*-associated partial lipodystrophy do also manifest variable degrees of cardiac and skeletal muscle impairment. As intermediate filaments, lamins clearly impact nuclear structure and transcriptional regulation of gene expression, but exactly why specific mutations are more strongly associated with particular phenotypes and why nuclear perturbation leads to partial lipodystrophy remains unclear (97, 98).

Finally, one specific variant (R707W) in mitofusin 2 (*MFN2*), the gene classically mutated in Charcot-Marie Tooth type 2A, has been linked to a striking adipose overgrowth-lipodystrophy phenotype known as multiple symmetric lipomatosis (99). Patients with biallelic R707W mutants develop fat hyperplasia on their back and neck with lower limb lipodystrophy, NAFLD, insulin resistance, and peripheral neuropathy (100). A particularly remarkable aspect of this phenotype is very low leptin levels despite the fact that patients retain excess upper body fat (100, 101). Mitochondrial fusion-fission dynamics are essential for all metabolically active tissues, but how this single variant confers an adipose phenotype is yet to be established (102).

As summarized in Tables 1 and 2, several additional genetic variants have been linked to specific forms of lipodystrophy. Further details related to all these disorders can be found in the references cited in Tables 1 and 2.

Gene and clinical syndrome	Pattern of inheritance	Clinical phenotype	Mechanism category	Gene product function	Reference
Congenital generalized lipodystrophies (CGL)					
AGPAT2 (CGL1)	Autosomal recessive	Near complete absence of adipose tissue from birth, severe insulin resistance (IR), profound hypertriglyceridemia, non-alcoholic fatty liver disease (NAFLD)	Failure of triglyceride synthesis	Lysophosphatidic acid acyltransferase: synthesis of triglycerides from glycerol-3-phosphate	(53, 57, 59, 60)
BSCL2 (CGL2)	Autosomal recessive	As for CGL1, plus intellectual disability and cardiomyopathy	Lipid droplet dysfunction and/or impaired adipogenesis	Endoplasmic reticulum-localised protein needed for lipid droplet formation and adipogenesis	(87, 103–108)
CAV1 (CGL3)	Autosomal recessive	Neonatal loss of adipose tissue, severe IR, dyslipidaemia, pulmonary hypertension, short stature	Perturbed caveolar function	Key component of plasma membrane caveolae, which may participate in lipid uptake	(109–112)
PTRF (CGL4)	Autosomal recessive	Generalised loss of adipose tissue, cardiomyopathy, (hypertrophic) skeletal myopathy, less severe IR	Perturbed caveolar function	*PTRF* encodes cavin-1, which forms a protein complex needed for assembling, regulating, and stabilising caveolae	(113, 114)
Familial partial lipodystrophies (FPLD)					
Polygenic (FPLD1 'Kobberling')	Polygenic	Distal lipoatrophy, increased visceral adiposity, NAFLD, IR, low leptin & adiponectin	Various	Polygenic influences impairing adipogenesis and fat distribution	(115)
LMNA (FPLD2, 'Dunnigan')	Autosomal dominant	Loss of subcutaneous fat (particularly gluteofemoral) with face & neck sparing, NAFLD, IR; cardiomyopathy and/or muscular dystrophy in some	Nuclear envelope perturbation	Nuclear envelope protein which influences transcriptional regulation but tissue-specific effects are poorly understood	(94, 96)
PPARG (FPLD3)	Autosomal dominant	Distal lipoatrophy with variable visceral adiposity, hypertension, (post-prandial) hypertriglyceridemia, NAFLD, and PCOS	Defect in adipogenesis	Nuclear receptor central to transcriptional control of adipogenesis and mature adipocyte function	(26, 28, 28, 39)
PLIN1 (FPLD4)	Autosomal dominant	Distal (particularly gluteofemoral) lipoatrophy, NAFLD, IR	Lipid droplet dysfunction	Lipid droplet protein that regulates triglyceride lipolysis	(66–68, 70)
CIDEC (FPLD5)	Autosomal recessive	Distal lipoatrophy with preserved neck and axillary fat, NAFLD, hypertriglyceridemia, pancreatitis, hypertension, microalbuminuria, multilocular adipocytes [N.B. single patient]	Lipid droplet dysfunction	Lipid droplet protein that is needed for the formation of large, unilocular lipid droplets	(79, 83, 116)
LIPE (FPLD6)	Autosomal recessive	Distal lipoatrophy, myopathy, dyslipidaemia, IR, NAFLD	Altered lipolysis	Encodes hormone-sensitive lipase, a key lipolytic enzyme	(117, 118)
AKT2 (Unclassified)	Autosomal dominant	Distal lipoatrophy and IR	Defect in adipogenesis	AKT2 (protein kinase B) is a component of the insulin signalling pathway and is required for normal adipogenesis	(119)
ADRA2A (Unclassified)	Autosomal dominant	Peripheral lipoatrophy with excess facial and neck adipose tissue, buffalo hump, IR, hypertension.	Altered lipolysis	Adrenergic receptor normally involved in reducing adipocyte lipolysis	(120)

Table 1. **The main congenital generalized and familial partial lipodystrophies with their involved genes and proposed pathogenic mechanism.** The four recognized CGL syndromes result in extreme IR with almost complete loss of adipose, whereas FPLD is associated with peripheral (lower limb) adipose loss and substantial IR. In some cases the mechanism linking the gene product and lipodystrophy and adipose tissue dysfunction is unclear. ADRA2A, alpha-2A-adrenergic receptor; AGPAT2, 1-acylglycerol-3-phosphate O-acyltransferase 2; AKT2, AKT Serine/Threonine Kinase 2; BSCL2, Berardinelli-Seip congenital lipodystrophy 2; CGL, congenital generalized lipodystrophy; CAV1, Caveolin 1; CIDEC, cell death inducing DFFA like effector C; FPLD, familial partial lipodystrophy; IR, insulin resistance; LIPE, hormone sensitive lipase; LMNA, lamin A/C; NAFLD, non-alcoholic fatty liver disease; PLIN1, perilipin 1; PPARG, peroxisome proliferator-activated receptor gamma; and PTRF, polymerase I and transcript release factor.

Gene and clinical syndrome	Pattern of inheritance	Clinical phenotype	Mechanism category	Gene product function	Reference
Unclassified genetic lipodystrophies					
MFN2 (Unclassified)	Autosomal recessive	Lower limb lipoatrophy with truncal & neck lipomatosis, peripheral neuropathy	Mitochondrial network perturbation	An outer mitochondrial membrane fusion protein that is also involved in mitochondrial-ER tethering	(99–101)
PCYT1A (Unclassified)	Autosomal recessive	Short stature, lipoatrophy, IR, NAFLD, cone-rod dystrophy, spondylometaphyseal dysplasia (variable penetrance of features with each mutation)	Key regulator of phosphatidylcholine synthesis	Enzyme involved in the rate-limiting step in phosphatidylcholine (PC) synthesis	(121–126)
FBN1 (Unclassified)	Autosomal dominant	Tall stature (Marfanoid), cranial abnormalities, progeroid facies, neonatal-onset lipodystrophy, variable IR.	Unclear	*FBN1* encodes profibrillin	(127–129)
Complex genetic syndromes associated with lipodystrophy					
BLM (*RECQL3*) (Bloom syndrome)	Autosomal recessive	Short stature, microcephaly, lipodystrophy, IR, telangiectasia	DNA repair	An ATP-dependent DNA helicase needed for control of homologous recombination repair	(130)
WRN (*RECQL2*) (Werner Syndrome)	Autosomal recessive	Progeroid, premature cataracts, hypogonadism, scleroderma-like skin changes, lipodystrophy, IR	DNA repair	An ATP-dependent DNA helicase needed for a variety of forms of DNA repair	(131, 132)
ZMPSTE24 (Mandibuloacral dysplasia and lipodystrophy)	Autosomal recessive	Mandibular & clavicular hypoplasia, acro-osteolysis, and cutaneous atrophy with lipoatrophy (progeroid-like faces), premature renal failure; also caused by mutations in *LMNA*	Lamin processing	A metallopeptidase needed for processing of pre-lamin A into functional lamin A	(133)
POLD1 (MDPL syndrome)	Autosomal dominant	Mandibular hypoplasia, Deafness, Progeroid features, and Lipodystrophy (MDPL syndrome)	DNA repair	The catalytic subunit of DNA polymerase delta, which is needed for lagging strand DNA replication	(134)
PIK3R1 (SHORT syndrome)	Autosomal dominant	Short stature, Hyperextensibility (and Hernias), Ocular depression, Rieger anomaly (anterior eye chamber abnormality), Tooth eruption delay, plus lipoatrophy, IR, and nephrocalcinosis	Defect in adipogenesis	Encodes a regulatory subunit of phosphatidylinositol 3-kinase, which is a key enzyme in the proximal insulin signalling pathway	(135, 136)
Autoinflammatory lipodystrophies					
PSMB8 (JMP or CANDLE syndrome)	Autosomal recessive	Joint contractures, Muscle atrophy, Microcytic anaemia, and Panniculitis-induced lipodystrophy (JMP); and Chronic atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE) syndrome	Adipocyte apoptosis	Encodes a subunit of the proteasome, which is required for degradation of immunogenic complexes. Lipodystrophy follows (or is concomitant with) autoimmune panniculitis	(137–139)
Lawrence syndrome	Acquired	Variable lipoatrophy with sparing of visceral adipose, IR, hepatic steatosis, and dyslipidaemia	Presumed autoimmune	Can be associated with low serum complement 4 and therefore may have aetiology involving the classical pathway of complement	(140)
Barraquer-Simmons syndrome	Acquired	Symmetrical loss of adipose in a cephalo-caudal pattern, may have increased gluteofemoral adipose, not insulin resistant	Presumed autoimmune	Low serum C3 and complement 3-nephritic factor antibody positive, which may result in complement-mediated destruction of adipocytes	(140)
Antiretroviral treatment associated lipodystrophy					
HAART-induced	Acquired	Distal (and facial) lipoatrophy with (variably) increased truncal and visceral adipose, mild IR, hypertriglyceridemia	Unclear	Variety of mechanisms have been proposed including mitochondrial toxicity and inhibition of prelamin A synthesis due to ZMPSTE24 inhibition	(141–143)

Table 2. **Other genetic and acquired lipodystrophies with their involved genes and proposed pathogenic mechanisms.** Lipodystrophy is an associated feature in several complex genetic syndromes and other isolated genetic defects, in most cases the mechanism of which is unclear. Acquired lipodystrophy is presumed to be autoimmune in origin or may be related to treatment for HIV. BLM/RECQL3, BLM RecQ like helicase; FBN1, fibrillin 1; HAART, highly active antiretroviral therapy; IR, insulin resistance; MFN2, mitofusin 2; NAFLD, non-alcoholic fatty liver disease; PCYT1A, phosphate cytidylyltransferase 1A; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; POLD1, DNA polymerase delta 1, catalytic subunit; PSMB8, proteasome subunit beta 8; WRN/RECQL2, Werner syndrome RecQ like helicase ; ZMPSTE24, zinc metallopeptidase STE24;

Lipodystrophy and insulin resistance

The central hallmark of the metabolic syndrome is insulin resistance and, other than obesity itself, compelling arguments exist linking almost all the features of the metabolic syndrome to underlying insulin resistance (144). Insulin resistance is a consistent feature of lipodystrophy and reveals a number of specific insights:

1. Despite the range of different genetic and acquired causes of lipodystrophy, almost all 'appreciable' (by which we mean at least partial in terms of extent) lipodystrophies are associated with insulin resistance. Exceptions which we are aware of include patients with *FBN1* mutations, though in this setting, the "apparent lipodystrophy" is more likely to be secondary to reduced food intake. In all other instances, lipodystrophies are associated with very or at least relatively low leptin levels, and thus a tendency to hyperphagia.

2. The severity of insulin resistance is broadly proportional to the extent of fat loss or dysfunction. In other words, generalized lipodystrophy is typically associated with more severe metabolic manifestations than partial lipodystrophy. Furthermore, upper body fat loss is less prone to be associated with metabolic disease than gluteofemoral fat loss. This is best exemplified by cases of Barraquer-Simons acquired partial lipodystrophy, where the fat loss proceeds in a cephalo-caudal pattern: this entity is often associated with the presence of C3 nephritic factor and sometimes with renal glomerular disease, and insulin resistance is usually not a feature unless fat loss extends down to the gluteofemoral adipose depot and/or patients are otherwise obese (140).

Another intriguing form of partial lipodystrophy is that associated with dermatomyositis – in these cases, lipodystrophy most prominently affects subcutaneous depots, whereas visceral fat is often preserved (145). The patients frequently manifest advanced NAFLD and insulin resistance.

Finally, in this context, metabolic disease is also typically more severe in affected girls/women than in boys/men, presumably because under normal circumstances fat mass in a lean women is roughly

twice that of a lean man (146). Collectively, the two points above indicate that lack and/or dysfunction of white fat is consistently associated with insulin resistance and the metabolic syndrome, particularly when the defect in white fat is compounded by hyperphagia due to relative leptin deficiency (147, 148).

3. NAFLD is a very consistent feature in insulin-resistant lipodystrophies, and is typically associated with metabolic dyslipidaemia (high triglycerides and low HDL cholesterol). Whilst there is limited data on liver histology in patients with lipodystrophy (149, 150), one study found that 40% of biopsied patients had bridging fibrosis or cirrhosis and 62% had definite steatohepatitis at a mean age of 29 years (38).

4. Patients with lipodystrophy are prone to early-onset cardiovascular disease. In some ways, this appears to be as severe as the cardiovascular disease associated with heterozygous familial hypercholesterolemia, as we have had several women present with ischaemic events well before the age of 50 years (151, 152).

5. Circulating markers of cellular or mitochondrial stress (e.g. FGF21, and GDF15) are elevated in both obesity (153, 154) and lipodystrophy (155). Patel et al. recently showed that chronic energetic overload results in an increase in serum GDF15 and FGF21 in mice (156), and at least in the case of GDF15, this change may help to alleviate ongoing surplus energy intake.

However, this potentially 'corrective' GDF15 signal is offset in lipodystrophic patients by relative or near-complete leptin deficiency, a key signal for the persistent hyperphagia observed in many patients with lipodystrophy. Unfortunately, hyperphagia compounds the relative deficiency of adipocyte energy storage capacity and is considered a major factor in the pathogenesis of metabolic disease in this disorder. Obese patients have elevated leptin levels, in keeping with their increased total fat mass (157), though it is does not seem to suppress hunger, and therefore the term 'leptin resistance' has been coined. In both lipodystrophy and obesity (158), the relative lack of leptin

action contributes to ongoing surplus energy intake and insulin resistance, although it should be noted that leptin signalling at its receptor is actually increased in obesity and that a lack of response to additional exogenous leptin is complex and incompletely understood (159).

Adiponectin is an adipokine that paradoxically falls in obesity and insulin resistance, though the mechanisms underlying control of its release is unclear. Adiponectin levels are also low in lipodystrophy, and this is generally in proportion to the loss of adipose tissue (i.e. lower in CGL than FPLD) and the severity of insulin resistance (160).

Insulin receptor signalling defects

"Insulin receptoropathies", a term used to describe insulin-resistant states caused by a mutation or acquired defect in one of the proximal insulin signalling components (most commonly the insulin receptor (INSR) itself), represent another cluster of monogenic disorders associated with severe insulin resistance (161). Examination of the differences between patients with obesity-related metabolic syndrome, lipodystrophy, and "insulin receptoropathies" (Table 3) indicates that whereas lipodystrophy- and obesity-associated metabolic syndrome are strikingly concordant, there are several marked differences between the latter and insulin receptoropathies. In particular, NAFLD and dyslipidaemia are typically not seen in insulin receptoropathies (162), and adiponectin levels tend to be high rather than low in these conditions (163).

Characteristic	Obesity with metabolic syndrome	Lipodystrophy	Insulin receptoropathy
Body mass index	↑	↓ in CGL ↑ or ↔ in FPLD	↔
Body fat percentage	↑	↓↓↓ in CGL ↓ in FPLD (especially gluteofemoral fat)	↔
Waist circumference	↑	↔ or ↑	↔
Hip circumference	Relative ↓	↓↓	↔
Waist : hip ratio	↑↑	↑↑	↔
Insulin resistance	↑	↑↑	↑↑↑
Triglycerides	↑	↑↑	↔
HDL-Cholesterol	↓	↓	↔
Leptin	↑↑	↓↓↓ in CGL Relative ↓ in FPLD	↔
Adiponectin	↓	↓↓	↑↑
NAFLD	↑	↑↑	Absent
PCOS	↑	↑↑	↑↑
Atherosclerosis	↑	↑↑	Unknown

Table 3. Comparison of obesity, lipodystrophy, and insulin receptoropathies. Key differences and similarities between patients with obesity and the metabolic syndrome, lipodystrophy, and insulin receptor defects. The number of arrows is indicative of the severity and/or magnitude of the perturbation. CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; and PCOS, polycystic ovarian syndrome.

Adipose inflammation

Histological assessment of adipose tissue from patients with the metabolic syndrome consistently demonstrates features of inflammation (164–166), the extent of which correlates with the severity of insulin resistance and NAFLD in humans (167). Inflammation appears to be more prominent in adipose tissue with higher lipolytic capacity (particularly visceral adipose); however, opinion remains divided on the extent to which macrophage infiltration is pathogenic in adipose dysfunction and/or insulin resistance (168). Obesity-associated insulin resistance is a state of chronic, systemic inflammation, as evidenced by elevated IL-6, high-sensitivity C-reactive protein, and GDF15, among other markers, but these derive from more than just adipose tissue. Nevertheless, adipose tissue macrophages certainly act as one source of inflammatory cytokines that contribute to the systemic inflammatory state, and their contribution appears to be ameliorated by weight loss (169).

There have been only a few studies examining the histology of adipose tissue in patients with inherited lipodystrophy. Patients with FPLD4 secondary to *PLIN1* mutations had similar features of inflammation and fibrosis to those reported in obese people, whereas patients with *CIDEC*-associated lipodystrophy (83), *MFN2*-associated lipodystrophy (100), and *LMNA* mutations (170) did not demonstrate gross inflammation. Collectively, evidence from genetic lipodystrophies that almost always cause severe insulin resistance tends to suggest that adipose inflammation is a second 'hit' rather than the primary driver of adipose dysfunction and so, at least in our view, raises questions about the widespread interest in anti-inflammatory strategies for obesity-associated metabolic disease.

NAFLD is a very consistent feature of lipodystrophies that are severe enough to cause insulin resistance and other features of the metabolic syndrome. In this scenario, non-alcoholic steatohepatitis (NASH) is very common and could conceivably be involved in causing hepatic insulin

resistance. However, here too the liver pathology is very likely to occur secondary to adipose tissue dysfunction.

Evidence for subtle lipodystrophy in the general population

The striking overlap between lipodystrophy and more prevalent forms of the metabolic syndrome (see Table 3) has long suggested that subtle forms of lipodystrophy may be relevant to the pathogenesis of metabolic syndrome and type 2 diabetes in particular (171–173). However, direct supportive evidence has been hard to come by so it has remained a largely hypothetical premise.

In 2014, Scott et al. undertook a GWAS that used fasting insulin as a proxy for insulin resistance (174). Intriguingly, just over half the loci associated with a higher fasting insulin were also associated with higher triglycerides, lower HDL cholesterol, and either a lower BMI and/or a reduction in gluteofemoral fat mass as measured by dual X-ray absorptiometry (DXA) scanning. Lotta et al. later performed a much larger GWAS focused on loci associated with a combination of BMI-adjusted insulin, higher triglycerides, and lower HDL cholesterol (175). This analysis identified 53 loci, which were replicated in a second cohort and shown to be significantly associated with gold-standard hyperinsulinaemic euglycaemic clamp-based measures of insulin resistance. In a large human cohort in whom fat mass and distribution were documented with DXA scans, there was a significant association between higher insulin-resistant SNP scores and lower levels of gynoid and leg fat mass (175). Interestingly, in this study, reduced expansion of gluteofemoral fat depot was also documented in response to weight gain (175). Importantly, this 53 SNP score was enriched in patients with FPLD1, which is in many ways an extreme form of apple-shaped fat distribution, implying that these common alleles contribute to both common insulin resistance and a specific form of partial lipodystrophy known as FPLD1 (Figure 3). This is also consistent with observations that there are a large number of patients with clinical features of FPLD1 (or FPLD2) with no known genetic diagnosis.

Waist-hip ratio (WHR) is a widely used non-invasive measure of adipose tissue distribution, and its relationship to diabetes and cardiovascular risk is well established (176, 177). Given the fact that

WHR is a ratio, it can be modified by changes in either the numerator or denominator. However, visceral fat accumulation (i.e. an increase in the numerator) is usually assumed to be the driving factor behind the link between this index of fat distribution and insulin resistance. This notion is also supported by considerable scientific evidence (178–182). However, when Lotta et al. generated SNP risk scores for loci shown to be associated with a higher WHR, through a specific association with either a reduction in hip circumference (22 out of a total of 202 loci) or with an increase in waist circumference (36 out of 202 loci), both scores were associated with cardiometabolic risk factors as well as an increase in the odds ratio of developing type 2 diabetes mellitus and coronary disease (183). Intriguingly, the odds ratio for the risk of type 2 diabetes was statistically significantly greater for the hip-specific risk score than the waist-specific score, whereas the odds ratios for cardiovascular disease were similar. Collectively these data are at least consistent with the notion that subtle partial lipodystrophy is a major factor in the pathogenesis of the metabolic syndrome in the general population (Figure 3). Put another way, people with an impaired capacity to increase hip fat mass in response to weight gain are more likely to develop insulin resistance and type 2 diabetes if they do increase their weight.

Shared treatment strategies for lipodystrophy and obesity

The implications of these observations are that therapeutic strategies in both lipodystrophy and obesity-related metabolic syndrome should aim to minimize adipocyte overload. This could be achieved by increasing adipocyte number/function or by reducing the energetic load on adipose tissue.

Increasing fat mass is a highly effective method for treating the metabolic syndrome in mice. Evidence from animal models has demonstrated the profound benefits associated with adipose transplant in severely lipodystrophic mice (184, 185). But, aside from being cosmetically unappealing, fat transplantation would also be technically challenging in humans. However, thiazolidinediones (TZDs), which selectively activate PPARγ, very effectively improve insulin sensitivity in the clinical setting, primarily by increasing subcutaneous fat mass (186).

Thus, reducing caloric intake is the mainstay of treatment for the metabolic syndrome and it is highly effective. Data suggests that whilst there are some mild benefits of diets of various composition (the Mediterranean diet, for example), the most effective therapy is considerable calorie restriction. Limiting intake to <650 kcal/day can result in complete remission of diabetes (187) in patients with a relatively short duration of type 2 diabetes. A similar approach can be achieved through bariatric surgery (188); though the metabolic impact varies depending on the technique used, the greater the reduction in net energy intake, the greater the reduction in weight and improvement in insulin sensitivity (7). Bariatric surgery has also been demonstrated to be very effective in a small number of patients with FPLD, despite these patients having a BMI lower than would be typically used as an eligibility criterion for surgery (4).

Lastly, as mentioned previously, leptin replacement therapy is highly effective in lipodystrophy (38, 189) but patients with obesity (who have high circulating leptin) do not appear to show a response

to additional exogenous leptin unless they are already in a weight-reduced state (190). However, there is ongoing interest in targeting leptin therapy to obese subjects with relatively low leptin levels.

Conclusion

Inherited lipodystrophies are a complex group of conditions, all of which ultimately impair adipose tissue function and particularly its capacity to efficiently store surplus energy. The metabolic sequelae of lipodystrophy are remarkably similar to those associated with obesity, and compelling human genetic evidence now suggests that this similarity reflects adipocyte overload in both settings. Thus the goal of treatment in both states is to alleviate the energetic burden on adipocytes by inducing negative energy balance and/or weight loss.

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Figures

Figure 1. White adipose tissue contains the body's major store of energy. Even lean adults store 600-800mJ of energy as triglyceride in adipose tissue, compared to 6-8mJ as glycogen in liver and muscle. They physiological regulation of triglyceride stores varies in different adipose tissue depots. Gluteofemoral subcutaneous white adipose is relatively insulin sensitive and its expansion is not associated with cardiometabolic disease, whereas visceral adipose tissue has a higher rate of lipolysis and is more closely linked with insulin resistance.

Figure 2. Some of the genes in which mutations cause lipodystrophy have well characterized roles in the function of adipocytes. PPARγ (mutated in FPLD3) is the 'master regulator' of adipogenesis. It heterodimerises with retinoid X receptor and co-ordinates transcription of multiple proteins central to adipocyte function (e.g. perilipin, CD36 and lipoprotein lipase). BSCL2, or seipin, (mutated in CGL2) is an ER (endoplasmic reticulum) protein required for early lipid droplet (LD) biogenesis. AGPAT2 (mutated in CGL1) is necessary for the conversion of glycerophosphates (G-3-P) into triacylglycerols (TAG) using fatty acids linked to co-enzyme A (FA-CoA). CAV1 (mutated in CGL3) and PTRF (mutated in CGL4) are required for the formation of caveolae, which may be sites for non-esterified fatty acid (NEFA) uptake. PLIN1 (mutated in FPLD4) regulates lipolysis from lipid droplets, and HSL (mutated in FPLD6) is one of the lipases involved in this process. Finally, CIDEC (mutated in FPLD5) is required for the formation of unilocular lipid droplets, though how this is achieved is unclear.

Figure 3. The severity of lipodystrophy and the degree of adipose dysfunction correlate broadly with the severity of insulin resistance. This principle extends from the most extreme form of lipodystrophy (congenital generalized lipodystrophy, CGL) through familial partial lipodystrophies (FPLD) to the general population. People in the highest quintile ("Q5") for a polygenic risk score for insulin resistance (see Lotta et al. (ref 153)) have less gluteofemoral fat, resulting in an 'apple-shape' fat distribution, whereas those in the lowest quintile ("Q1") manifest a protective "pear-shaped" fat distribution and are less insulin resistant. FLPD type 1 ("FPLD1") represents an intermediate state between other monogenic forms of FPLD and the highest risk individuals from the general population.

The degree of genetic disruption of adipose tissue also correlates with these phenotypes as exemplified by the impact of a range of PPARG mutations: complete loss of PPARG function can cause CGL; dominant negative PPARG mutants cause FPLD3; and common PPARG variants impact on insulin resistance at a population level. Exemplar PPARG mutations in each of these categories have been included. Each black dot represents a distinct monogenic disease (see Table 1 for classifications) and each red diamond represents a common genetic variant that influences adipogenesis and insulin resistance.