

LIPODYSTROPHY SYNDROMES: PRESENTATION AND TREATMENT

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ABSTRACT

Lipodystrophy syndromes are a heterogeneous group of diseases, characterized by selective absence of adipose tissue. In one sense, these diseases are lipidpartitioning disorders, where the primary defect is the loss of functional adipocytes, leading to ectopic steatosis, severe dyslipidemia, and insulin resistance. These syndromes have attracted significant attention since the mid-1990s as the understanding of adipose tissue biology grew, initially spurred by the discovery of the pathways leading to adipocyte differentiation and maturation, and then by the discovery of leptin. Although lipodystrophy syndromes are known since the beginning of the 20th century, significant progress in understanding these syndromes were made in the last two decades, placing these syndromes at the forefront of the translational metabolism field. Currently, more than 20 distinctive molecular etiologies have been attributed to cause human diseases most of which map to adipocyte differentiation or lipid droplet pathways. Seemingly acquired syndromes are recently reported to have a genetic basis, suggesting that our "pre-genome" understanding of the syndromes was inadequate and that we need to likely change our classification schemes. Regardless of the etiology, it is the selective absence of adipose tissue and its function, leading to

the reduced ability to store long-term energy that perturbs insulin sensitivity and lipid metabolism. The treatment of these syndromes has also attracted considerable interest. The most successful example of the treatment of these syndromes came from the demonstration that leptin replacement strategy improved insulin resistance and dyslipidemia in the most severely affected forms of the disease, leading to an FDA approved therapy for generalized lipodystrophy syndromes. In the partial forms of the disease, the phenotypes are more complex, and the efficacy of leptin is not as uniform. Currently, standard treatment-resistant partial lipodystrophy is an EMAapproved indication, and numerous trials are in progress, either evaluating the efficacy of leptin in familial partial lipodystrophy or aiming to develop potential new treatments for the partial forms of the disease. These rare metabolic diseases are likely to continue to fuel novel breakthroughs in the field of metabolism in the foreseeable future.

INTRODUCTION

Lipodystrophy syndromes comprise a heterogeneous group of disorders characterized by either generalized or partial lack of adipose tissue depending on the type of lipodystrophy (1, 2). Lipodystrophy classically has been classified as congenital or acquired. Patients with partial lipodystrophy may exhibit excess adipose tissue accumulation in preserved areas of the body. Lipodystrophy syndromes usually manifest with several metabolic abnormalities associated with severe insulin resistance that include diabetes mellitus, hypertriglyceridemia, and hepatic steatosis which can progress to steatohepatitis. Other common manifestations are acanthosis nigricans, polycystic ovarian syndrome (PCOS), and eruptive xanthomas (due to severe hypertriglyceridemia) (3, 4). Metabolic derangements are mostly responsible for the serious comorbidities associated with lipodystrophy; some of which are chronic complications of poorly controlled diabetes. acute pancreatitis, hepatic cirrhosis, proteinuria and renal failure, and premature cardiovascular disease (Fig.1) (1, 2). Typically, standard treatments fail to achieve good glycemic control in most patients with lipodystrophy, although episodes of diabetic ketoacidosis have rarely been

reported (5). The severity of the comorbidities depends on the subtype, extent of fat loss, and other clinical characteristics such as gender and age. Major causes of mortality are cardiovascular diseases (6-9), liver diseases (2, 10), acute pancreatitis (2), renal failure (10), and sepsis (3). In certain areas of the world, infectious etiology also rises to the surface suggesting that perturbed immune function may be at play (11). Clinical features of lipodystrophy are shown in Table 1. It is important to note that there are additional components of the disease that may be specific to each molecular etiology. In addition, we are beginning to recognize that patients often report reduced quality of life with increased overall pain (requiring frequent use of pain medications), sleep disturbances and sleep apnea, gastrointestinal dysmotility, mood disturbances such as depression and anxiety and psychiatric diseases (12, 13).

Loss of sc fat

Primary event
Ectopic storage of fat

Severe hypertriglyceridemia • Acute pancreatitis

Heart disease

- · Atherogenic lipid profile
- Atherosclerosis
- Cardiomyopathy
- Arrhythmias

Liver disease

Increased de novo lipogenesis

- MAFLD
- MASH
- Cirrhosis

Neuromuscular disease • Bone cysts

Bone cyst
 Myopathy

High mortality

- Cardiovascular disease
- Sepsis
- Liver disease
- Kidney disease





Leptin deficiencyHyperphagia

Core pathophysiology leading to metabolic abnormalities

Severe insulin resistance
Poorly controlled diabetes

Complications of diabetes

Kidney diseaseProteinuria

End stage renal disease

Reproductive abnormalities in females

- · Failure in puberty progression
- Hyperandrogenism
- Polycystic ovaries
- Infertility

Autoimmunity in acquired cases

- Autoimmune hepatitis
- Glomerulonephritis

Poor quality of life

- Low self esteem
- High rates of depression and anxiety
- Attention deficit problems
- Fatigue
- Pain

 Table 1. Shared Clinical Features That Raise Suspicion for Lipodystrophy

Loss or absence of adipose tissue in a partial or generalized fashion

Disproportionate hyperphagia (inability to stop eating, waking up to eat, fighting for food)

Muscle hypertrophy and prominent veins (phlebomegaly)

Cushingoid appearance (e.g., familial partial lipodystrophy)

Pseudo-acromegaloid appearance

Progeroid appearance (progeroid forms)

Acanthosis nigricans (associated with insulin resistance)

Proteinuria, renal dysfunction

Reproductive dysfunction (reduced fertility, hyperandrogenism, oligomenorrhea, hirsutism and/or polycystic ovaries)

Musculoskeletal abnormalities (occasionally)

Cardiomyopathy (occasionally)

Metabolic abnormalities

• Relatively early onset of insulin resistant diabetes which can be severe in some patients with requirement for high doses of insulin, e.g., requiring ≥200 U/day, ≥2 U/kg/day, or U-500 insulin, early development of complications.

• Dyslipidemia which is characterized by elevated triglycerides and low HDL cholesterol. Hypertriglyceridemia can be very severe (≥500 mg/dL) and is unresponsive to treatment with associated history of acute pancreatitis.

• Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease (e.g., viral hepatitis). Hepatic steatosis (e.g. radiologic evidence), Hepatomegaly, Metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis.

Lipodystrophy is an intriguing rare disease that helps us obtain а better understanding of the pathophysiology of metabolic abnormalities associated with insulin resistance. The main cause of insulin resistance in lipodystrophy is the fact that the excess energy cannot be stored in adipose tissue, which is secondary to either the near total lack of adipocyte storage in patients with generalized lipodystrophy or a limited capacity to store in partial lipodystrophy. Limited lipid storage capacity causes the failure of buffering for postprandial lipids and secreting substantial adipokines, which in turn results in excessive levels of triglycerides and lipid intermediates in circulation. The body stores fat at ectopic sites such as the liver because of inability to store energy in the subcutaneous adipose depots. Levels of adipokines and hormones secreted from the adipose tissue, most characteristically leptin, are decreased in these patients especially if fat loss is extensive (1, 2, 9, 14, 15). Leptin has a fundamental role in glucose and lipid homeostasis, but more importantly, leptin is the key hormone responsible for regulating food intake (16). Low levels of leptin in lipodystrophy trigger hyperphagia, which is often extreme (17-19). In addition, leptin protects pancreatic beta cells from lipotoxicity at least in rodent models (20, 21). Leptin improves insulin sensitivity by increasing glucose uptake in peripheral tissues such as muscle via sympathetic nervous system activation. Leptin also decreases hepatic gluconeogenesis (22-24).

DIAGNOSIS

The diagnosis of lipodystrophy is usually made clinically based on history, body distribution of adipose

tissue, physical examination, and metabolic profile. Lipodystrophy should be suspected in any person with partial or complete lack of subcutaneous adipose tissue. However, the diagnosis of lipodystrophy is often delayed because of the rarity of these syndromes and the failure of the physicians to recognize this disease. Although patients with congenital generalized lipodystrophy lack subcutaneous adipose tissue from birth, specific diagnosis is usually made during childhood or even adulthood when they start developing metabolic abnormalities. This is at least partly because the awareness of lipodystrophy is still low among physicians. The problem of recognition is much more common for partial lipodystrophy. The distribution of fat loss varies in different types of partial lipodystrophy. At first glance, certain types of partial

lipodystrophy cannot be clearly distinguished from other common metabolic diseases (e.g., poorly controlled diabetes mellitus with truncal obesity) based on phenotype unless the physician is suspicious for lipodystrophy and checks carefully for certain characteristic such as the appearance of the limbs which look thinner than in a normal person. Also, the onset of fat loss may be gradual and delay the diagnosis both in genetic and acquired forms (3, 4). Lipodystrophy syndromes should be considered in the differential diagnosis in patients with relatively early onset insulin resistant diabetes mellitus, persistent hypertriglyceridemia, hepatic steatosis, PCOS, and hepatosplenomegaly. Other diseases that should be considered in the differential diagnosis of lipodystrophy are listed in Table 2.

Table 2. Differential Diagnosis of Lipodyst	rophy Syndromes	
Generalized Lipodystrophy Syndromes	Constitutional thinness	
	Uncontrolled type 1 diabetes mellitus	
	HIV-associated wasting	
	Anorexia nervosa, cachexia and starvation	
	Chronic infections	
	Adrenocortical insufficiency	
	Thyrotoxicosis	
	Acromegaly	
	Diencephalic syndrome	
Partial Lipodystrophy Syndromes	Cushing's syndrome	
	Truncal obesity	
	Type 2 diabetes (lipodystrophy like	
	phenotype)	
	HIV associated lipodystrophy	
	Multiple symmetric lipomatosis	

Progeroid syndromes
Acromegaly

A thorough physical examination is required for clinical diagnosis of lipodystrophy. Clinicians should pay specific attention to evaluating the extremities and the gluteal region for leanness and muscularity. In addition, other body parts should be examined for accumulation of excessive amounts of fat. Due to marked abdominal obesity and excessive fat accumulation in the neck, patients with familial partial lipodystrophy (FPLD) may be misdiagnosed as Cushing's syndrome (2).

The absence of subcutaneous fat can be quantified by using conventional anthropometric measurements, dual energy x-ray absorptiometry (DXA) scan, wholebody magnetic resonance imaging (MRI), and computed tomography (CT) scan (4). Anthropometry including skinfold thickness and limb circumference measurements are easy and affordable ways to estimate the fat loss and redistribution (9). Use of skin calipers may aid, but when unavailable, simple inspection and palpation of skin thickness may be very useful. We have used a cut-off of 11 mm in men and 22 mm in women in mid-thigh thickness as a screening point to suspect clinical presence of lipodystrophy that warrants further detailed work-up. For facial fat loss, serial photography may be used to evaluate the gradual loss of facial fat. DXA, MRI, and CT scans are non-invasive modalities that may be used for quantification of fat on a tissue-specific basis, but at least in the United States, none are covered for this purpose by insurance companies (3, 4, 25).

New Diagnostic Strategies and Technological Tools

Due to the complex nature, heterogeneity, and rarity of lipodystrophy syndromes, the need for accurate and objective diagnostic tools is increasing. Imaging techniques play an important role in visualizing fat distribution and assisting in the diagnosis of lipodystrophy. While measuring subcutaneous fat tissue thickness with high-resolution ultrasound is a practical and non-invasive method, results vary significantly depending on age, gender, and ethnicity (26).

Body fat distribution can be quantitatively determined using whole body Dual Energy X-ray absorptiometry (DXA scans). Work from our group indicates that images obtained with the "Fat Shadows" method, based on highlighting only the fat tissue in DXA images, can support the diagnosis of FPLD and generalized lipodystrophy (GL). Using this approach, FPLD was distinguished from control subjects with 85% sensitivity and 96% specificity, while GL was distinguished from nonobese control subjects with 100% sensitivity and specificity (27). In addition, Garg and colleagues reported that the DXA-derived lower limb fat (%) is diagnostic of FPLD2 with 99% specificity and 100% sensitivity in adult females below the 1st percentile (28).

A study by our group also suggests that the combined use of measurements performed on pelvic MRI images can be promising for the reliable diagnosis of FPLD. The combination of gluteal fat thickness \leq 13 mm and pubic/gluteal fat ratio \geq 2.5 was found to have 97% sensitivity and 91% specificity in the overall cohort and 100% sensitivity and 90% specificity in females for the diagnosis of FPLD (29).

Technological applications are also being developed to increase awareness of lipodystrophy and provide practical solutions for non-experts. LipoDDx, designed as a new mobile app, stands out with its 80% effectiveness in recognizing lipodystrophy subtypes when screening patients with adipose tissue loss, but more research is still needed in this area (30). In addition, integrating artificial intelligence (AI) into medical diagnosis may hold promise for diagnosing lipodystrophy syndromes in the future. In this regard, a study by da Cunha Olegario NB et al. (31) was designed to enable the identification of the CGL phenotype from patient images with a deep learning model, analyzing more than 330 images, including individuals of different ages with phenotypically confusing features. After a fourfold cross-validation technique, the CGL phenotype could be identified with a mean accuracy, sensitivity, and specificity of over 90% (31).

These developments in diagnostic methods and technological tools for lipodystrophy syndromes not only increase diagnostic accuracy but also pave the way for creating a more personalized and effective treatment algorithms.

Laboratory Testing

Laboratory testing is a valuable tool for physicians to support the diagnosis. If the physical phenotype is not recognized, hyperglycemia, insulin resistance, and severe hypertriglyceridemia that is non-responsive to therapy may provide important clues for the diagnosis. When fat loss is not confirmed by the physical examination or by an imaging modality, hyperglycemia and hypertriglyceridemia that are resistant or unresponsive to conventional treatment may serve as surrogate indicators to the clinician that a patient may have lipodystrophy. Lipodystrophy should be suspected in patients with uncontrolled diabetes (e.g., requiring ≥200 units/day (≥2 units/kg/day) of insulin) or triglyceride levels that remain persistently elevated (e.g., ≥500 mg/dL) despite fully optimized therapy and diet modifications. All patients except those with localized lipodystrophy, should be tested for blood glucose levels, glycated hemoglobin (HbA1c), serum lipids (especially triglyceride levels), and liver function tests on the initial evaluation and during subsequent In addition to these laboratory encounters. evaluations, leptin levels may be used in support of the diagnosis. However, it should be noted that leptin

assays are not standardized, and low leptin levels may be observed in other conditions such as hypothalamic amenorrhea and malnutrition. Thus, low leptin level is not specific for the diagnosis lipodystrophy (4, 32). Circulating adiponectin though not a clinically available test, may be helpful in differentiating patients with generalized lipodystrophy from those who have constitutional leanness, fat loss due to calorie imbalance or excessive exercise as well as poorly controlled diabetes mellitus with insulin deficiency. In all of the cases except lipodystrophy, adiponectin levels will be normal or even higher than normal whereas in lipodystrophy including familial partial lipodystrophy, serum adiponectin levels are usually low.

Genetic Testing

In the genetic forms of lipodystrophy, parental consanguinity and the mode of inheritance should be questioned (2). Genetic testing is available for known genetic forms of lipodystrophy. In our earlier version of this review, we had mentioned that genetic tests to be available only in certain clinical and research laboratories; however, there has been incredible growth in the availability of genetic testing through commercial or certified clinical labs in the US since 2016. Because additional loci for genetic lipodystrophy syndromes are presumed to be present, negative genetic tests do not rule out a genetic condition. When commercial panels are not positive, an attempt for whole exome or even whole genome testing with mitochondrial gene evaluation has evolved as viable and increasingly more available strategies. If these latter tests cannot be undertaken commercially, ongoing research in specialty centers can be considered where pipelines to analyze VUS (variant of uncertain significance) and evaluate transcriptomic profiles from PBMCs or tissues may be considered.

Gauging Disease Severity in Lipodystrophy: Roadmap for Clinical Follow Up

Given that lipodystrophy syndromes are complex and may impact multiple organs and systems, it is important to start a follow-up schedule while paying attention to all aspects of the conditions. To help assess the status and disease progression of patients with lipodystrophy, the LD Severity Score study group has developed the 'LD Severity Score (LDS)', an online tool easily accessible to all clinicians. This online application generates an overall score using multisystem assessments across eight domains (diabetes and its complications, lipid status, cardiovascular conditions, liver and kidney function, reproductive system status, and other conditions) to capture the various clinical manifestations of the disease holistically. The Clinical Global Impression (CGI) and the global improvement (GI) scores were generated based on the subjective assessments of all these categories by a group of experts during a representative patient visit as part of the app's validation. The LDS demonstrated high content validity and feasibility, along with high reliability indicated by interclass correlation coefficients greater than 0.95 (33). The results of the lipodystrophy severity scores calculated for each patient in the app are shown in a figure, compared to the Clinical Global Impression scores generated by the experts. The LD Scoring tool, developed to predict the clinical outcomes and/or treatment effects of lipodystrophy, can be accessed at https://ldscoring.com/.

CLASSIFICATION OF LIPODYSTROPHY SYNDROMES

Lipodystrophy syndromes can be classified as genetic or acquired. However, they are simply classified as generalized and partial in clinical practice most of the time (Table 3).

Table 3. Classification of Lipodystrophy Syndromes			
Туре	Lipodystrophy Phenotype	Subtype (Genes Involved)	Key Clinical Features
Generalized lipodystrophy syndromes			
		CGL1 (AGPAT2)	Loss of metabolically active fat
	Near total	Autosomal	with sparing of mechanically
Congenital	absence of the	recessive	functioning fat
Generalized	body fat starting	CGL2 (BSCL2)	Generalized absence of adipose
Lipodystrophy	at birth or shortly	Autosomal	tissue
(CGL)	after, generalized	recessive	
	muscularity,	CGL3 (CAV1)	Short stature, vitamin D
	metabolic	Autosomal	resistance, hypocalcemia,
	abnormalities	recessive	hypomagnesemia, achalasia
		CGL4 (PTRF)	Myopathy, skeletal abnormalities,
		Autosomal	pyloric stenosis and
		recessive	gastrointestinal motility problems,
			cardiac arrhythmias
	Other genes associ	ated with GL	LMNA (e.g., T10I, biallelic lamin A
	phenotype		specific variants), PPARG
			(biallelic variants), PCYT1A,
			PLAAT3

	Near total	Autoimmune	AGL follows an autoimmune
Acquired	absence of the		disease, e.g. JDM
Generalized	body fat	Panniculitis-	Tender subcutaneous nodules
Lipodystrophy	commonly	associated	that herald the onset of AGL
(AGL)	develops during	Idionathic	No history of auto-immune
	childhood or	lalopatilio	disease or panniculitis
	adolescence,		
	metabolic		
	abnormalities		
Partial lipodyst	rophy syndromes		
		FPLD1, Kobberling	Loss of subcutaneous fat from the
		(Unknown)	limbs, although they usually have
			truncal obesity. Palpable "ledge"
			formation between the normal and
			lipodystrophic areas
		FPLD2, Dunnigan	Increased muscularity and loss of
		(LMNA)	fat in the limbs, excess fat
		Autosomal	accumulation in the face and neck
Familial	Loss of fat from	dominant	
Partial	the limbs,	FPLD3 (PPARG)	Loss of subcutaneous fat from the
Lipodystrophy	metabolic	Autosomal	limbs, specifically distally
(FPLD)	abnormalities	dominant	
		FPLD4 (<i>PLIN1</i>)	Loss of subcutaneous fat from the
		Autosomal	limbs, histologically; small
		dominant	adipocytes, macrophage
			infiltration and fibrosis of adipose
			tissue
		FPLD5 (CIDEC)	Loss of subcutaneous fat from the
		Autosomal	limbs, small, multilocular lipid
		recessive	droplets in adipocytes
			Increased visceral fat,
		FPLD6 (<i>LIPE</i>)	dyslipidemia, hepatosteatosis,
		Autosomal	insulin resistance, and diabetes,
		recessive	some may present with muscular
			dystrophy and elevated serum
			creatine phosphokinase
	Loss of		Coinciding autoimmune disorders;
	subcutaneous fat	Autoimmune	dermatomyositis/polymyositis and
	starts from the		SLE are most associated
Acquired	tace, neck, upper		disorders
	extremities, and		Low serum complement 3,
Lipodystrophy	progresses to the	MPGN-associated	glomerulonephritis, hematuria,
(APL)	trunk. Lower		urinary casts, proteinuria, nephritic
	limbs are typically		syndrome, renal failure

	spared, some patients have excess fat over the gluteal region, thighs and calves	Idiopathic	No history of auto-immune disease or MPGN
Progeria		LMNA, ZMPSTE24,	Progeroid features: most present
associated		POLD1, WRN,	with partial lipodystrophy, though
lipodystrophy		MTX2, FBN1,	in rare cases, fat loss can occur in
		BANF1, KCNJ6,	a more generalized fashion
		SPRTN,	
		ALDH18A1,	
		ERCC8, ERCC6	
		(34) BUD13 (35) ,	
		EPHX1 (36), OPA3	
		(37), PDGFRB (38),	
		SLC25A24 (39),	
		SUPT7L (40)	
Other genes		AKT2, PCYT1A,	Various presentations of
associated		PIK3R1, MFN2,	lipodystrophy
with		PSMB8, ADRA2A	
lipodystrophy			

GENERALIZED LIPODYSTROPHY SYNDROMES

Generalized lipodystrophy syndromes are rare disorders that are either inherited (Berardinelli-Seip Syndrome) (41-43) or acquired (Lawrence Syndrome) (9).

Congenital Generalized Lipodystrophy

Congenital Generalized Lipodystrophy (CGL) or Berardinelli-Seip syndrome is a rare syndrome which manifests with near total absence of adipose tissue. It is inherited in an autosomal recessive manner. Fat loss is usually recognized shortly after birth or in the first years of life, although patients may be diagnosed later during teenage years or adulthood. There have been over 300 reported cases to date (14, 44, 45).

In addition to lack of subcutaneous fat, patients may present with hepatomegaly and umbilical protuberance during infancy. Extensive acanthosis nigricans and prominent musculature may also contribute to the striking phenotype of these patients (46). Affected females may have irregular menstrual cycles, oligomenorrhea, clitoromegaly, and hirsutism. Premature menarche and pubarche are also rarely seen. Most males were reported to be fertile whereas only a few females had successful pregnancies (47). Sperm abnormalities have been reported in CGL. Other clinical manifestations include advanced bone age, bone cysts which may progress over time, mild mental retardation, cardiomyopathy, and cardiac rhythm disturbances (48-50). A significant association has been found between diabetic foot ulcers and, specifically, generalized lipodystrophy; foot ulcer complications may arise earlier in GL than in partial lipodystrophy (PL) (51).

Children with CGL usually have a voracious appetite and accelerated growth. Basal metabolic rate may be increased. Patients also report heat intolerance, especially after meals and sometimes gustatory sweating. Hypertriglyceridemia usually presents with high levels of chylomicrons and very low-density lipoproteins (VLDL) and reduced levels of high-density lipoproteins (HDL). Low HDL cholesterol levels are the most common lipid abnormality (49). Severe hypertriglyceridemia usually results in recurrent acute pancreatitis. Insulin resistance commonly results in diabetes in adolescence or later. Diabetes is rarely responsive to insulin therapy. Serum leptin levels are very low (32). Metabolic dysfunction-associated liver disease (MASLD) and steatohepatitis are common in individuals with CGL and have the potential to advance to cirrhosis at relatively early stages of life (49, 52). A study conducted in Brazil determined that the average age of death of 20 CGL patients who died between 1997-2017 was 27.1±12.4 years. In this patient group, most of whom were CGL2, the most common causes of death were infectious causes (35%), such as pneumonia and liver complications (35%), such as cirrhosis (11).

The genetic defect can be determined in the majority of patients with CGL. There are at least four molecularly distinct types of CGL. However, it is noteworthy that there are some cases of CGL reported without any pathogenic variants in any of the four genes described below.

CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 1 (CGL1)

2 1-acylglycerol-3-phophate O-acyltransferase (AGPAT2), a key enzyme in triglyceride synthesis, is deficient in CGL1. AGPAT2 gene is located on chromosome 9q34. AGPAT2 catalyzes the acvlation of lysophosphaditic acid to form phosphaditic acid, a key intermediate in the biosynthesis of triglyceride and glycerophospholipids (53). Precisely how AGPAT2 deficiency causes lipodystrophy remains unsolved, possible mechanisms include but impaired lipogenesis, altered differentiation of preadipocytes to adipocytes. altering normal activation of phosphatidylinositol 3-kinase (PI3K)/Akt and PPARG pathways in the early stages of adipogenesis, and apoptosis/necrosis of adipocytes (2, 54, 55). More recent findings suggest that lysophosphatidic acid (LPA) could potentially trigger inflammation and fibrosis in the adipose tissue, leading to eventual loss of adipose tissue. In addition, LPA accumulation in the liver can also trigger the progress of metabolic dysfunction-associated fatty liver disease (MAFLD) to MASH (56).

Adiposity is preserved in certain body parts such as orbits, palms and soles, which constitute the mechanical adipose tissue (32, 57-59) (Fig.2). *AGPAT2* pathogenic variants along with *BSCL2* pathogenic variants are responsible for the majority of the CGL cases.



Figure 2. CGL1. Near total absence of adipose tissue in CGL1 (2A, 2C, 2D). Magnetic resonance images document the lack of subcutaneous fat (2B). Liver biopsy reveals severe hepatic steatosis with both micro and macrovesicular steatosis (Hematoxylin and eosin staining; magnification 200X), 2E).

CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 2 (CGL2)

CGL2 is caused by pathogenic variants in the *BSCL2* gene which have been mapped to chromosome 11q13. This gene encodes a 398-amino acid integral endoplasmic reticulum membrane protein called *seipin* (60). This protein is assumed to take part in lipid droplet formation and adipocyte differentiation (61, 62). Patients with *BSCL2* pathogenic variants have the most severe disease and are born without any adipose tissue. Hypertriglyceridemia and hepatic steatosis can be detected in early childhood; and hepatic involvement can be more severe in CGL2 than other subtypes (49, 63). Intellectual disability and

cardiomyopathy are more common than in CGL1. CGL2 patients are also distinguished from the CGL1 patients with the loss of mechanical adipose tissue (64) (Fig.3). Although the mechanism is not clear, adiponectin levels are relatively higher in patients with CGL2 despite severely suppressed leptin levels which can help in the differential diagnosis (65).

In addition, rare specific variants of the *BSCL2* gene that lead to the skipping of exon 7 are associated with Celia's encephalopathy (Progressive Encephalopathy with/without Lipodystrophy, PELD), a severe progressive neurodegenerative disorder that also presents with a GL phenotype. (66-68).



Figure 3. CGL2. Near total absence of adipose tissue in a patient with CGL2 (3A, 3B). Also note that the patient shown now deceased was only 29 years old at the time the picture was taken, suggesting the possibility of accelerated aging.

CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 3 (CGL3)

CGL3 is caused by pathogenic variants in the CAV1 gene which are located on chromosome 7q31 (9, 15, 69). This gene encodes the protein caveolin-1, which is an integral part of caveolae found in plasma membranes. Caveolin 1 binds fatty acids on the plasma membranes and translocates them into lipid droplets. Mutated caveolin 1 disrupts lipid droplet formation and adipocyte differentiation (70). CGL3 is distinguished from other CGLs by the presence of unique features such as preserved bone marrow fat, vitamin D resistance. hypocalcemia, hypomagnesemia, and decreased bone density (48). In addition to this classical presentation, whole exome sequencing has identified *de novo* heterozygous null CAV1 pathogenic variants in two patients of European origin with generalized fat loss, thin mottled skin, and progeroid features at birth: however, no differences in the number and morphology of caveolae have been found in dermal fibroblasts (71), which suggests that this observation needs to be confirmed in further pedigrees. Heterozygous CAV1 frameshift mutations have also been reported to be associated with partial lipodystrophy (Fig.4) (72). Several features such as congenital cataracts and cerebellar progressive ataxia were also present (73). Apart from this, a novel p.(His79GInfs*3) CAV1 variant was identified in four consanguineous patients diagnosed with CGL3. In addition to typical findings, two patients had esophageal achalasia, while the other had atypical retinitis pigmentosa findings (74).



Figure 4. Partial LD with Heterozygous CAV1 Pathogenic Variant.

CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 4 (CGL4)

Type 4 CGL (CGL4) is caused by pathogenic variants in the *PTRF* gene. The product of this gene, CAVIN, is a polymerase 1 and transcript release factor which regulates caveolae 1 and 3 (75). CGL4 can be recognized by distinct clinical characteristics. The majority of CGL4 patients that have been documented so far have had null mutations in the *CAVIN1/PTRF* gene. However, a novel homozygous mutation (c.21T>A; p.Tyr7Ter) was described in this gene in two pediatric siblings who exhibited slight variations in their phenotypical presentation, and whose clinical manifestations were compatible with CGL4 (76).

This rare subtype of CGL is associated with myopathy, pyloric stenosis, gastrointestinal dysmotility, arrhythmias that include exercise-induced ventricular tachycardia and sudden death, and skeletal abnormalities such as atlantoaxial instability and scoliosis (77-79) (Fig.5). Regardless of metabolic illness, patients with CGL4 are more prone to suffering life-threatening arrhythmias and cardiac problems throughout childhood (49).



Figure 5. CGL4. Lack of subcutaneous fat (5A), scoliosis (5A), gastrointestinal dysmotility (5B), and exercise-induced ventricular arrhythmia (5C) in CGL4.

OTHER GENES ASSOCIATED WITH GENERALIZED LIPODYSTROPHY

Biallellic loss-of-function pathogenic variants in phosphate cytidylyltransferase 1 alpha (PCYT1A), the rate-limiting enzyme in the Kennedy pathway of de novo phosphatidylcholine synthesis, have been associated reported to be with generalized lipodystrophy, severe hepatic steatosis and low HDL cholesterol levels (80). Although widely involved in the familial partial lipodystrophy pathogenesis, several pathogenic variants in the LMNA and PPARG genes have been associated with generalized lipodystrophy. Heterozygous LMNA p.T10I pathogenic variant was associated with reported to be generalized lipodystrophy, diabetes mellitus, acanthosis nigricans, hypertriglyceridemia, and hepatomegaly (Fig.6) (81).

Biallelic pathogenic variants in *PPARG* has also been reported to cause generalized lipodystrophy (82).

Furthermore, research has shown that a deficiency of phospholipase A/acyltransferase 3 (PLAAT3), an modifies and enzyme that phospholipids is predominantly found in neural and white adipose tissue (WAT), leads to monogenic lipodystrophy syndrome. Patients with biallelic loss-of-function variants in PLAAT3 show varying degrees of fat loss, from partial to generalized, insulin resistance, diabetes. hypertriglyceridemia, fatty liver. and polycystic ovary syndrome. Additionally, these patients exhibit numerous neurogenic symptoms, including demyelinating neuropathy, migraines, and intellectual disability, along with musculoskeletal dysmorphisms (83).



Figure 6. Heterozygous *LMNA* p.T10I Pathogenic Variant. Generalized lack of subcutaneous fat (6A), eruptive xanthomata (6B), and lipemia retinalis (6C) secondary to severe hypertriglyceridemia in a patient with heterozygous LMNA p.T10I pathogenic variant.

Acquired Generalized Lipodystrophy

Acquired generalized lipodystrophy (AGL), also known as Lawrence Syndrome, is very rare. Generalized fat

loss is not present at birth but develops later in life. It occurs over a variable period, ranging from a few weeks to years (Fig.7) (9).



Figure 7. AGL. Generalized loss of subcutaneous fat in two patients with AGL (7A-D). Note the distal fat loss around the feet as opposed to patients with CGL phenotypes.

Although the pathogenesis of AGL has been elusive previously, it has always been hypothesized to be linked to autoimmune destruction of adipocytes. Autoantibodies against adipocyte membranes have been reported (84-86). Recently, the presence of antibodies against the lipid droplet surface protein perilipin-1 (PLIN1), an essential regulator of the lipolytic pathway, has been demonstrated in some AGL patients (87-90). Anti-PLIN1 autoantibodies in AGL patients were first detected in 2018 in three out of five patients (90). Subsequently, in a study focused on anti-PLIN1 antibodies, 50% of the 40 AGL patients examined exhibited the antibodies, whereas in another investigation, 37% of the 46 patients were found to have these antibodies (88, 89). Interestingly, one of the AGL patients with perilipin-1 antibody also had a mutation in the AIRE gene that causes autoimmune polyendocrine syndrome type 1 (APS1) (88). Considering these studies, whether perilipin-1 antibodies can be a potential biomarker in AGL patients and the relationship between APS1 and lipodystrophy are still curious.

AGL is associated with panniculitis in approximately 25% of the patients. This type may manifest with subcutaneous inflammatory nodules (panniculitis), which heal by localized loss of fat and eventually results in complete loss of subcutaneous fat (9). Another one fourth of the AGL patients present with an disease that autoimmune include juvenile dermatomvositis (JDM). Sjogren's syndrome. rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus (9, 85). Of these, JDM particularly correlates with AGL. 8-40% of patients with JDM develop AGL (Fig.8) (86, 91, 92). In the remaining 50% of the cases, AGL is not associated with any autoimmune or inflammatory condition (9). Some patients with AGL exhibit low serum complement 4 levels and auto-immune hepatitis, sometimes together with type 1 diabetes, which suggests the involvement of classical complement pathway in AGL pathogenesis (93). Recently, with the groundbreaking and increasing use of immune checkpoint inhibitors in cancer treatments, it has been reported in the literature that acquired generalized lipodystrophy developed after anti-PD-1 treatment

(nivolumab and pembrolizumab) in four patients (94-96).

As mentioned above, it is of note that some of the patients with AGL are recently recognized to have additional progeroid features and may harbor a specific pathogenic of *LMNA* gene at position 10 (p.T10I). We have reported clinical presentations of these patients recently in a case series report. One of these patients also had biopsy proven juvenile dermatomyositis suggesting that the long-recognized

association between AGL and JDM may be linked through distinctive molecular mechanisms (81).

In patients with AGL, metabolic abnormalities associated with severe insulin resistance that include hypertriglyceridemia, diabetes mellitus, hepatic steatosis, acanthosis nigricans, menstrual irregularities and PCOS may develop soon after the recognition of fat loss. Patients have suppressed levels of leptin and adiponectin (9, 32).



Figure 8. Juvenile Dermatomyositis and AGL. Generalized loss of subcutaneous fat in a patient with juvenile dermatomyositis associated AGL (8A, 8B). Note the absence of muscle tissue as well in this severely affected patient.

PARTIAL LIPODYSTROPHY

Fat loss affects only part of the body in partial lipodystrophy. Partial lipodystrophy is categorized into inherited (familial partial lipodystrophy, FPLD) and acquired forms (acquired partial lipodystrophy, APL). Both patients with FPLD and APL start losing fat at some point during their life. Lower limbs are most frequently affected in FPLD. There might be accumulation of adipose tissue in the face and neck. On the other hand, APL is characterized by fat loss

that spreads through a cephalocaudal distribution from the face, neck, shoulders, arms, and forearms and that extends to the thoracic region and upper abdomen. There are numerous genes associated with FPLD. Despite the growing number of proven genetic markers, about half of the patients do not have a discernible single gene variation.

Inherited Partial Lipodystrophy Syndromes

Patients with these syndromes usually notice partial fat loss around puberty. Fat loss pattern is very heterogeneous in patients with FPLD. Even among patients with pathogenic variants of the same gene, fat loss patterns may vary.

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 1 (FPLD1)

The loss of adipose tissue is mainly limited to the extremities in patients with FPLD1 or Kobberling-type lipodystrophy (97). There is a normal or slightly increased fat in the face and neck. Truncal obesity is a common finding. The hallmark of this syndrome is the formation of a palpable "ledge" between the normal and lipodystrophic areas (98). It is believed that women are diagnosed more easily as they usually present with a more severe disease. Metabolic complications usually develop in early adulthood. Insulin resistant diabetes and metabolic syndrome are common and may cause premature coronary artery

disease. Hypertriglyceridemia may trigger episodes of acute pancreatitis. Acanthosis nigricans is commonly seen. Leptin levels are variable and correlate with body mass index (BMI), which suggests that the levels of leptin are appropriate for the fat content in FPLD1 (98). The Cambridge group recently reported that this form of lipodystrophy may have a polygenic etiology (99). There is a remarkable phenotypical heterogeneity among patients with FPLD1. In this spectrum of FPLD1, patients with significant central obesity are likely polygenic. This type of presentation is relatively more common, and it is sometimes difficult to make a distinction between FPLD1 and truncal obesity complicated with metabolic syndrome (100). The use of radiological methods such as DXA, CT, or MRI can help in this population to further define body fat distribution in addition to physical examination and skinfold measurements. On the other hand, some FPLD patients with no increase in truncal fat are classified as FPLD1, if no gene is identified. These patients can still have a monogenic form of FPLD that has not been discovered. Two different presentations of FPLD1 are shown in Fig.9.



Figure 9. FPLD1. Heterogeneity in FPLD1. Patient in A to D presented with decrease in peripheral fat depots and preservation of abdominal fat. Patient in E to H has increased abdominal adiposity. The formation of a palpable "ledge" between the normal and lipodystrophic areas is shown (9C and 9E). (Images E-H used with permission by Dr. Jonathan Q. Purnell from publication Diabetes Care 2003;26(6):1819-24).

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 2 (FPLD2)

FPLD2 or Dunnigan Variety lipodystrophy is an autosomal dominant syndrome which is characterized by gradual onset of subcutaneous fat loss from the extremities during puberty. Affected individuals have prominent muscularity in their extremities. Excess fat accumulates in the neck causing a buffalo hump (Fig.10). This phenotype sometimes can be misdiagnosed as Cushing's syndrome at first glance (15). Pathogenic variants in the *LMNA* gene, which is located on chromosome 1q21-22, cause FPLD2. The *LMNA* gene codes nuclear lamina proteins, lamin A and C. Pathogenic variants in the *LMNA* gene can be scattered across many exons of the gene and are missense mutations (101). Mutant lamins disrupt the interaction between nuclear lamina and chromatin and may result in apoptosis, which may be followed by premature adipocyte death (102).



Figure 10. FPLD2. Subcutaneous adipose tissue loss from the extremities, excess fat accumulation in the face and neck, and Cushingoid appearance in FPLD2 (10A-D; Note that one of the patients (10A) previously underwent liposuction for removal of unwanted excess fat from the neck).

Females have a more recognizable phenotype and more severe metabolic complications (103). Most patients with FPLD2 develop diabetes in their twenties and thirties. Other components of insulin resistance are usually present. Patients with FPLD2 are at high risk for cardiovascular diseases that usually develop at relatively younger ages (104). Arrhythmias such as atrial fibrillation or flutter are more common in patients with *LMNA* pathogenic variants and may occur at an earlier age. Detailed cardiac analyses among patients with *LMNA* pathogenic variants showed that individuals with non-482 *LMNA* variants exhibited a high possibility of suffering from vigorous cardiac complications such as myocardial infarction, atrial fibrillation/flutter, cardiomyopathy, and congestive heart failure (105). Our retrospective analysis of 494 patients with *LMNA*-associated lipodystrophy revealed that the most prevalent *LMNA* variants were R482Q and R482W. This paper also highlights that patients with the R482W variant are diagnosed with diabetes at a significantly younger age compared to those with the R482Q variant (27 years vs. 40 years, respectively) (106).

There is a phenotypic heterogeneity among patients with FPLD2. For instance, less severe loss of fat has been reported in patients with exon 11 LMNA pathogenic variants which affects only lamin A protein (107). LMNA R349W pathogenic variant (exon 6) is associated with facial fat loss which is uncommon in FPLD2 (104, 108, 109). Exon 1 variants are associated with severe cardiac disease that require cardiac transplant at an early age and may be coupled with arrhythmias and conduction system abnormalities. Variants across exon 4 through 8 have been noted to cause muscular dystrophy related symptoms together with fat distribution abnormalities. In a retrospective evaluation of 12 pediatric FPLD2 patients, although all patients had the same LMNA variant p.(R482W), there were marked differences in

the severity of the phenotype. Despite the absence of comorbidities in patients under the age of ten, the earliest age of onset of diabetes in the cohort was 12, and the earliest age of onset of hepatic steatosis was observed to be 10 (110). *LMNA* gene pathogenic variants are also involved in the pathogenesis of progeroid disorders including Hutchinson-Gilford progeria syndrome (HGPS), mandibuloacral dysplasia, and atypical progeroid syndrome (APS).

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 3 (FPLD3)

FPLD3 is caused by pathogenic variants in the *PPARG* gene, a key regulator of adipocyte differentiation. Patients with FPLD3 usually show milder fat loss; and there is no accumulation of adipose tissue in the face and neck (Fig.11); however, they manifest metabolic complications at a similar rate and severity to those with FPLD2 (104, 111-115). Even more, in a retrospective analysis, FPLD3 patients exhibited a notably greater prevalence of hypertriglyceridemia and diabetes, along with elevated levels of median serum triglycerides and mean HbA1c, compared to FPLD2 patients (116).



Figure 11. FPLD3. Moderate partial subcutaneous adipose tissue loss in a patient with FPLD3 (11A-C).

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 4 (FPLD4)

FPLD4 is caused by pathogenic variants in the *PLIN1* gene encoding perilipin 1, which is an essential lipid droplet coat protein (117). Although frameshift mutations in *PLIN1* are known to cause partial lipodystrophy, a recent comprehensive study suggests that null variants in the *PLIN1* gene are not associated with the formation of lipodystrophy (118).

Perilipin plays a key role in coordinating access of lipases to the core triacylglycerol. It is characterized by the loss of adipose tissue which is most striking in the lower limbs and femorogluteal depot, severe insulin resistance, diabetes, hypertriglyceridemia, and hepatic steatosis (119-121).

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 5 (FPLD5)

FPLD5 is an autosomal recessive syndrome caused by pathogenic variants in the *CIDEC* gene. It is characterized by partial lipodystrophy, acanthosis nigricans, severe insulin resistance leading to diabetes, and hepatic steatosis. The *CIDEC* gene is located on chromosome 3 (3p25.3) and encodes the CIDEC protein, which is expressed in the lipid droplets. Pathogenic variants of the *CIDEC* gene are postulated to result in the loss of ability of lipid droplets to store fat (122).

FAMILIAL PARTIAL LIPODYSTROPHY TYPE 6 (FPLD6)

FPLD type 6 is caused by pathogenic variants in the *LIPE* (lipase E, hormone sensitive type) gene which has an autosomal recessive inheritance (123). This FPLD subtype is characterized by late-onset partial fat loss from the lower extremities and also multiple symmetric lipomatosis and progressive distal symmetric myopathy (123, 124). Hormone sensitive lipase is the predominant regulator of lipolysis from

adipocytes. Pathogenic variants in the *LIPE* gene appear to result in impaired lipolysis which may induce lipomatosis and partial fat loss at the same time that is associated with hypertriglyceridemia, hepatic steatosis, and insulin resistant diabetes (124).

NEWER AND EMERGING GENES ASSOCIATED WITH FAMILIAL PARTIAL LIPODYSTROPHY

FPLD has also been reported to be caused by pathogenic variants in the AKT2 gene (125). AKT is a serine/threonine protein kinase, which is involved in cell signaling/growth, glycogen synthesis, and insulinstimulated glucose transport. Lipodystrophy in patients with AKT2 mutations is thought to be due to defective adipocyte differentiation and post-receptor insulin signaling (126). Additional variants may be found through extensive sequencing platforms of ongoing studies such as UK Biobank (127), RADIANT (128) or All of Us (129) studies. Exome sequencing has identified a heterozygous variant in the adrenoceptor α 2A (ADRA2A) gene, which encodes the main presynaptic inhibitory feedback G proteincoupled receptor regulating norepinephrine release, in an African-American pedigree with atypical FPLD (130), which needs to be confirmed in additional pedigrees and to date, no additional cases have been reported with similar phenotypes.

Progeroid Syndromes and Lipodystrophy

Mandibuloacral Dysplasia (MAD) is a rare progeroid syndrome which manifests with craniofacial, skeletal and cutaneous abnormalities and lipodystrophy (Fig.12) (131). The clinical manifestations present gradually over time, most commonly during childhood. There are two types of MAD currently recognized. Mandibuloacral dysplasia type A (MADA) is characterized by the loss of subcutaneous fat from the extremities along with normal or excessive fat in the face and the neck. Mandibuloacral dysplasia type B manifests with a more generalized loss of subcutaneous fat (131-134).



Figure 12. Mandibuloacral Dysplasia. Hypoplasia of the mandible in a patient with Mandibuloacral Dysplasia.

MADA is caused by mutations in the *LMNA* gene which results in the accumulation of prelamin A protein (135). This, in return disrupts the interaction between nuclear lamina and chromatin (134-136). Compound heterozygous pathogenic variants in the zinc metalloproteinase (*ZMPSTE24*) gene have been reported to cause MADB associated lipodystrophy (137, 138). *ZMPSTE24* is essential in the post-translational proteolytic cleavage of carboxy terminal residues of farnesylated prelamin A to form mature lamin A and vimentin processing (137, 139, 140).

In addition, homozygous mutation in the *MTX2* gene causes mandibuloacral dysplasia progeroid syndrome (MDPS), an autosomal recessive severe laminopathy-like disorder characterized by mandibular recession, clavicular hypoplasia and acroosteolysis, progeroid appearance and loss of subcutaneous fat (141).

MDP (mandibular hypoplasia, deafness and progeroid features syndrome) has been reported to be caused by pathogenic variants of the POLD1 gene that encodes catalytic subunit of DNA polymerase δ which play an essential role in the lagging-strand DNA synthesis during DNA replication (142). In addition to progressive lipodystrophy and severe insulin resistance, patients with MDP suffer from mandibular hypoplasia, sensorineural deafness. progeroid features, scleroderma and skin telangiectasia, ligament contractures, reduced mass of limb muscles, hypogonadism and undescended testes in males (142-145). We recently observed a mother daughter pair with a different POLD1 variant near the carboxyl terminal of the protein at a very highly conserved residue (Fig.13).



Figure 13. Partial Lipodystrophy in a Patient with *POLD1* Variant.

Biallelic *WRN* null mutations linked to partial lipodystrophy with severe insulin resistance in adult progeria Werner syndrome (Fig.14) (146). The *WRN* gene encodes a RecQ DNA helicase which plays a critical role in repairing damaged DNA (147). An

unusual Werner syndrome with the absence of progeroid findings, early-onset diabetes, severe dyslipidemia, and hepatic fibrosis has been reported in a patient with partial lipodystrophy who had a novel variant in the *WRN* gene (148).



Figure 14. Werner Syndrome.

Fibrillin-1 (*FBN1*) gene pathogenic variants are found in more than 90% of patients with Marfan syndrome (149). Pathogenic variants in the penultimate exon of FBN1 have been reported to be associated with a distinct phenotype of generalized lipodystrophy that share some clinical features with neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome), a very severe disorder with only a few patients described who could reach their late childhood (150-152). Although these patients have marfanoid/progeroid appearance, skeletal features, dilated aortic bulb, bilateral subluxation of the lens, myopia in addition to the severe generalized lipodystrophy, no significant metabolic abnormality caused by the lack of adipose tissue has been reported (150, 151, 153).

Pathogenic variants in *BANF1* have been reported to be associated with progeroid features, growth retardation, decreased subcutaneous fat, thin limbs, and stiff joints. This disease is also called Néstor-Guillermo progeria syndrome (NGPS) (154).

Heterozygous pathogenic variants in *KCNJ6* (*GIRK2*), which encodes an inwardly rectifying potassium channel, cause Keppen-Lubinsky syndrome that is characterized by severe developmental delay and intellectual disability, microcephaly, large prominent eyes, an open mouth, progeroid appearance, and generalized lipodystrophy (155).

Pathogenic variants of the Spartan (*SPRTN*) gene, which encodes a protein that is essential in the maintenance of genomic stability, have reported to be associated progeroid features, lipodystrophy and hepatocellular carcinoma (156).

Pathogenic variants in the *ALDH18A1* gene, which encodes pyrroline-5-carboxylate-synthetase, a mitochondrial enzyme important in ornithine biosynthesis, cause Cutis Laxa Autosomal Dominant 3 syndrome. This syndrome is characterized by intellectual disability, hypotonia, retinal abnormalities, craniofacial dysmorphism, joint laxity, and abnormal fat distribution (34, 157).

Several other genes associated with progeroid lipodystrophy are listed in Table 3.

Complex Syndromes and Their Genes Associated with Lipodystrophy

Pathogenic variants in the phosphatidylinositol 3kinase, regulatory subunit 1 (*PIK3R1*), which mediates insulin's metabolic actions, have been reported in patients with SHORT syndrome (short stature, joint hyperextensibility, ocular depression, Rieger anomaly, and teething delay) that is associated with lipodystrophy in many patients (158, 159). It has also been reported that patients with C-terminal *PIK3R1* pathogenic variants exhibit severe insulin resistance but normolipidemia and no hepatic steatosis (160).

Pathogenic variants in the proteasome subunit, betatype, 8 (*PSMB8*) gene, which encodes a catalytic subunit of the 20S immunoproteasomes called β 5i, has been linked to an autosomal-recessive autoinflammatory syndrome characterized by joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP syndrome) (161-163).

CANDLE syndrome is another rare autoinflammatory syndrome characterized by chronic atypical neutrophilic dermatitis, recurrent fever, and partial loss of adipose tissue from the upper limbs and face (164). An eponym for the syndrome was proposed as Nakajo-Nishimura (165, syndrome 166). Homozygous or compound heterozygous mutations in the gene PSMB8 have been reported in patients with CANDLE syndrome (167, 168).

Two families with AREDYLD syndrome that is characterized by acrorenal field defect, ectodermal dysplasia, generalized lipodystrophy, and multiple abnormalities have been reported (169, 170). The genetic basis of this very rare syndrome is still unknown.

Lipomatosis Syndromes

In studies conducted in 2016-2018, a pathogenic variant in the *MFN2* gene that encodes mitofusin 2, a membrane-bound mediator of mitochondrial membrane fusion and inter-organelle communication, have been reported to be associated with partial lipodystrophy, upper body adipose hyperplasia, and suppression of leptin expression (171) (Fig.15). *MFN2*

gene-related Multiple Symmetric Lipomatosis (MSL) is an unusual type of lipodystrophy that includes both lipomatous masses and lipoatrophy (172). In these cases, one may observe various indicators, including insulin resistance, diabetes, non-alcoholic fatty liver disease, dyslipidemia, peripheral neuropathy, autonomic neuropathy, and extremely low leptin and adiponectin levels. Fibroblast growth factor 21 (FGF21) serum levels were found to be remarkably higher in these cases (173). Of note, there are additional etiologies linked to the development of lipomatosis, with or without lipodystrophy.



Figure 15. Disease progression in a patient with a pathogenic variant in the MFN2 gene (15A-D).

Acquired Partial Lipodystrophy

Acquired partial lipodystrophy (APL) is characterized by fat loss typically starting in childhood or early adulthood. Loss of adipose tissue first manifests in the face and gradually progresses to the upper extremities, thorax, and upper abdomen symmetrically. It typically proceeds in a cephalocaudal fashion but spares the lower extremities (Fig.16). There might be accumulation of fat in the lower abdomen, gluteal region, and lower extremities.



Figure 16. APL. Typical cephalocaudal adipose tissue loss pattern in two patients with APL (16A-D). Note preservation of fat depots below the waist line.

Although the etiology of APL is still unknown, some patients may have coinciding autoimmune conditions. Systemic lupus erythematosus and dermatomyositis/polymyositis are among the most frequently associated auto-immune diseases (174). In recent years, cases of APL associated with hematopoietic stem cell transplantation and total body irradiation have also been described. These patients are thought to constitute a subset of APL (175, 176). APL has been associated with abnormalities of the alternative complement pathway that may cause membranoproliferative glomerulonephritis (MPGN) (177). Subsequent chronic renal disease constitutes the major cause of morbidity in these patients. It has been suggested that C3-nephritic factor might be the cause for the lysis of adipocytes expressing factor D, although there is no solid evidence supporting this hypothesis (178). A comprehensive review of renal complications in lipodystrophy by the Turkish Lipodystrophy Study Group verified low complement C3 levels in more than 45% of APL patients (179, 180).

Rare variants in *LMNB2* were previously reported in five patients with APL, but two of four variants were also present in normal controls (181). In addition, subcutaneous loss of fat from the legs and the gluteal region, presence of diabetes, type IV and V hyperlipoproteinemias were atypical presentations in these patients (181).

Metabolic complications are less common compared to other types of lipodystrophy syndromes (4). Not all patients develop insulin resistance, diabetes, or hypertrialyceridemia. Leptin levels vary from hypoleptinemia to normal range (32, 174). However, patients may develop metabolic abnormalities such as diabetes, hypertriglyceridemia, low HDL cholesterol levels, and hepatic steatosis in later stages of the disorder. In addition, several patients with APL have been reported to develop diabetes or other metabolic abnormalities at a relatively young age, which are apparently associated with insulin resistance (182). It is also known that metabolic complications such as hepatic steatosis, poorly controlled diabetes, and pancreatitis are severe in a group of APL patients who are thought to have advanced fat loss (180). Thus, patients with APL should also be followed for metabolic abnormalities, as is done for other subtypes of lipodystrophy.

ANIMAL MODELS OF LIPODYSTROPHY

Numerous animal models of lipodystrophy have shown that adipose tissue dysfunction triggers the development of severe insulin resistance, which is associated with metabolic abnormalities and endorgan complications as mentioned above and shown in Fig.1. Extensive and authoritative reviews of these studies can be found in articles by Drs. David B. Savage (183) and by Xavier Prieur (121). The introduction of these animal models has allowed researchers to explore the fundamental characteristics of lipodystrophy and insulin resistance and allowed studies of the effects of different treatment approaches. Regardless of the strategy used, ablation of white adipose tissue led to the development of insulin resistance, hypertriglyceridemia, and hepatic steatosis (sometimes 6-fold elevation in total liver weight). In now classical experiments of Reitman and colleagues, fat transplantation from littermates rescued metabolic derangements in the famous A-ZIP mice (184-186). Dr. Beutler's group identified kelch repeat and BTB (POZ) domain containing 2 (KBTBD2) deficiency as a cause of lipodystrophy associated with insulin resistance and diabetes and they also showed that transplantation of wild-type adipose tissue hepatic rescued diabetes and the steatosis of Kbtbd2^{-/-} mice phenotypes (187). The aP2-SREBP-1c administration of leptin into transgenic mice from the Brown and Goldstein laboratory resulted in dramatic benefits in glycemic parameters, insulin action, and hepatic steatosis, which could not be explained by its effect on food intake alone, providing the premise to undertake leptin replacement in human patients (188). What was also striking was that if fat from the leptin deficient obese mice was transplanted into littermates of the A-ZIP mice, the metabolic rescue was far less effective, suggesting that leptin played an important role in the regulation of metabolism in lipodystrophy in rodents (189). The replacement of deficient leptin in a small but severely affected cohort of human patients with lipodystrophy with human recombinant leptin (metreleptin) was first reported in 2002 and brought further attention to lipodystrophy research (190). Longer-term studies subsequently confirmed the role of metreleptin therapy in lipodystrophy syndromes especially in the most severe forms (32, 41, 42).

Recent Animal Models Advancing Our Understanding of Lipodystrophy and Fat Dysfunction

While we are not intending to provide a comprehensive review of all animal models generated recently, we selected a few to highlight recent advances in this field. A study by Tapia et al.'s (191) showed that a generalized lipodystrophy gene and a critical enzyme in triglyceride synthesis AGPAT2 is essential for the expression of critical mitochondrial proteins. In this study, genes involved in the type-1 interferon response were overexpressed differentiated Agpat2^{-/-} adipocytes, and this condition could be associated with their defective mitochondria. They also showed that differentiated $Agpat2^{-/-}$ brown adipocytes have a lower proportion of lipid-laden cells, Adiponectin and Perilipin1 synthesis, indicating that these cells were able to initiate brown adipogenesis but could not carry it to further stages (191). Interestingly, another study of Agpat2 null mice, demonstrated the absence of caveolae in adipocytes lacking AGPAT2, which hints at a possible mechanistic connection between different Congenital Generalized Lipodystrophy (CGL) types (121, 192, 193).

The Macdougald lab and our group collaboratively developed adipocyte specific knock out of *LMNA* gene which recapitulates most of the features of human FPLD2 (194). Loss of adipocyte-specific lamin A/C in mice (Lmna^{ADKO}) caused a significant reduction in the weight of posterior subcutaneous white adipose tissue (WAT), gonadal WAT, pericardial WAT, renal WAT, and retroperitoneal WAT, as well as markedly reduced circulating adiponectin and leptin levels in both sexes. Hyperglycemia, hyperinsulinemia, liver enlargement, and ectopic fat accumulation in the liver were also noted in these mice under a high-fat diet, consistent with the clinical presentation of FPLD2 (194).

A novel mouse model was generated to explore whether maintaining intact *BSCL2* expression in the liver prevents the onset of metabolic disorders in mice with specific *BSCL2* deficiency in adipose tissue. *BSCL2* was simultaneously targeted for ablation in adipose tissue and hepatocytes. It was observed that liver-specific seipin deficiency did not result in hepatosteatosis and insulin resistance. These results suggest that most of the metabolic pathophysiology is driven by the function of *BSCL2* outside of hepatocytes, and likely in adipose tissue (195).

In an animal model created to elucidate the molecular mechanisms of lipomatosis and lipodystrophy associated with the MFN2 gene, which encodes an outer membrane GTPase required for mitochondrial fusion (196), no change in mitochondrial oxidative observed capacity was in homozygous Mfn2^{R707W/R707W} mice (197). Although the triggering of a cellular integrated stress response and selective impairment in mitochondrial morphology and function were detected in adipose tissues, no significant changes in glucose and lipid metabolism were observed in homozygous mice, unlike humans. Interestingly, leptin and adiponectin levels were low in these mice (197).

A new animal model study showed that a novel R133L heterozygous mutation in the *LMNA* gene causes signs of aging, such as impaired mitochondrial functions, decreased lipid storage capacity in subcutaneous adipose tissue, as well as metabolic disorders such as insulin resistance and ectopic lipid accumulation. *Lmna*^{R133L/+}mice exhibited findings consistent with lipodystrophy, such as a reduction in epididymal white adipose tissue (eWAT) mass, as well as smaller adipocytes and upregulated inflammation genes in the inguinal subcutaneous white adipose tissue (iWAT) (198).

Furthermore, the importance of the lipid kinase phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3) in the function of white adipose tissues (WATs) and brown adipose tissues (BATs) has been demonstrated using adipocyte-specific Pik3c3 knockout model. Deletion of PIK3C3 has been linked to lipodystrophy due to impaired adipocyte differentiation. thermogenesis autophagy, and mechanisms (199).

We have also covered recent animal models of novel gene therapies under a new heading: Emerging Therapeutic Technologies and Gene Replacement Therapy Approaches.

TREATMENT

Currently, treatment modalities are restricted to ameliorating or preventing the comorbidities of the lipodystrophic syndromes. There is no cure for these syndromes. For the metabolic disturbances, lifestyle modification (diet and exercise as needed), metformin, and fibrates (and/or statins) are generally required. Insulin or other antidiabetics (e.g., metformin, thiazolidinediones) can also be used if needed. Metreleptin, a leptin analog, is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with generalized lipodystrophy.

Lifestyle Modification

There is limited knowledge on the effectiveness of diet and exercise in the management of metabolic disturbances in patients with lipodystrophy. In general, balanced macronutrient composition а is recommended. with In patients severe hypertriglyceridemia, a balanced low- fat diet (<15% of daily caloric intake) is appropriate. To control diabetes, increased physical activity and carbohydrate restriction are advised. Dietary fiber intake and foods that are rich in omega-3 fatty acids are suggested (3).

Most patients with lipodystrophy are encouraged to be physically active. In patients with cardiomyopathy and cardiac arrhythmias strenuous exercise should be avoided. Patients with CGL4 should avoid exercise as they may develop exercise-induced ventricular arrhythmias (75, 79). Contact sports are not advised to patients with severe hepatosplenomegaly and CGL patients presenting with lytic bone lesions.

Patients should abstain from drinking alcohol due to the risk of developing acute pancreatitis and metabolic dysfunction-associated steatohepatitis (MASH). Patients should also be advised to avoid smoking and maintain an optimal blood pressure to decrease the risk of cardiovascular disease.

Insulin Resistance

In patients presenting with lipodystrophy and diabetes, both metformin and thiazolidinediones are somewhat effective to treat hyperglycemia and hyperlipidemia (200-204). Metformin is used as the first-line agent in insulin resistant diabetes. Thiazolidinediones may improve the metabolic profile in partial lipodystrophy syndromes (204). The very first thiazolidinedione to be approved in the United States troglitazone actually worked remarkably well in lowering both HbA1c and triglyceride levels in a cohort of patients with predominantly partial lipodystrophy syndromes. data currently However, on the approved thiazolidinediones are limited and contradictory (202, 205, 206). Thiazolidinediones should be considered in the management of diabetes in patients with partial lipodystrophy, however they should not be routinely used in generalized lipodystrophy as their efficacy has not been studied (3, 204). Insulin is usually needed in very high doses and concentrated forms, such as U-500. Patients with extreme insulin resistance, however, may not respond to concentrated insulin. Administration of insulin-like growth factor-1 (IGF-1) has been shown to be effective in maintaining glycemic control and insulin resistance in short-term studies, as well as in type 2 diabetes (207-209). A retrospective study found that administration of sodium-glucose cotransporter 2 (SGLT2) inhibitors resulted in a 0.8% drop in HbA1c levels after one year in individuals with partial lipodystrophy. Additionally, SGLT-2 inhibitors led to a significant decrease in both systolic and diastolic blood pressure (210). In clinical practice, it should be considered that combination therapy with metreleptin and SGLT2 inhibitors may contribute to prognosis by improving insulin resistance adipose tissue and reducing the in risk of cardiovascular events (211).Many other hypoglycemic agents have been used in

lipodystrophy, but their efficacy has not been studied (3). Recently we published a retrospective review of GLP-1 agonist use in FPLD syndromes showing substantial improvement in glucose control and body weight (212). Dual incretin therapeutic tirzepatide is postulated to have even more efficacy due to the potential impact of GIP agonism and potentially improving inflammation.

Dyslipidemia

Statins are normally used as first-line agents to treat hypercholesterolemia but patients with FPLD have low tolerance to statins. Rosuvastatin and pravastatin have been proven to reduce total LDL cholesterol levels (213, 214). Statins are used with caution to prevent side effects such as myopathy and hepatotoxicity. Along with diet, fibrates and fish oil rich in omega-3 fatty acids, should be prescribed for serum triglyceride levels >500 mg/dL and may be considered for triglycerides >200 mg/dL. Combining fibrates with statins has proved to be effective in dyslipidemia; however, there is an increased risk for muscle toxicity. Therapeutic apheresis can be used in extreme hypertriglyceridemia to prevent recurrent episodes of acute pancreatitis in acutely life-threatening situations (190).

Cosmetic Treatment

Cosmetic correction of lipoatrophy and fat excess is associated with improved quality of life in patients with lipodystrophy. Autologous adipose tissue transplantation, facial reconstruction with free flaps and silicone or other implants have been used in lipoatrophic areas. In addition, liposuction or surgical excision is used for removal of unwanted excess fat from body parts such as the chin, buffalo hump and vulvar region.

Bariatric Surgery

Roux-en-Y Gastric Bypass Surgery (RYGB) is associated with effective weight loss and resolution of

metabolic comorbidities in patients with obesity (215). RYGB was used with success in several patients with FPLD1 and with FPLD2 (216-218). RYGB resulted in weight loss and significant improvements in metabolic parameters in patients with FPLD1 that allowed patients to stop using insulin (216). FPLD2 patients also benefited from RYBG. Substantial improvements in metabolic parameters and a significant weight loss were reported after the surgery (218, 219).

Leptin

A large group of lipodystrophy patients present with low leptin levels. Metreleptin (r-metHuLeptin) is an analog of human leptin made through recombinant DNA technology. It has been tested in congenital and acquired forms of lipodystrophy and has been shown to ameliorate the metabolic derangements (43, 190).

Leptin replacement therapy is approved in Japan as a therapy indicated specifically for the treatment of diabetes and/or hypertriglyceridemia in patients with congenital or acquired lipodystrophy. In the United States, metreleptin, now called MYALEPT, has been approved by the FDA in 2014 for use in patients with congenital generalized or acquired generalized lipodystrophy for the treatment of complications of leptin deficiency as an adjunct to diet and lifestyle modifications. There is no lower age limit for initiation of Myalept nor a specific degree of metabolic abnormality so long as the diagnosis of generalized lipodystrophy can be substantiated. However, it is not approved for use in human immunodeficiency virus (HIV)-related lipodystrophy, or in patients with metabolic diseases such diabetes as and hypertriglyceridemia, or partial lipodystrophy in the US. Metreleptin is an approved treatment for generalized lipodystrophy (GL) and partial lipodystrophy (PL) in the European Union (EU), United Kingdom (UK), Canada, and Brazil. However, there is an age limit of \geq 2 years for GL. The approval for PL states that patients with confirmed PL can initiate treatment if they are aged \geq 12 years and only when standard treatments have not achieved adequate

metabolic control. Based on this indication, in the EU, UK, Canada, Brazil, and Japan, patients with PL who do not respond to available diabetes and lipid-lowering agents can be treated with recombinant leptin therapy. It is still controversial whether basal endogenous leptin levels can be used to predict response to metreleptin treatment in lipodystrophy patients. However, a recent study revealed that baseline endogenous leptin levels are poor predictors for response to metreleptin therapy among individuals with partial lipodystrophy (220). The clinical effects of leptin treatment in patients with lipodystrophy are summarized below.

APPETITE

Metreleptin decreases hyperphagia, leading to weight loss that usually stabilize with long-term treatment (190, 221-223). This effect can be noted by the patients right after the treatment with metreleptin. Functional MRI studies combined with behavioral assessments showed that metreleptin treatment is associated with long-term improvements of hedonic and homeostatic central nervous networks regulating appetite and food intake (224-226). Food related neural activity and development of satiety were effectively restored by leptin replacement in lipodystrophy (227).

METABOLIC PARAMETERS

Metabolic changes become evident quickly within days to weeks of treatment with metreleptin. Metreleptin therapy has been shown to improve fasting plasma glucose levels starting from the first week. In the first set of patients with lipodystrophy treated with metreleptin, four months of therapy with metreleptin decreased average triglyceride levels by 60%. The absolute decrease in HbA1c was 1.9% among patients with diabetes. Liver volume reduced by an average of 28% and led to the discontinuation of or a large reduction in antidiabetic therapy (190). In the long term, more than three-fourths of patients with GL treated with metreleptin discontinued concomitant treatments, including insulin and oral antidiabetics (228).

In clinical studies, metreleptin led to significant improvements in patients with GL. After 1 year of treatment initiation, a mean change of -2.2% in HbA1c and a mean percent change of -32.1% in triglycerides were observed. Significant reductions in alanine aminotransferase levels occurred. Mean liver volume decreased by 33.8% at month 12. Nearly 80% of patients with GL achieved a $\geq 1\%$ actual decrease in HbA1c or a \geq 30% decrease in triglycerides after 1 year of treatment with 66% achieving decreases of ≥2% in HbA1c or a \geq 40% in triglycerides. Among patients with baseline HbA1c of 7% or greater, the mean reduction at Month 12 was 2.8%. In subjects with baseline TG level 500 mg/dL or greater, the mean percent reduction in triglycerides at month 12 was 72%. Patients with GL overall sustained clinically significant reductions in HbA1c and triglycerides in the longer term follow up.

In patients with PL, metreleptin treatment led to statistically significant reductions in HbA1c (-0.6%), fasting TGs (-20.8%), and liver volume (-13.4%) after 1 year treatment. In a subgroup of patients with baseline HbA1c \geq 6.5% or triglycerides \geq 5.65 mmol/L, more prominent reductions were observed in HbA1c (-0.9%) and fasting TGs (-37.4%). In this subgroup, 68% of patients had a \geq 1% decrease in HbA1c or \geq 30% decrease in fasting TGs, and 43% had a \geq 2% decrease in HbA1c or \geq 40% decrease in fasting triglycerides. Longer-term treatment in the PL subgroup led to significant reductions at months 12, 24, and 36 in HbA1c and fasting triglycerides (229).

12 months of long-term metreleptin therapy has been shown to reduce mean fasting plasma glucose levels by 2.8 mmol/L in the generalized lipodystrophy group and 1.2 mmol/L in the partial lipodystrophy group (228, 229). In a subset of patients undergoing hyperinsulinemic-euglycemic clamp studies, leptin replacement therapy improved peripheral glucose disposal and decreased both hepatic glucose output and hepatic steatosis (230). It is generally recommended to lower the insulin doses by 50% on initiation of metreleptin therapy (especially in GL) to avoid hypoglycemia in well-controlled patients with diabetes. Metreleptin treatment has no suppressive effect on beta cell function in patients with lipodystrophy (231). On the contrary, it has been reported that metreleptin therapy improves insulin secretion in the setting of diabetes (232). A prospective study observed that metreleptin administration for two weeks suppressed basal gluconeogenesis (GNG) by reducing carbon sources for GNG and increasing insulin-mediated suppression of GNG. Peripheral insulin sensitivity increased significantly throughout the 6-month follow-up of these patients (233).

Apolipoprotein C-III and angiopoietin-like protein 8 (ANGPTL8), recognized as inhibitors of lipoprotein lipase, play a role in modulating hypertriglyceridemia. A notable reduction of these hepatokine plasma concentrations is observed, especially after six months of metreleptin treatment (234). While about a 60% decrease in TG values was detected in 1-year follow-up in GL patients using concomitant lipidlowering medications, a 30% decrease was observed in patients with partial lipodystrophy. These reductions were less in individuals who did not take concomitant medication (235). In a real world study from France, during a follow-up period of more than 15 months, TG levels decreased by approximately 150 mg/dL in patients with generalized lipodystrophy (236). It should be noted that acute withdrawal of metreleptin therapy might result in acute pancreatitis episodes (237, 238). Metreleptin also decreased total cholesterol and LDLcholesterol levels (237, 239). But did not alter HDL cholesterol levels (236, 237, 239).

As we have noted, the beneficial effect of metreleptin on glycemic and lipid measures in generalized lipodystrophy are clear and usually quite remarkable. Although the response is variable in patients with partial lipodystrophy and it is not approved for this indication in the US, studies have shown that some patients can benefit from metreleptin treatment. A selected cohort of partial lipodystrophy patients with moderately to severely low leptin and significant baseline metabolic abnormalities is more likely to benefit from metreleptin therapy (13, 235, 236, 240-242). Recent studies confirm that most partial lipodystrophy patients with inadequate metabolic control also respond to metreleptin treatment (235, 236). Furthermore, when comparing the metabolic responses to metreleptin treatment of patients with PPARG and LMNA pathogenic variants in the FPLD group, both groups reported remarkable and similar reductions in HbA1c, insulin dose, and triglyceride levels after 12 months of treatment (243). However, the real-life study from France showed that leptin treatment did not significantly change HbA1c levels (7.7 [7.1-9.1]% at baseline vs. 7.7 [7.4-9.5]% at one year) in 19 patients with partial lipodystrophy. In the same group of patients, a significant decrease in the median value of fasting triglycerides from 3.3 mmol/L (1.9-9.9) to 2.5 mmol/L (1.6-5.3) was observed with short-term metreleptin treatment (p<0.01), whereas the median serum triglyceride levels were 5.2 mmol/L (2.2-11.3) at the last evaluation after long-term leptin treatment (p=0.94) (236). When a responder analysis is performed, however, 61% of the patients with PL showed improvements in glucose homeostasis, with responders exhibiting lower leptin levels compared to non-responders. Similarly, 61% of the PL patients in the French real-world study cohort were responders regarding hypertriglyceridemia.

LIVER

Starting from the earliest studies, leptin replacement therapy was observed to improve hepatic steatosis and lower serum transaminases within 6-12 months (Fig.17) (223, 230, 244).The liver volume decreases in

244). parallel (222, Metabolic associated steatohepatitis (MASH) score has been reported to metreleptin improve after treatment and no progression in hepatic fibrosis has been reported (245, 246). When treated at least for a year, the majority of patients showed improved liver histology, steatosis and hepatocyte ballooning, and only 33% of patients continued fulfilling the criteria for MASH after 1 year of treatment with metreleptin (247, 248). A significant improvement in the metabolic dysfunction-associated steatotic liver disease (MASLD) score has been reported after metreleptin treatment in pediatric patients who underwent liver biopsies (249). Also, our study showed that metreleptin can induce improvements in hepatic steatosis and injury in patients with MASH associated partial lipodystrophy (246). In a mechanistic study, leptin therapy resulted in significant increase in insulin suppression of hepatic glucose production (230). This improvement in insulin action helps reverse hepatic steatosis by decreasing triglyceride content (230). Other mechanisms associated with reducing hepatic steatosis may be leptin effectively increases hepatic VLDL-TG secretion via possibly vagal effect (250) and decreases de novo lipogenesis (251). These observations suggest that the effect of metreleptin on hepatic steatosis can be somewhat blunted when the autonomic innervation of the liver is not intact. However, it should be noted that the liver disease can still benefit from improving metabolic profile and hepatic steatosis can diminish as a result of controlled de novo lipogenesis after improved insulin sensitivity with leptin replacement. To support this view, metreleptin has also been reported to result in rapid clearance of fat from the liver and normalization of liver histology in an AGL patient with recurrence of MASLD in the first few months of liver transplantation (252).



Figure 17. Liver Histology Before and After Metreleptin. Liver histology shows regression of hepatic steatosis and ballooning injury after metreleptin treatment (left before metreleptin and right 4 months on metreleptin treatment, Hematoxylin and eosin staining; magnification 200X).

KIDNEYS

Patients with lipodystrophy may develop proteinuric kidney disease. Metreleptin decreases proteinuria in most patients (223, 253). The reduction in proteinuria coincided with improvement in hyperfiltration in 11 of 15 patients treated with metreleptin. However, four patients had worsening renal function. Hence, renal functions should be closely monitored during metreleptin therapy (253). In further studies, metreleptin significantly reduced proteinuria in patients with GL (254).

CARDIOVASCULAR SYSTEM AND OVERALL SURVIVAL

A study conducted in lipodystrophic mice showed that metreleptin treatment inhibited proatherosclerotic cytokine growth/differentiation factor 15 (GDF15) and reduced macrophage accumulation in atherosclerotic lesions via endothelial to mesenchymal transition. Thus, the positive effect of leptin on the endothelium by reducing inflammation has been reported (255). Metreleptin treatment provides a significant improvement in serum levels of atherogenic lipoproteins, which are known to be associated with increased cardiovascular disease risk (256). A potential increase in cardiovascular risk was detected in a prospective coronary calcium score (CCS) evaluation in 19 individuals diagnosed with CGL, although not sufficiently powered, this study did not report a significant change after metreleptin in CCS score (257). Another recent study, on the other hand, reported an approximately 30% regression in left ventricular hypertrophy and an improvement in septal e' velocity in the GL patients after leptin treatment (258). Cardiovascular problems are a significant risk of mortality in lipodystrophy patients. Our large retrospective evaluation from a large multicenter dataset, found that after adjusting covariates such as lipodystrophy diagnosis, triglyceride levels, elevated HbA1c, \geq 1 episode of pancreatitis, and abnormalities in the heart or kidneys, metreleptin treatment resulted in a mortality reduction of over 60% (259).

CENTRAL NERVOUS SYSTEM AND OTHER EFFECTS

A functional MRI study revealed that leptin may induce alterations in brain activity in the subgenual area

(Brodmann area 25), a region not strictly linked to eating behavior, known for its connections to the reward network. This suggests that leptin may also affect brain regions other than eating behavior (260). Another observational study of ten individuals with partial lipodystrophy who were naïve to metreleptin found a rapid decline in Beck's depression inventory score one week after metreleptin therapy. In the first 3-month follow-up of the individuals, a significant improvement was observed compared to their initial scores. Although this shows that metreleptin treatment may have an antidepressant effect, the findings need to be supported by long-term clinical studies (261). Metreleptin treatment also significantly contributes to improving indirect findings related to guality of life, such as hyperphagia, inability to go to work/school, and deterioration in physical appearance (262).

REPRODUCTIVE SYSTEM

In females, metreleptin was found to normalize gonadotropin secretion. It led to normal progression of puberty, normalized menstrual cycles, and improved fertility (223, 263-265). Leptin replacement improved low estradiol levels and corrected the attenuated luteinizing hormone (LH) response to luteinizing hormone-releasing hormone (LHRH) in young women with lipodystrophy and leptin deficiency (263). Oneyear treatment with metreleptin resulted a significant decrease in testosterone and sex hormone binding globulin (SHBG) levels in lipodystrophic women with PCOS (266). Several pregnancies have occurred in patients with lipodystrophy while they were on metreleptin without any evidence for teratogenicity (47, 267), although it has not been approved for use in pregnancy. Leptin replacement was associated with a small increase (clinically non-significant) in serum testosterone and SHBG in males. No change was observed in serum LH response to LHRH (264). No impact of leptin therapy on bone mineral density and content and bone metabolism has been reported in both sexes (244, 268, 269).

ADVERSE EFFECTS

Majority of patients treated with metreleptin in clinical studies experienced ≥1 treatment-emergent adverse event, which mainly were mild-to-moderate in severity (228, 229). The most common side effects were hypoglycemia, nausea, decreased appetite and injection site reactions e.g. erythema and urticaria. Headache, fatigue, weight loss, and abdominal pain were also seen (228). During metreleptin treatment, iron parameters might be affected, and a decrease in ferritin levels might be observed (270). There may also be a need to make dose adjustments or cessation of concomitant treatments such as insulin, oral antidiabetics, and lipid lowering drugs after metreleptin therapy. In some cases, in vivo neutralizing antibodies to metreleptin have been reported (271, 272) and is the main reason underlying the FDA's restriction of Anti-metreleptin metreleptin use. antibodies developed in most patients with lipodystrophy; however, neutralizing activity concurrent with worsened metabolic control has been reported only in a small number of patients treated with metreleptin (267, 271). In addition, in the few patients who presented with neutralizing antibody formation, occurrence of severe infections such as sepsis has been reported. Two of these patients developed multiple sepsis episodes around the time of detection of neutralizing antibody (271). T-cell lymphoma has been reported in three patients with acquired generalized lipodystrophy receiving metreleptin (273). In acquired lipodystrophy patients with autoimmunity and immunodeficiency before metreleptin therapy, Tcell lymphoma development was also described (273, 274), suggesting that lymphoma development in acquired lipodystrophy is more likely to be associated with the disease itself rather than being related to metreleptin treatment.

In other cases with acquired generalized lipodystrophy, progression of kidney disease and liver disease have been observed while receiving metreleptin therapy (275). Since patients with AGL with distinct autoimmune conditions clearly benefit

from metreleptin, treatment for their metabolic abnormalities should be considered in patients with AGL with close clinical follow up considering the cautionary preclinical data (276, 277).

More recently attention has been devoted to emergence of new cancers while on metreleptin therapy. Data on these parameters has been reported with the prospective, non-randomized, open-label clinical trial of metreleptin in lipodystrophy. Ten patients with general lipodystrophy had neoplasm development throughout the research period. These included peripheral T-cell lymphoma, granular cell tumor, breast cancer, ovarian neoplasm, papillary thyroid cancer, and basal cell carcinoma. However, only the anaplastic large cell lymphoma case was thought to be drug-related (228). During the study period, neoplasms (e.g., adrenal adenoma, benign ovarian germ cell teratoma, schwannoma, and a nervous system neoplasm) were observed to develop in five partial lipodystrophy patients. Still, none of them were considered drug-related (229).

Additionally, MEASuRE (Metreleptin Efficacy and Safety Registry), a voluntary registry that collects longterm safety and effectiveness data on metreleptin, was developed as a post-authorization requirement by the FDA and EMA. This database contains comprehensive data on long-term adverse effects and drug efficacy in lipodystrophy patients using commercially available metreleptin (278).

Investigational Treatments for Lipodystrophy

Since in the United States partial lipodystrophy has been without medical therapy, several companies with interesting compounds have initiated development of their products for this indication. Current and recently completed investigational treatments with registered studies in ClinicalTrials.gov are presented in Table 4. Data on these trials will be updated as results become available. The BROADEN study which was the largest global double blinded placebo controlled study published in 2022 revealed that treatment with volanesorsen, an antisense oligonucleotide to apolipoprotein C-III, significantly reduced serum triglyceride levels by over 88% and improved hepatic steatosis in patients with FPLD by 53 % from original level (279, 280). While the exact mechanisms of how volanesorsen led to the effects observed in the FPLD population are unclear, a small scale study showed that hepatic insulin resistance concurrently improved in parallel to an increase in lipoprotein lipase (LPL) activity in a few FPLD patients treated with this drug (281).While Volanesorsen is not approved in the US due to the adverse events of systemic inflammation and thrombocytopenia, this drug has been approved for use in FPLD in Brazil under the name Waylivra, marketed by PTC Therapeutics. The same drug is also available in Canada and EU for treatment of familial hyperchylomicronemia syndrome and can be an offlabel option for patients with recurrent pancreatitis and severe hypertriglyceridemia. Currently, second generation anti-sense inhibitors of ApoCIII are under development in the US for severe hypertriglyceridemia and patients with FPLD are not excluded from these studies if they meet the trial population criteria (282-284). We are aware of a few patients with FPLD who are in ongoing studies.

A therapeutic compassionate use trial with the melanocortin-4 receptor agonist setmelanotide was conducted in a patient with atypical partial lipodystrophy, whose metabolic status continued to worsen despite the presence of neutralizing antibodies to metreleptin. The reported findings indicated that the treatment had no improving effect on the lipid profile, insulin resistance, and liver fat percentage (285). The patient was successfully treated with same Mibavademab a monoclonal leptin receptor agonist antibody and remains on long term treatment (286). The promising results obtained from this patient experience led to the development of this therapeutic option for patients with generalized as an lipodystrophy. A small-scale proof of concept study in

FPLD patients was also started but very recently discontinued and results are not yet available. Treatment of 16 enrolled patients with generalized lipodystrophy over a year resulted in meaningful

changes in metabolic parameters which are similar to metreleptin effects; but final completion of the study and the definitive dosing schema has not been published so far (287).

Table 4. Ongoing	g or Recently Compl	eted Investigational T	herapies for Lipod	ystrophy
Investigational agent	Status	Type of lipodystrophy	Primary outcome	Results
Volanesorsen (anti-sense oligonucleotide to apoC-III)	Completed	Familial partial lipodystrophy	Change in fasting triglycerides	88% reduction in triglycerides, 53% reduction in hepatic steatosis
Vupanorsen (Targeting angiopoietin-like 3 "ANGPTL3") (288)	(Pfizer and Ionis announced discontinuation of vupanorsen clinical development program due to concern for increase in liver fat	Familial partial lipodystrophy	Reduction in fasting triglycerides and free fatty acids	59.9% reduction in triglycerides, 54.7 % reduction in ANGPTL3, 53.5% reduction in VLDL cholesterol, 41.7% reduction in free fatty acids (FFA)
Obeticholic Acid (farnesoid X receptor agonist)	Completed	Familial partial lipodystrophy	Change in liver triglycerides	 6.8% reduction in liver triglycerides median value, 16.9 mg/dL reduction in serum triglycerides, 0.5 U/L reduction in serum alanine aminotransferase (ALT) median value
Cholic Acid (primary bile acid)	Completed	Various forms of lipodystrophy	Reduction in liver triglyceride content	7.9% reduction in hepatic triglycerides median value (Fat/Fat+Water)
Setmelanotide (melanocortin-4 receptor agonist) (285)	Expanded access in a single patient	Partial lipodystrophy associated with leptin deficiency	Treatment of refractory hypertriglyceride mia leading to recurrent bouts of pancreatitis	No sustained improvement in glycemic control or hypertriglyceridemia, slight decrease in visceral fat
Gemcabene (monocalcium salt of a dialkyl	Completed	Familial partial lipodystrophy	Change in fasting	The mean percentage change in fasting serum

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dicarboxylic acid)			hepatic steatosis	between weeks 12 and 24 in group 1 (receiving 300 mg Gemcabene daily) was -0.44 (-41.27 to 40.38), and in group 2 (receiving 600 mg Gemcabene daily) was -20.27 (-53.98 to 12.77)
Baricitinib (inhibitor of Janus kinases 1 and 2 "JAK1/2")	Expanded access available	Autoinflammatory syndromes, familial partial lipodystrophy type 2, Hutchinson- Gilford Progeria Syndrome, and MAD (289)	Clinical benefit from JAK 1/2 inhibition, improves adipogenesis and lipid droplet formation	Increased number of adipocytes and formation of lipid droplets, higher adipocyte differentiation ability, increased lipid droplet size (~76 µm2) in the FPLD2 group
Evinacumab (Anti- ANGPTL3)	Completed	Patients with severe hypertriglyceridemia	Percent lowering of triglycerides	59.9% reduction in mean fasting triglycerides levels from baseline at the end of the treatment (week 27)
Mibavademab	Active, not recruiting	Generalized lipodystrophy	Meaningful improvements in metabolic parameters	Reduction in HbA1c (mean: -1.9%, SD: 2.0) and triglycerides (median: -102.1 mg/dL, IQR: 1355.5 mg/dL, -49.3% [57.2%]) (290) With longer treatment there was a further 0.7% reduction in HbA1c and 42% reduction in fasting triglycerides in patients receiving

high dose
mibavademab (287)

Emerging Therapeutic Technologies and Gene Replacement Therapy Approaches

Research on novel and emerging technologies is ongoing to broaden therapy options and better understand diseases of complex nature like lipodystrophy. LipocyteProfiler, a sophisticated imagebased tool for deep phenotypic analysis, facilitates assessing numerous morphological and cellular profiles that can be methodically associated with genes and genetic variations that have significance in cardiometabolic diseases. LipocyteProfiler is algorithmically generated from over 3.000 morphological and cellular features that map to the cell, cytoplasm, and nucleus across channels differentiating the organelles, namely DNA. mitochondria, AGP (actin, Golgi, plasma membrane), and Lipid. It was observed that LipocyteProfiler was able to detect significant changes in cell profiles during white and brown adipocyte differentiation after genetic and pharmacological manipulations and transcriptional states in adipocytes. Also, profiles associated with the polygenic risk of lipodystrophy confirmed increased mitochondrial activity, reduced actin cytoskeleton remodeling, and reduced lipid accumulation capacity in subcutaneous adipocytes. This tool may shed light on a deeper insight into both known and novel mechanisms by generating cellular profiles that are specific to the processes occurring in response to polygenic metabolic events, particularly in hepatocytes and adipocytes. Analyzing deep phenotypic profiles, especially in lipocytes, can enhance our understanding of lipodystrophy pathophysiology and allow us to develop better therapies (291).

Gene therapy studies conducted in recent years are an emerging and promising approach to treating various genetic lipodystrophy syndromes. A novel study shows that the in vivo embryonic re-expression of human AGPAT2 (hAGPAT2) induces adipocyte differentiation and regenerates 30%–50% of the WAT and BAT depots in Agpat2–/– mice when compared to age-matched wild-type mice. Due to this genetic reorganization in Agpat2-null mice, it was observed that the differentiation of adipocytes, specifically the metabolically active depots (SubQ, Gonadal, and BAT) and dWAT (dermal) was stimulated (292).

An in vivo gene therapy study demonstrated that delivering the human BSCL2 gene using an adenoassociated virus (AAV) in seipin knockout mice resulted in the restoration of adipose tissue, and this led to a significant improvement in metabolic disease (293). Following AAV-mediated gene therapy, it has been documented that there was a reduction in serum triglyceride levels, an improvement in insulin sensitivity and glucose tolerance, and a partial enhancement in the development of visceral WAT depots in seipin knockout mice. However, a dramatic increase in circulating leptin and adiponectin levels could not be achieved. Nevertheless, this study suggests a potential therapeutic approach for treating metabolic conditions related to CGL2 and other lipodystrophy syndromes (293).

Introducing a functional copy of the defective gene associated with the condition or modulating the expression of related genes to restore normal adipose tissue function holds promise for alleviating severe metabolic complications in patients with lipodystrophy. CrispR-cas editing of single nucleotide variants is also rapidly approaching clinical use in all rare diseases. However, further studies are required to move gene therapies from the experimental stage to clinical applications.

CONCLUSION

Lipodystrophy syndromes are a group of fascinating diseases that are caused by mechanisms that disrupt predominantly adipocyte differentiation or lipid droplet formation. LMNA gene defects, the most common single gene defects leading to the development of lipodystrophy syndromes, leads to lipodystrophy possibly due to inducing adipocyte apoptosis or death, but more work is needed on this front. Regardless of the mechanism and whether the diseases present with generalized or partial fat loss, common metabolic complications include severe insulin resistance, hypertriglyceridemia, and ectopic fat deposition, especially hepatic steatosis. This common theme is recapitulated in numerous animal models as well. The diseases are typically progressive and lead to multiorgan involvement and increased mortality. Molecular advances understanding of in the disease mechanisms may lead to better and specific treatments for lipodystrophy syndromes. So far, the

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most exciting therapeutic development for the treatment of lipodystrophy syndromes has been the approval of leptin replacement therapy for generalized lipodystrophy in the form of metreleptin which started a new era in lipodystrophy research; leading to the launch of registries and natural history studies (e.g. the LD Lync Study-Natural History Study of Lipodystrophy Syndromes (NCT03087253) (294-296), organization of research consortia around the world (e.g., European Consortium of Lipodystrophies (ECLip) (297) and country specific patient advocacy foundations or organizations. All these efforts will contribute to discovery of new disease forms and disease mechanisms, understanding of the natural course of lipodystrophy diseases, development of improved treatment options and possibly cures.

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