The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline

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Objective: Lipodystrophy syndromes are extremely rare disorders of deficient body fat associated with potentially serious metabolic complications, including diabetes, hypertriglyceridemia, and steatohepatitis. Due to their rarity, most clinicians are not familiar with their diagnosis and management. This practice guideline summarizes the diagnosis and management of lipodystrophy syndromes not associated with HIV or injectable drugs.

Participants: Seventeen participants were nominated by worldwide endocrine societies or selected by the committee as content experts. Funding was via an unrestricted educational grant from Astra Zeneca to the Pediatric Endocrine Society. Meetings were not open to the general public.

Evidence: A literature review was conducted by the committee. Recommendations of the committee were graded using the system of the American Heart Association. Expert opinion was used when published data were unavailable or scarce.

Consensus Process: The guideline was drafted by committee members and reviewed, revised, and approved by the entire committee during group meetings. Contributing societies reviewed the document and provided approval.

Conclusions: Lipodystrophy syndromes are heterogeneous and are diagnosed by clinical phenotype, supplemented by genetic testing in certain forms. Patients with most lipodystrophy syndromes should be screened for diabetes, dyslipidemia, and liver, kidney, and heart disease annually. Diet is essential for the management of metabolic complications of lipodystrophy. Metreleptin therapy is effective for metabolic complications in hypoleptinemic patients with generalized lipodystrophy and selected patients with partial lipodystrophy. Other treatments not specific for lipodystrophy may be helpful as well (eg, metformin for diabetes, and statins or fibrates for hyperlipidemia). Oral estrogens are contraindicated. **(*J Clin Endocrinol Metab* 101: 4500–4511, 2016)**

The lipodystrophy syndromes are a heterogeneous group of rare disorders that have in common selective deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state (Figure 1). Lipodystrophies are categorized based on etiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regions (partial). This yields four major categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL) (Figure 1). Additional subtypes include progeroid disorders, autoinflammatory disorders, and others (Table 1). This practice guideline will not discuss lipodystrophy in HIV infected patients or localized lipodystrophy (eg, from injectable drugs).

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Abbreviations: AGL, acquired generalized lipodystrophy; APL, acquired partial lipodystrophy; C3, complement 3; CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPGN, membranoproliferative glomerulonephritis; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

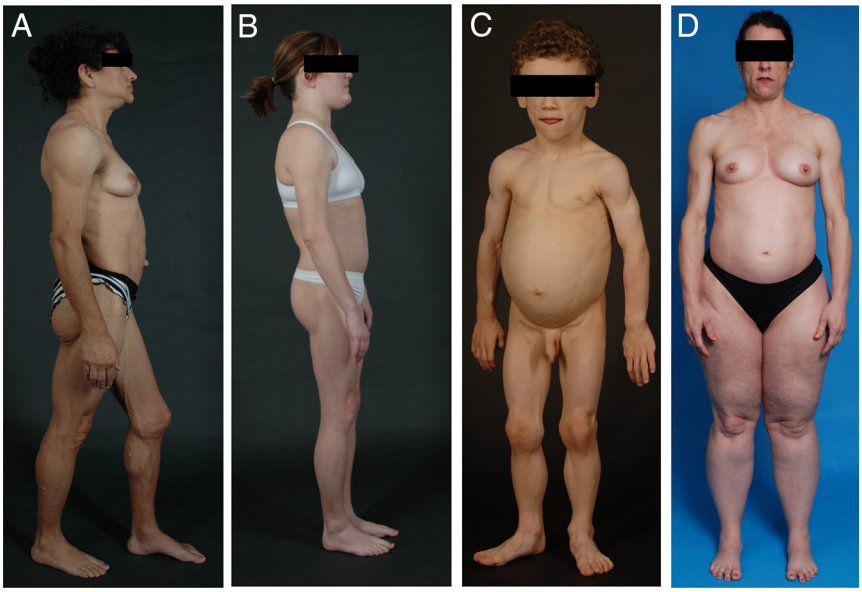

Figure 1. Physical appearance of patients with the four main subtypes of lipodystrophy syndromes. A, Lateral view of a 33-year-old Hispanic female with congenital generalized lipodystrophy (also known as Berardinelli-Seip congenital lipodystrophy), type 1 due to homozygous c.589–2A>G; p.(Val197Glufs*32) mutation in the *AGPAT2* gene. The patient had generalized loss of subcutaneous (sc) fat with acanthosis nigricans in the axillae and neck. She has umbilical prominence and acromegaloid features (enlarged mandible, hands, and feet). B, Lateral view of a 26-year-old female with familial partial lipodystrophy of the Dunnigan variety due to heterozygous c.575A>T; p.(Asp192Val) mutation in the *LMNA* gene. She had marked loss of sc fat from the upper and lower extremities and accumulation of sc fat in the face and chin. C, Anterior view of an 8-year-old German boy with acquired generalized lipodystrophy. He had severe generalized loss of sc fat with marked acanthosis nigricans in the neck, axillae, and groin. D, Anterior view of a 45-year-old Caucasian female with acquired partial lipodystrophy (Barraquer-Simons syndrome). She had marked loss of sc fat from the face, neck, upper extremities, and chest but had lipodystrophy on localized regions on the anterior thighs. She had increased sc fat deposition in the lower extremities.

Lipodystrophy syndromes are frequently associated with hormonal and metabolic derangements resulting in severe comorbidities (Table 2) that depend on the subtype, extent of fat loss, age, and gender. Many complications of lipodystrophy are secondary to deficient adipose mass, resulting in ectopic lipid storage in the liver, muscle, and other organs and causing insulin resistance. Insulin resistance leads to diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and nonalcoholic fatty liver disease (NAFLD) (1).

Major causes of mortality include heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia) (2–5), liver disease (liver failure, gastrointestinal hemorrhage, hepatocellular carcinoma) (6, 7), kidney failure (6), acute pancreatitis (7), and sepsis.

Due to the rarity of lipodystrophy syndromes, many clinicians are unfamiliar with their diagnosis and management. In December 2015, an expert panel including representatives from endocrine societies around the world convened to generate this practice guideline. Evidence was rated using the system of the American Heart Association (Supplemental Table 1) (8). Details of the literature review, consensus, and endorsement process are provided in the Supplemental Data.

Overview of Lipodystrophy Syndromes

This section reviews major categories of lipodystrophy. Details on individual subtypes are in Supplemental Table 2.

Congenital generalized lipodystrophy (Berardinelli-Seip syndrome)

CGL is an autosomal recessive disorder characterized by near-complete lack of fat starting at birth or infancy, prominent muscles, phlebomegaly, acanthosis nigricans, hepatomegaly, umbilical prominence, and voracious appetite in childhood (9, 10). Multiple genetic causes have been identified, each with unique clinical features (11–13).

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Table 1. Subtypes and Inheritance of Lipodystrophy

Inheritance Pattern	Subtype	Lipodystrophy Phenotype	Genes Involved	Refs.
Autosomal recessive	CGL	Near total absence of body fat, generalized muscularity, metabolic complications	*AGPAT2*, *BSCL2*, *CAV1*, *PTRF*, *PCYT1A*, *PPARγ*	11, 84–88
	Progeroid syndromes	Partial or generalized absence of body fat, progeroid features, variable metabolic complications	*LMNA*, ZMPSTE24, *SPRTN*, *WRN*, *BANF1*	89–93
	FPLD	Absence of fat in limbs, metabolic complications	*CIDEC*, *LIPE*, *PCYT1A*	87, 92, 94–96
	Autoinflammatory	Variable absence of fat, variable metabolic complications	*PSMB8*	97
Autosomal dominant	FPLD	Absence of fat from the limbs, metabolic complications	*LMNA*, *PPARG*, *AKT2*, *PLIN1*	98–103
	Progeroid syndromes	Partial or generalized absence of body fat, progeroid features, variable metabolic complications	*LMNA*, *FBN1*, *CAV1*, *POLD1*, *KCNJ6*	104–109
	SHORT syndrome	Variable loss of body fat, metabolic complications	*PIK3R1*	110
Acquired	AGL	Near total absence of body fat, metabolic complications	None	4
	APL	Absence of fat in upper body with increased fat in lower body, mild or no metabolic complications	None	17

Metabolic complications are frequent and may be severe. Cardiomyopathy or rhythm disturbances may occur.

Familial partial lipodystrophy

FPLD is a group of usually autosomal dominant disorders characterized by loss of fat affecting the limbs, buttocks, and hips (10). Regional excess fat accumulation is frequent, varies by subtype, and may result in a Cushingoid appearance. Fat distribution is typically normal in early childhood, with loss of fat occurring around puberty. Muscular hypertrophy is common. Metabolic complications are common in adulthood (14), with increased risk of coronary heart disease (15) and occasionally early cardiomyopathy.

Acquired generalized lipodystrophy (Lawrence syndrome)

AGL is more common in females (females:males, 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles (4). Some fat accumulation can appear in the face, neck, or axillae. Meta-

Table 2. Major Comorbidities and Complications of Lipodystrophy

Complication	Affected Subtypes	Refs.
Hyperphagia	AGL, CGL, ±FPLD	4, 10, 111
Dyslipidemia (high triglycerides, low HDL-cholesterol, acute pancreatitis, eruptive xanthomas)	AGL, CGL, FPLD	4, 5, 7, 9, 13, 21, 30
Insulin resistance/diabetes, acanthosis nigricans (and diabetes complications)	AGL, CGL, FPLD	4, 5, 7, 9, 13, 17, 20, 21, 69
Reproductive dysfunction (PCOS, oligomenorrhea, reduced fertility, hirsutism, preeclampsia, miscarriage, macrosomia)	AGL, CGL, FPLD	4, 5, 7, 10, 14, 20, 55, 112
NAFLD (ranging from simple steatosis to cirrhosis)	AGL, CGL, FPLD, ±APL	4, 7, 10, 17, 19, 49, 51, 69, 113
Renal dysfunction (proteinuria, MPGN, FSGS, diabetic nephropathy)	AGL, CGL, FPLD, APL	17, 34, 114
Heart disease (hypertension, cardiomyopathy, arrhythmias, conduction abnormalities, CAD)	AGL, CGL, FPLD	3–5, 9, 13, 15, 25
Autoimmune disease	AGL, APL	4, 10, 17, 19, 20

Abbreviations: CAD, coronary artery disease; FSGS, focal segmental glomerulosclerosis. Many of these features are also found in other forms of lipodystrophy, including progeroid disorders.

bolic complications are frequent and may be severe. AGL is often associated with autoimmune diseases (4, 16).

Acquired partial lipodystrophy (Barraquer-Simons syndrome)

APL is more frequent in females (females:males, 4:1) and usually begins in childhood or adolescence. Loss of fat follows a cranio-caudal trend, progressively affecting the face, neck, shoulders, arms, and trunk. Fat accumulation can appear in the hips, buttocks, and legs (17). APL is associated with autoimmune diseases, especially membranoproliferative glomerulonephritis (MPGN) in approximately 20% (17). Most patients have low serum complement 3 (C3) levels, and some have presence of C3 nephritic factor. Metabolic complications are uncommon (17).

Diagnosis of Lipodystrophy

- Diagnosis of lipodystrophy is based on history, physical examination, body composition, and metabolic status. (Class I, Level B)
- There are no defined serum leptin levels that establish or rule out the diagnosis of lipodystrophy. (Class IIa, Level C)
- Confirmatory genetic testing is helpful in suspected familial lipodystrophies. (Class I, Level A)
- Genetic testing should be considered in at-risk family members. (Class IIa, Level C)
- Serum complement levels and autoantibodies may support diagnosis of acquired lipodystrophy syndromes. (Class IIa, Level B)

Firm diagnostic criteria for lipodystrophy have not been established. Figure 2 shows a suggested diagnostic approach.

Establishing the presence of lipodystrophy

Lipodystrophy should be suspected in patients with regional or generalized lack of adipose tissue outside of the normal range by physical examination, which can be supported by anthropometry, dual energy x-ray absorptiometry, and whole-body magnetic resonance imaging (Supplemental Table 3) (18). Recognizing the loss of sc fat is particularly challenging in partial lipodystrophy and especially in men, in whom low body fat overlaps with normal variation and metabolic manifestations of lipodystrophy are less severe. In both genetic and acquired lipodystrophies, the loss of fat may be gradual, delaying diagnosis.

Physical, historical, and comorbid features that increase the suspicion of lipodystrophy (18) are shown in Table 3.

Because serum leptin assays are not standardized and leptin concentrations in patients with lipodystrophy (especially partial forms) overlap the general population, leptin levels do not help in diagnosis but may help with the choice of therapies.

Differential diagnosis

Differential diagnosis should include conditions presenting with severe weight loss (malnutrition, anorexia nervosa, uncontrolled diabetes mellitus, thyrotoxicosis, adrenocortical insufficiency, cancer cachexia, HIV-associated wasting, chronic infections). Especially difficult is differentiating lipodystrophy from uncontrolled diabetes because both may have extreme hypertriglyceridemia. However, restoring glycemic control in patients with nonlipodystrophic diabetes leads to a regain of body fat. Generalized lipodystrophies can be confused with mutations of the insulin receptor or acromegaly/gigantism, and FPLD with Cushing's syndrome, truncal obesity, and multiple symmetric lipomatosis.

Establishing the subtype of lipodystrophy

Pattern of fat loss

Although the pattern of body fat loss in patients with a particular subtype of genetic lipodystrophy is quite characteristic, heterogeneity occurs in the onset, severity, and pattern of fat loss, even within families.

Distinguishing genetic from acquired lipodystrophy

Pedigree analysis can suggest genetic vs acquired lipodystrophy. Review of photographs from infancy may distinguish CGL from AGL because infants typically show absent fat in CGL and normal fat in AGL. However, there have been cases of AGL with loss of fat during the first few months of life (4). Patients with AGL lack family history but can be confused with any type of genetic lipodystrophy, especially de novo mutations.

The presence of autoimmune diseases (myositis, type 1 diabetes, autoimmune hepatitis, and others) (4, 10, 16, 17, 19, 20) increases the suspicion of acquired lipodystrophy. In APL, low serum C3, C3 nephritic factor, proteinuria, or biopsy-proven MPGN support the diagnosis.

Genetic testing

Genotyping may include limited candidate gene sequencing, a panel of candidate genes, or whole-exome/whole-genome sequencing. The website www.genetests.org lists clinical and research laboratories conducting genetic testing for lipodystrophy syndromes. Because there is strong evidence for additional loci for genetic lipodystrophies, negative tests do not rule out a genetic condition.

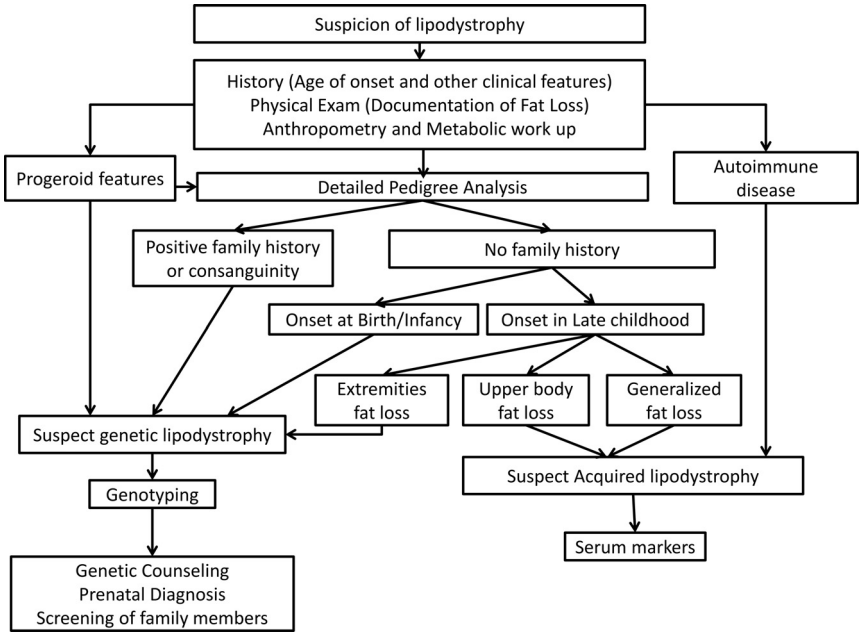

Figure 2. Diagnostic approach to lipodystrophy syndromes. Lipodystrophy should be suspected in patients with regional or generalized lack of adipose tissue. History should assess age of onset of fat loss and comorbidities. Physical examination should determine distribution of sc fat loss and presence of prominent muscles, phlebomegaly, acanthosis nigricans, hepatomegaly, xanthomas, and acromegaloid or progeroid appearance. All patients should undergo a metabolic workup for insulin resistance, diabetes, dyslipidemia, and fatty liver disease. Conventional anthropometry including skinfold thickness measurements, ± dual energy x-ray absorptiometry, and whole-body magnetic resonance imaging (if available) should be performed to confirm the pattern of fat loss. Common genetic lipodystrophies include CGL, FPLD, and progeroid lipodystrophies. They require genotyping to confirm the diagnosis, followed by genetic counseling and screening of family members. Patients with progeroid lipodystrophies have progeroid features like bird-like facies, high-pitched voice, skin atrophy and pigmentation, alopecia, and nail dysplasia. Patients with FPLD have fat loss of the extremities typically occurring around puberty and can have a positive family history. Patients with CGL have near-complete lack of fat starting at birth or infancy. Acquired lipodystrophies have fat loss typically in late childhood. Patients with AGL have generalized loss of sc fat and often have associated autoimmune diseases. Patients with APL have cranio-caudal fat loss affecting the face, neck, shoulders, arms, and upper trunk, and most patients have low serum C3 levels.

Genetic counseling and screening of family members

Genetic counseling must take into consideration that the current understanding of the natural history of genetic lipodystrophies is incomplete. In affected pedigrees, premarital counseling with genetic testing to detect carrier status can be considered.

Clinical diagnosis of lipodystrophy may be difficult in men (21), and some genotypes are associated with mild lipodystrophy phenotypes (22, 23). Genetic screening of family members may help identify individuals with subtle phenotypes. Genetic screening may be particularly important for families with specific *LMNA* mutations associated with cardiomyopathy and arrhythmia.

Screening for Comorbidities

All patients should be screened for diabetes, dyslipidemia, NAFLD, and cardiovascular and reproductive dysfunction. Because patients with APL are at low risk for metabolic complications, clinical judgment should guide follow-up screening. Screening for comorbidities specific to individual lipodystrophy subtypes is not extensively discussed here.

Diabetes mellitus

- Diabetes screening should be performed annually. (Class IIa, Level C)

Diabetes screening should follow the guidelines of the American Diabetes Association (fasting plasma glucose, oral glucose tolerance test, or glycosylated hemoglobin [HbA1c]). Patients with AGL may develop type 1 diabetes in addition to insulin resistance (24); measurement of autoantibodies may clarify the diagnosis.

Dyslipidemia

- Triglycerides should be measured at least annually and with occurrence of abdominal pain or xanthomata. (Class I, Level C)
- Fasting lipid panel (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides) should be measured at diagnosis and annually after age 10 years. (Class IIa, Level C)

Liver disease

- Alanine aminotransferase and aspartate aminotransferase should be measured annually. (Class IIa, Level C)
- Liver ultrasound should be performed at diagnosis, then as clinically indicated. (Class IIa, Level C)
- Liver biopsy should be performed as clinically indicated. (Class IIa, Level C)

In addition to physical examination, ultrasound and elastography are useful to estimate liver and spleen size, severity of steatosis and fibrosis, and existence of portal hypertension. Patients with CGL2 are at high risk for early cirrhosis, and those with AGL may have autoimmune hepatitis in addition to NAFLD (19).

Table 3. Clinical Features That Increase the Suspicion of Lipodystrophy

Essential feature
Generalized or regional absence of body fat
Physical features
Failure to thrive (infants and children)
Prominent muscles
Prominent veins (phlebomegaly)
Severe acanthosis nigricans
Eruptive xanthomata
Cushingoid appearance
Acromegaloid appearance
Progeroid (premature aging) appearance
Comorbid conditions
Diabetes mellitus with high insulin requirements
≥200 U/d
≥2 U/kg/d
Requiring U-500 insulin
Severe hypertriglyceridemia
≥500 mg/dL with or without therapy
≥250 mg/dL despite diet and medical therapy
History of acute pancreatitis secondary to hypertriglyceridemia
Non-alcoholic steatohepatitis in a non-obese individual
Early-onset cardiomyopathy
PCOS
Other historical clues
Autosomal dominant or recessive pattern of similar physical features or metabolic complications
Significant hyperphagia (may manifest as irritability/aggression in infants/children)

Adapted from Ref. 18.

Reproductive dysfunction

- Gonadal steroids, gonadotropins, and pelvic ultrasonography should be performed as clinically indicated. (Class IIa, Level C)
- Pubertal staging should be performed annually in children. (Class IIa, Level C)

Early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalized lipodystrophy. Oligo/amenorrhea, decreased fertility, and PCOS are common in women.

Cardiac disease

- Blood pressure should be measured at least annually. (Class I, Level C)
- Electrocardiogram and echocardiogram should be performed annually in CGL and progeroid disorders, at diagnosis, and as clinically indicated in FPLD and AGL. (Class IIa, Level C)
- Evaluation for ischemia and rhythm monitoring should be considered in patients with progeroid disorders and FPLD2 with cardiomyopathy. (Class IIa, Level C)

Hypertension is common (25), even in children. In patients with CGL4, atypical progeroid syndromes, and FPLD2 due to *LMNA* mutations, cardiac abnormalities including ischemic heart disease, cardiomyopathy, arrhythmias, and sudden death are reported (3, 23, 26–33).

Kidney disease

- Urine protein should be measured annually using 24-hour urine collection or spot urine protein-to-creatinine ratio. (Class IIa, Level C)

Proteinuria is common (34). Kidney biopsy should be performed as clinically indicated, and pathology may include diabetic nephropathy, focal segmental glomerulosclerosis (especially in CGL) (34) or MPGN (especially in APL) (17).

Malignancy

Lymphomas, particularly peripheral T-cell lymphoma, occur in AGL, with a prevalence of approximately 7% (4, 35). Appropriate screening has not been established but would reasonably include annual skin and lymph node examination. Generalized lipodystrophy has been reported as a paraneoplastic manifestation of pilocytic astrocytoma in three children who regained body fat after cancer therapy (36). Clinicians should consider screening for brain tumors in children who present with idiopathic AGL or atypical CGL. Specific progeroid syndromes (eg, Bloom and Werner syndromes) are associated with increased malignancy risk (Supplemental Table 2).

Treatment of Lipodystrophy Syndromes

Current therapies prevent or ameliorate the comorbidities of lipodystrophy syndromes. There is no cure for lipodystrophy and no treatment that can regrow adipose tissue.

Diet

- Most patients should follow diets with balanced macronutrient composition. (Class IIa, Level C)
- Energy-restricted diets improve metabolic abnormalities and may be appropriate in adults. (Class I, Level C)
- Very-low-fat diets should be used in chylomicronemia-induced acute pancreatitis. (Class I, Level C)
- A dietician should be consulted for specialized dietary needs, especially in infants and young children.Overfeeding should be avoided. (Class IIa, Level C)
- Medium-chain triglyceride oil formulas can provide energy and reduce triglycerides in infants. (Class IIa, Level C)

The cornerstone of therapy for metabolic complications of lipodystrophy is diet. Studies of specific diets in

lipodystrophy are lacking, and recommendations rely on sparse literature and clinical experience.

Patients with lipodystrophy, especially generalized forms, are typically hyperphagic due to leptin deficiency. Energy-restricted diets in adolescents and adults lower triglycerides and glucose (37), but dietary restriction is challenging to achieve. Food restriction to control metabolic complications must be balanced by requirements for growth in children. Overfeeding to achieve normal weight may worsen metabolic complications and hepatic steatosis. Assessment of weight-for-length and body mass index by comparison to reference growth data is not appropriate because body composition is atypical. Low weight-for-length or body mass index is acceptable provided linear growth is maintained.

Patients should follow a 50–60% carbohydrate, 20–30% fat, and approximately 20% protein diet. Simple sugars should be restricted in preference for high-fiber complex carbohydrates, distributed evenly among meals and snacks and consumed in combination with protein or fat. Dietary fat should be primarily cis-mono-unsaturated fats and long-chain omega-3 fatty acids. In extremely hypertriglyceridemic infants, medium-chain triglyceride-based formula may help (38, 39). During acute pancreatitis, bowel rest followed by a very-low-fat (<20 g) diet should be used.

Exercise

- Patients with lipodystrophy should be encouraged to exercise in the absence of specific contraindications. (Class IIa, Level C)
- Patients with subtypes of lipodystrophy predisposed to cardiomyopathy should undergo cardiac evaluation before initiating an exercise regimen. (Class III, Level C)

Individuals with lipodystrophy engaged in intense exercise have amelioration of metabolic complications. Most patients should be encouraged to be physically active. However, strenuous exercise should be avoided in patients with cardiomyopathy. Contact sports should be avoided in patients with severe hepatosplenomegaly and CGL patients with lytic bone lesions.

Metreleptin

- In generalized lipodystrophy, metreleptin (with diet) is a first-line treatment for metabolic and endocrine abnormalities (Class I, Level B) and may be considered for prevention of these comorbidities in children. (Class IIb, Level C)
- Metreleptin may be considered for hypoleptinemic (leptin <4 ng/mL) patients with partial lipodystrophy and severe metabolic derangements (HbA1c >8% and/or triglycerides >500 mg/dL). (Class IIb, Level B)

Currently, metreleptin (recombinant human methionyl leptin) is the only drug approved specifically for lipodystrophy. It is approved in the United States as an adjunct to diet for treatment of metabolic complications in patients with generalized lipodystrophy (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm387060.htm). In Japan, it is approved for both generalized and partial lipodystrophy (http://www.shionogi.co.jp/en/company/news/2013/pmrltj0000000ufd-att/e_130325.pdf). It is available in other parts of the world (eg, Europe) through compassionate use programs. There is no age limit for initiation of metreleptin; children as young as 6 months have been treated. A dosing algorithm is provided in Supplemental Table 4 (40). Dose adjustments should be made in response to metabolic parameters and weight change, with clinical and laboratory assessment performed every 3–6 months.

Metreleptin in generalized lipodystrophy

Metreleptin decreases hyperphagia (41–45), frequently leading to weight loss. Reduced food intake is at least partially responsible for many of the metabolic improvements. If excessive weight loss occurs, the dose of metreleptin should be reduced (Supplemental Table 4) (40).

Metreleptin markedly improved fasting glucose as early as the first week (42) and lowered HbA1c by 2% after 1 year (46). To reduce the risk of hypoglycemia, frequent glucose monitoring is recommended. Providers should consider reducing insulin doses by approximately 50% on initiation of metreleptin in patients with well-controlled diabetes. Many young patients with CGL are able to discontinue insulin (46).

Metreleptin lowered triglycerides within 1 week (42), reaching 60% reduction at 1 year (46). Metreleptin also decreased LDL- and total cholesterol but did not change HDL-cholesterol (47, 48). Acute pancreatitis due to hypertriglyceridemia has occurred in patients who acutely discontinued or reduced metreleptin (47).

Metreleptin reduced hepatic steatosis, serum transaminases, and NASH scores within 6 to 12 months (42, 49–51). In one case, metreleptin ameliorated recurrence of severe hepatic steatosis after liver transplantation (52).

Metreleptin decreased proteinuria in most patients (34, 42). However, four patients had worsened renal disease during metreleptin treatment, so renal function should be monitored closely with preexisting renal disease (34).

In females, metreleptin normalized gonadotropin secretion, leading to normal progression of puberty, normalization of menstrual periods (42, 45, 53, 54), and improved fertility (1). Metreleptin decreased T in women but

did not alter ovarian morphology (45, 53, 55). In males, metreleptin increased T (45).

Metreleptin in partial lipodystrophy

The response to metreleptin in partial lipodystrophy is less robust than in generalized lipodystrophy. In one study, metreleptin reduced hypertriglyceridemia and improved glycemia in severely hypoleptinemic patients with partial lipodystrophy and severe metabolic derangements (baseline HbA1c >8%, triglycerides >500 mg/dL, leptin <4 ng/mL) (46). In a second study, metreleptin improved triglycerides and indices of insulin sensitivity and secretion in FPLD2 patients with moderate to severe hypoleptinemia (56). However, in a third study, no glycemic improvement was observed in FPLD2 patients with serum leptin <7 ng/mL (57). Metreleptin is only available to patients with partial lipodystrophy through clinical trials, compassionate use programs, and in Japan.

Side effects of metreleptin

Approximately 30% of patients experience side effects (47). The most clinically important are hypoglycemia (in patients receiving concomitant insulin) and infrequent injection-site reactions (erythema, urticaria).

In vivo neutralizing antibody activity to leptin has been reported (58, 59). The clinical implications remain unclear, but may include treatment failure and sepsis (59). Additional serious adverse events occurring during metreleptin treatment are likely related to the underlying lipodystrophy syndrome, rather than metreleptin. These include T-cell lymphoma in patients with AGL (35), pancreatitis (47), and worsening of liver (47) and kidney (34) disease.

Additional treatments for specific comorbidities

Diabetes

- Metformin is a first-line agent for diabetes and insulin resistance. (Class IIa, Level C)
- Insulin is effective for hyperglycemia. In some patients, concentrated preparations and high-doses may be required. (Class IIa, Level C)
- Thiazolidinediones may improve metabolic complications in partial lipodystrophy but should only be used with caution in generalized lipodystrophy. (Class IIb, Level B)

Among the oral hypoglycemic agents, metformin is used most frequently. In patients with partial lipodystrophy, thiazolidinediones improved HbA1c, triglycerides, hepatic volume, and steatosis but may increase regional fat excess (Supplemental Table 5) (60, 61). In patients with high insulin requirements, concentrated insulins should be considered (62). Insulin glargine and degludec kinetics may be altered when injected in lipodystrophic areas because their long duration of action requires sc fat (63, 64). Patients with generalized lipodystrophy may have to take insulin by im routes for the lack of sc fat. Many other hypoglycemic agents have been used in lipodystrophy, but their efficacy has not been studied.

Dyslipidemia

- Statins should be used concomitantly with lifestyle modification (after consideration of age, reproductive status, and tolerance). (Class 1, Level C)
- Fibrates and/or long-chain omega-3 fatty acids should be used for triglycerides >500 mg/dL and may be considered for triglycerides >200 mg/dL. (Class IIb, Level C)

Lipids should be managed in accordance with U.S. and European guidelines for the general population, with statins as first-line therapy (65–67). Statins and fibrates should be used with caution due to increased risk of myopathy, especially in the presence of known myositis or muscular dystrophy (68). Because cardiovascular risk may be enhanced in lipodystrophic syndromes independent of other risk factors, clinicians may consider applying stricter lipid targets (eg, LDL-cholesterol <100 mg/dL, non-HDL-cholesterol <130 mg/dL, triglycerides <200 mg/dL), even in patients without diabetes. In addition to diet, fibrates and long-chain omega-3-fatty acids from fish oils have wide clinical use to avoid acute complications of severe hypertriglyceridemia (46) but have not been formally studied. Plasmapheresis has been used in extreme hypertriglyceridemia, but must be repeated frequently (69). Additional lipid-lowering drugs have not been studied in patients with lipodystrophy.

Hypertension

- Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes. (Class IIa, Level C)

As in other patients with diabetes, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used for hypertension (70).

Liver disease

Cholic acid did not reduce hepatic steatosis in patients with FPLD in a double-blind, placebo-controlled crossover study (71). In NAFLD not associated with lipodystrophy, diet and exercise are first-line treatments (72), and among pharmacological treatments, vitamin E (in children and adults) (73, 74) and pioglitazone (in adults) (73, 75) have shown the most consistent benefit for liver histopathology. However, these treatments have not been

studied in patients with lipodystrophy and are not approved for NAFLD.

Cosmetic treatment

- Patients should be assessed for distress related to lipodystrophy and referred as necessary to mental health professionals and/or plastic surgeons. (Class IIa, Level C)

Changes in physical appearance from lipodystrophy can cause psychological distress and physical discomfort (eg, from absent fat pads in feet or buttocks). Data regarding cosmetic surgery are limited. For facial lipoatrophy, autologous fat transfer (in APL), dermal fillers (7, 76), or muscle grafts (77) may be used. Excess fat from the head, neck, or vulva may be surgically reduced or ameliorated by liposuction (7). Breast implants are helpful in some women (78, 79). Acanthosis nigricans is improved through successful treatment of insulin resistance (80, 81). Management of hirsutism is reviewed elsewhere (82).

Contraception and hormone replacement therapy

- Oral estrogens are contraindicated. (Class IIa, Level C)
- If contraception is needed, progestin-only or nonhormonal contraceptives should be considered. (Class IIa, Level C)
- If estrogen replacement is needed, transdermal estrogen should be used. (Class IIa, Level C)

Oral estrogens are contraindicated in lipodystrophy syndromes due to the risk of severe hypertriglyceridemia and acute pancreatitis. Transdermal estrogens may be safer due to lesser hepatic exposure (83). There is clinical experience in the safe use of oral progestins and progestin-containing intrauterine devices.

Pregnancy

- Pregnant patients should receive prenatal care from an obstetrician experienced in managing diabetes and a physician experienced in managing lipodystrophy. (Class IIa, level C)
- Should a patient become pregnant while taking metreleptin, clinicians may consider continuing metreleptin if withdrawal would harm the mother and fetus and the patient understands that the effects of metreleptin in pregnancy are unknown (FDA category C), and wishes to continue. (Class IIc, level C)

In patients with lipodystrophy with extreme insulin resistance, worsening insulin resistance during pregnancy may make diabetes management difficult, with attendant fetal risks. Furthermore, metreleptin withdrawal has been associated with rebound hypertriglyceridemia (41), placing patients at risk for pancreatitis, endangering both mother and fetus.

Conclusions

Lipodystrophy syndromes are heterogeneous with diverse pathophysiology. For diagnosis, clinical recognition and physical examination are critical. In management efforts, attention should be paid to metabolic derangements and to many other facets of these syndromes affecting multiple organs and quality of life.

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