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Lipodystrophy: Pathophysiology and Advances in Treatment

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Abstract

Lipodystrophy is a medical condition characterized by complete or partial loss of adipose tissue. Not infrequently, lipodystrophy occurs in combination with pathological accumulation of adipose tissue at distinct anatomical sites. Patients with lipodystrophy suffer from numerous metabolic complications, indicating the importance of adipose tissue as an active endocrine organ. Not only does the total amount but also the appropriate distribution of fat deposits contribute to the metabolic state. Recent genetic and molecular research has improved our understanding of the mechanisms underlying lipodystrophy. Circulating levels of hormones secreted by adipose tissue, such as leptin and adiponectin, are greatly reduced in distinct subsets of patients with lipodystrophy, rationalizing the use of such hormones or agents that increase their circulating levels, such as peroxisome proliferator-activated receptor gamma (PPARγ) agonists, in a subset of patients with lipodystrophy. Other novel therapeutic approaches, including the use of growth hormone (GH) and GH-releasing factors, are also being studied as potential additions to the therapeutic armamentarium. Insights from recent research efforts and clinical trials could potentially revolutionize the treatment of this difficult-to-treat condition.

Introduction

Lipodystrophy is an umbrella term used to describe a diverse group of metabolic disorders characterized by either complete or partial loss of fat (lipoatrophy), which may occur in conjunction with pathological accumulation of fat in other distinct regions of the body. Metabolic abnormalities, including insulin resistance, diabetes mellitus, hypertriglyceridemia, and hepatic steatosis, are frequently observed, and the severity of such complications typically correlates with the degree of fat loss. Other common complications include acanthosis nigricans, polycystic ovarian disease, hypertension, and proteinuric kidney disease[1].

Lipodystrophy can be inherited or acquired, though inherited lipodystrophic syndromes are exceedingly rare. Currently, the most prevalent type of lipodystrophy is an acquired form occurring among human immunodeficiency virus (HIV)-infected individuals treated with highly active antiretroviral therapy (HAART). Up to 40–70% of patients on HAART are reported to have HIV-associated lipodystrophy syndrome (HALS)[2,3].

Lipodystrophy is a clinical diagnosis based on findings from the physical examination. While not necessary for the diagnosis of lipodystrophy, the degree of fat loss or fat redistribution can be measured in clinical settings but more commonly is performed for

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research purposes. Fat loss and/or redistribution can be estimated with anthropometry. While measurements of skin folds, hip, waist, and limb circumferences are cost-effective and practical, and thus frequently used, they are not the most accurate methods available. Dual-energy x-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and computed tomography (CT) offer superior objectivity and precision[4]. These techniques, however, are not used in everyday clinical practice due to cost and lack of availability. Ultrasound imaging is an emerging alternate quantitative tool that is accurate as well as comparatively affordable and accessible[5].

Recent research efforts have improved our understanding of the molecular mechanisms underlying lipodystrophy and are thus providing new treatment approaches. This review aims to provide a current description of the various types of lipodystrophy and provide future perspective based on advancements in research by first describing the classification of lipodystrophic syndromes and mechanisms responsible for concomitant metabolic abnormalities, and then discussing the current treatment options and novel therapeutic approaches, with a focus on the adipokines leptin and adiponectin.

Types of Lipodystrophy

Lipodystrophies are categorized according to both the etiology (congenital or acquired) and the pattern of fat loss, which can be either generalized (affecting the whole body) or partial (affecting specific body regions). The more common types of lipodystrophy are discussed herein. For information regarding rarer types, refer to Table 1.

Generalized Lipodystrophy

Congenital Generalized Lipodystrophy—Congenital generalized lipodystrophy (CGL), or Berardinelli-Seip Syndrome, is a rare autosomal recessive disorder in which patients have a near total lack of body fat. CGL occurs more frequently in instances of parental consanguinity. Approximately 250 cases of CGL have been described in the literature. It is ubiquitous to all geographic regions[6] with the highest frequency reported in Brazil[7,8].

CGL is diagnosed soon after birth. Despite voracious appetites and accelerated linear growth rates, children with CGL demonstrate significantly reduced subcutaneous adiposity. CGL is also associated with diabetes mellitus, hypertriglyceridemia, hepatic steatosis, cirrhosis, acromegaloid features, and acanthosis nigricans. Cardiomyopathy, mild mental retardation, advanced bone age[6], cervical spine instability, and muscular weakness have also been reported[9]. Reproductive function is severely affected in women but usually unaffected in men. Females commonly present with clitoromegaly, hirsutism, amenorrhea or irregular menstrual cycles, and ovarian cysts[6]. Finally, levels of leptin and adiponectin, hormones produced by adipose tissue, are low[10].

CGL is classified as type 1 or type 2, depending on the genetic mutation and the clinical features. CGL type 1 is associated with mutation of the 1-acylglycerol-3-phosphate-O-acyltransferase 2 (*AGPAT2*) gene on chromosome 9q34. AGPAT2 catalyzes the formation of phosphatidic acid, an intracellular signaling molecule that is critical for normal adipocyte function and plays a role in triacylglycerol synthesis in adipose tissue[11]. Only metabolically important adipose tissue (e.g., subcutaneous, bone marrow, intraabdominal, intermuscular, and intrathoracic depots) and not mechanically important adipose tissue (e.g., scalp, periarticular, soles, palms, and orbital region) is markedly reduced in patients with CGL1[12]. CGL type 2 is associated with mutations of the Berardinelli-Seip Congenital Lipodystrophy 2 (*BSCL2*) gene on chromosome 11q13[13]. *BSCL2* encodes the protein seipen, a molecule

hypothesized to influence adipocyte differentiation[14] and lipid droplet formation[15]. In CGL2, patients lack both metabolically and mechanically important adipose tissue.

Additionally, several other gene mutations have recently been associated with CGL, two of which result in primary or secondary caveolin deficiency. The caveolins are critical elements of the caveolae, invaginations of the plasma membrane involved in signal transduction and cellular transport[16]. Mutations in *CAV-1*[17], a gene which encodes the protein caveolin-1, and *PTRF*, a gene encoding a caveolar-associated protein (polymerase I and transcript factor)[18] have both been associated with a lipodystrophic phenotype. In addition to lipodystrophy, patients with *PTRF* mutations also suffer from muscular dystrophy[18].

Acquired Generalized Lipodystrophy—Acquired generalized lipodystrophy (AGL), or Lawrence syndrome, shares many features with CGL, including severely reduced subcutaneous adiposity, insulin resistance or diabetes mellitus, acanthosis nigricans, hypertriglyceridemia, hepatic steatosis, hypoleptinemia, and hypoadiponectinemia[10,19]. In addition to reduced subcutaneous fat, adipose tissue is lost from the palms, soles, and intraabdominal area. AGL is usually diagnosed during childhood or adolescence and affects three times more females than males.

Approximately 25% of AGL cases are caused by panniculitis, 25% by autoimmune disease, and 50% are of idiopathic origin[19]. Autoimmune disorders that have been associated with AGL include juvenile-onset dermatomyositis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome[20].

Partial Lipodystrophy

Inherited Partial Lipodystrophy—There are many types of inherited partial lipodystrophy, most of which are extremely rare. Although a genetic locus has not yet been identified for familial partial lipodystrophy type 1 (FPLD1), numerous genetic mutations have been implicated for other types of inherited partial lipodystrophy, including the *LMNA* gene in FPLD2[21] and the *PPARγ* gene in FPLD3[22]. Mutations in *AKT2*[23,24] and *CIDEC*[25] have also been reported in a small number of patients with inherited partial lipodystrophy. Patients with partial lipodystrophy associated with mandibuloacral dysplasia have mutations in the *LMNA* gene (type A)[26] or *ZMPSTE24* gene (type B)[27]. These rare forms of inherited partial lipodystrophy are described in Table 1.

The most prevalent form of inherited partial lipodystrophy is FPLD2, also known as the Dunnigan-Variety, and has been reported in over 200 patients and with an estimated prevalence of 1 in 15 million persons. FPLD2 develops during puberty, resulting in gradual atrophy of subcutaneous fat in the extremities followed by fat loss in the anterior abdomen and chest, giving the appearance of increased muscularity. Patients also have fat accumulation in the face, neck, and intraabdominal areas, causing a Cushingoid appearance[28].

Metabolic complications, such as diabetes, hypertriglyceridemia, low HDL cholesterol levels, and high fasting serum free fatty acid concentrations, are prevalent in patients with FPLD2 and affect women more severely than men[29]. Additionally, women with FPLD2 have an elevated risk for many reproductive abnormalities including polycystic ovarian syndrome (PCOS), infertility, and gestational diabetes[30]. Cardiac and skeletal muscle abnormalities are common; muscle hypertrophy, multiple nerve entrapment syndromes, and severe myalgias have been reported in a number of patients with FPLD2[31]. In contrast to other types of lipodystrophy, patients with FPLD2 have only modestly reduced leptin and adiponectin levels[10], perhaps because lipoatrophy is less extensive in this type.

FPLD2 is inherited in an autosomal dominant manner and is caused by mutations in the *LMNA* gene located on chromosome 1q21-22[21]. The *LMNA* gene encodes the nuclear envelope protein lamins A and C, which are architectural proteins that mediate the integrity and assembly of the nucleus. Lamin A has also been associated with adipocyte differentiation, insulin signaling, and PPARγ signaling[32].

Acquired Partial Lipodystrophy—Approximately 250 cases of acquired partial lipodystrophy (APL), or Barraquer-Simons syndrome, have been described. The majority of patients with APL are of European descent. The condition affects 4 to 8 times as many females as males and typically has a childhood or adolescent onset. A unique, cephalocaudal progression of fat loss is observed with APL. Fat loss begins in the face and subsequently spreads to the neck, upper extremities, thorax, and abdomen. The lower extremities, lower abdomen, and gluteal region do not exhibit lipoatrophy but rather accumulate excess adipose tissue. With the exception of hepatomegaly, metabolic complications are rarely seen in association with APL[33].

Infections (including measles) and autoimmune diseases (including systemic lupus erythmatosus and dermatomyositis) have been linked to the development of APL[33]. There is also a high association between APL and membranoproliferative glomerulonephritis (MPGN). Patients with both APL and MPGN tend to have low serum levels of C3 and exhibit polyclonal immunoglobulin C3 nephritic factor in the serum. It has been hypothesized that C3 nephritic factor induces the lysis of adipocytes that express factor D (a serine protease enzyme also referred to as adipsin), and differential expression of factor D by various tissues in the body dictates the cephalocaudal pattern of fat loss characteristic of APL[33,34]. However, APL may also be caused by mutations in the *LMNB2* gene, as a recent report found a rare mutation in this gene to be more frequent in patients with APL than control subjects[35].

HAART-associated lipodystrophy syndrome—Although HAART has greatly reduced mortality rates in patients with HIV/AIDS, HAART-associated lipodystrophy syndrome (HALS) and its associated metabolic complications have become a significant concern. HALS, which is considered to be primarily a side-effect of HAART, is distinct from HIV-related wasting in that HIV-related wasting is caused by either HIV-infection itself or opportunistic infections and cancers. Additionally, HIV-related wasting involves not only adipose tissue but also other tissues, such as muscle tissue. The pattern of fat loss is also different. HALS patients may experience lipoatrophy, lipohypertrophy, or a combination of both[36]. Wasting of the face, arms, legs, and buttocks is common[36] and can occur along with fat accumulation in the abdomen and dorsocervical area (Figure 1), the latter of which is less common[37]. Risk factors for HALS include older age, greater severity of HIV-infection, increased viral load, low CD4 count, and coinfection with hepatitis C[38,39]. HALS increases the risk for insulin resistance, diabetes mellitus, dyslipidemia, and cardiovascular disease[40].

Although antiretroviral regimens used to treat HALS have been implicated in the etiology of the condition, mechanisms whereby antiretroviral therapies contribute to HALS are incompletely understood. Nucleoside reverse transcriptase inhibitors (NRTIs) may contribute to lipodystrophy via several mechanisms, including mitochondrial toxicity[41], which is characterized by abnormal changes in mitochondrial proliferation, morphology, and mitochondrial DNA (mtDNA) content[41,42]. Protease inhibitors (PIs) have been shown to disrupt adipocyte differentiation via the down-regulation of several adipogenic transcription factors (including PPARγ and C/EBP-α)[43]. Additional metabolic disturbances that occur in HIV-infected individuals taking PIs include the generation of reactive oxygen species (ROS)[44,45], increased macrophage recruitment[44], inhibition of glucose-transport-4

(GLUT-4)-mediated glucose transport, impairment of insulin signaling, impairment of leptin and/or adiponectin secretion, and enhanced production of cytokines, such as interleukin-6 (IL-6) and TNF-α[2].

Compared to PIs and NRTIs, there is less direct evidence that non-nucleoside reverse transcriptase inhibitors (NNRTIs) cause lipodystrophy and other metabolic changes. Several trials have reported that lipodystrophy is rare among HIV-infected individuals taking NNRTIs, and the risk of developing lipodystrophy and other metabolic complications may be more dependent on drugs used in combination with NNRTIs[46,47]. However, there is some recent conflicting evidence which suggests that the NNRTI, efavirenz, when combined with either stavudine or zidovudine, may result in greater fat loss than lopinavir/r combined with either NRTI[48]. Lipoatrophy was lowest with the NRTI-sparing regimen of lopinavir/r and efavirenz, but this combination resulted in higher cholesterol levels[48]. Additionally, *in vitro* data has shown that efavirenz may prevent the accumulation of lipids in preadipocytes[49], reduce lipid content in mature adipocytes[49], inhibit SREBP-1c expression[49], inhibit mitochondrial activity[50], increase the production of reactive oxygen species[50], and increase intracellular lipids in hepatic cells[50]. Further research is needed to determine if and how specific antiretroviral regimens contribute to lipodystrophy and the associated metabolic abnormalities.

Genetic background may predispose patients on HAART to develop pathological distribution of fat and other metabolic abnormalities. A single nucleotide polymorphism in the resistin gene has been associated with elevated risk for developing high lipid levels, insulin resistance, and limb fat loss when on HAART[51]. Other studies have implicated the tumor necrosis factor-α-238 (TNF-α-238) promotor region gene polymorphism in a more rapid onset of HALS[52], but this needs to be confirmed by further studies.

It has also been suggested that viral proteins and mechanisms relating to HIV-1 infection could directly influence fat distribution. In *in vitro* experiments, HIV-1 viral protein R has been found to act as a corepressor of PPARγ-mediated gene transcription, which may inhibit adipocyte differentiation *in vivo*[53].

As described above, drug-induced lipoatrophy involves not only impairments in adipocyte differentiation but also increased lipolysis[54]. The combination of lipolysis and deficient subcutaneous fat storage can lead to elevated serum free fatty acids (FFAs), accumulation of FFAs intracellularly, and ectopic deposition of FFAs in the visceral adipose tissue, skeletal muscle, liver, and pancreas, an environment which has been described as lipotoxic[37]. This lipotoxic environment exacerbates metabolic disturbances, particularly dyslipidemia and insulin resistance[37].

Furthermore, HIV-1 infection per se is thought to lead to a pro-inflammatory environment, which could contribute to lipodystrophy and related metabolic disturbances[37]. HALS has been associated with increased expression of pro-inflammatory cytokines, including TNF-α, monocyte chemoattractant protein-1 (MCP-1), and macrophage markers, including CD68, integrin αM, epidermal growth factor-like module containing mucin-like hormone receptor-like (EMR) 1, and a disintegrin and metalloproteinase domain (ADAM) 8, in adipose tissue[55]. Biopsies of subcutaneous adipose tissue have revealed increased TNF-α secretion, increased macrophages, and increased mitochondrial expression of interleukin-1β in patients with HALS compared to HIV-infected patients without lipoatrophy[56,57]. In addition, HALS is associated with increased systemic cytokine activity, including elevated levels of IL-6 and soluble TNF receptors I and II[57]. Inflammation is thought to contribute to insulin resistance via impaired adipocyte metabolism and lipolysis[58]. In addition, TNF-α mediates insulin resistance by reducing insulin receptor kinase activity, down-regulating insulin receptor

substrate (IRS)-1 and GLUT-4 phosphorylation and activity, and inducing lipolysis[2]. Chronic elevation of IL-6 promotes hepatic gluconeogenesis and induces hepatic triglyceride secretion, possibly through impairing insulin signaling via IRS-1 and phosphatidylinositol 3-kinase[2]. In mice, MCP-1 has been shown to down-regulate GLUT-4, beta-adrenergic receptors, and PPARγ expression, resulting in insulin resistance, hepatic steatosis, and increased adiposity[59].

Finally, lower levels of adipocyte-secreted hormones, such as leptin and adiponectin, may contribute to the metabolic abnormalities associated with HALS and is discussed further below[3,60].

Current Treatment of Lipodystrophy

Given the heterogeneous nature of lipodystrophy, it is not surprising that the treatment options are diverse and have variable efficacy depending on the type of lipodystrophy and individual presentation of the disorder. The treatment of lipodystrophy aims to ameliorate both the metabolic disturbances and pathological changes in fat distribution. An overview of current treatment strategies is provided herein, with a focus on the treatment of HALS, the most prevalent form of lipodystrophy.

General Approach: Lifestyle Modification

Diet and Nutritional Therapy: Dietary guidelines for lipodystrophy have not been established. However, given their elevated risk for cardiovascular disease and diabetes, patients with lipodystrophy should adhere to the guidelines of the American Heart Association, which recommends that less than 30% of daily calories come from fat[61], and the America Diabetes Association, which recommends that carbohydrate and monounsaturated fat should provide 60–70% of daily calories[62].

Although limited data has been published regarding the Mediterranean diet and other types of lipodystrophy, recent evidence suggests that the Mediterranean diet, which consists of plentiful intake of vegetables, fruits, whole grain cereals, and olive oil; moderate intake of fish, dairy products, and alcohol; and low intakes of red meat, saturated fats, and sweets, may benefit individuals with HALS[63,64]. A cross-sectional study has shown that greater adherence to a Mediterranean diet decreases cardiovascular risk factors in patients with HALS, specifically, by improving insulin resistance and raising HDL cholesterol[64]. Supplementation with fiber[65,66], fish oil containing high doses of omega-3 fatty acids[65,67], and vitamin E[68] may also benefit patients with HALS. There is some evidence that serum triglyceride levels and insulin resistance can be improved by substituting long-chain fatty acids with medium-chain or n-3 polyunsaturated fatty acids[69].

Exercise: Although very few studies have examined the effects of exercise on congenital lipodystrophies, exercise has been shown to benefit patients with HALS. Small clinical trials suggest that resistance training may be more important than aerobic exercise. Aerobic exercise has not been consistently shown to improve metabolic parameters or anthropometric features[65,70,71], although a combination of aerobic and resistance training has been shown to improve cholesterol levels, triglyceride levels, and body composition[72]. Resistance training alone increases total lean mass and decreases total, truncal, and limb fat as well as reduces triglyceride levels, increases HDL cholesterol levels, and improves peripheral insulin sensitivity[71,73]. Overall, increased physical activity of any kind is likely beneficial in preventing and improving lipodystrophy[74,75] and augments pharmacologic therapy[76]. However, in low-weight patients exhibiting primarily lipoatrophy, exercise may exacerbate fat loss and is thus not always recommended[77].

Management of Diabetes

Metformin: Metformin is an FDA-approved drug for use in patients with Type II diabetes but not lipodystrophy; however, many patients with lipodystrophy have concurrent diabetes and are thus on this medication. The data for metformin, which improves insulin sensitivity by decreasing hepatic gluconeogenesis and enhancing peripheral glucose utilization, are mainly from studies on patients with HALS. An initial small, randomized controlled trial showed that treatment with metformin significantly reduced insulin resistance, weight, and diastolic blood pressure and also found a trend towards decreased visceral abdominal fat[78]. These results were sustained during an open-label extension of the trial[79]. A subsequent trial comparing metformin and rosiglitazone for the treatment of HALS found that metformin improves insulin sensitivity to the same degree as rosiglitazone but also improves visceral fat accumulation, fasting lipid profile, and endothelial function, effects not seen in the rosiglitazone arm[80]. Metformin is safe and generally well-tolerated; although gastrointestinal symptoms are common, they are mild and usually transient. However, not all subsequent studies have shown consistent improvements in insulin resistance, lipid profile, or anthropometric features[81,82]. Furthermore, metformin may worsen peripheral fat loss, and should therefore be used with caution in lipoatrophic patients[83].

Thiazolidinediones (TZDs): TZDs, including pioglitazone and rosiglitazone, are FDA-approved for use in patients with Type II diabetes but not specifically for lipodystrophy. They bind and activate the nuclear transcription factor PPARγ, which regulates adipocyte differentiation, maintenance, and survival and promotes production of adiponectin[84]. In case reports of familial partial lipodystrophy, treatment with TZDs has been more effective than metformin. Pioglitazone improves insulin resistance, hyperinsulinemia, and hypertriglyceridemia as well as reverses features of polycystic ovarian syndrome and non-alcoholic steatohepatitis (NASH), which were proven to be resistant to treatment with metformin alone[85–88]. Rosiglitazone also improves insulin sensitivity and hyperglycemia[89,90] but may worsen lipid profile in these patients[91]. Data regarding TZD therapy and the restoration of adipose tissue in lipoatrophic areas has been conflicting; it appears as though TZDs do not improve lipoatrophy in patients with FPLD2, but pioglitazone may be efficacious in patients with HALS[92,93].

Pioglitazone shows more promise than rosiglitazone for the treatment of HALS[93]. Overall, trials show that rosiglitazone improves insulin sensitivity and possibly lipoatrophy[94,95] but worsens the lipid profile, including increased total cholesterol, LDL cholesterol, and triglyceride levels[96–99]. Rosiglitazone may promote a more atherogenic lipid profile[100] and has recently been proposed, but not proven beyond any doubt, to increase cardiovascular risk in diabetics. Furthermore, treatment with rosiglitazone may reduce the bioavailability of some antiretroviral medications, including nevirapine[101].

Due to the rather inconsistent results with rosiglitazone, the attention has turned to pioglitazone. We have reported that treatment with pioglitazone for 12 months improves blood pressure, lipid profile, and insulin resistance in patients with HALS[102]. In a recent randomized, placebo-controlled trial, pioglitazone improved limb fat atrophy, although the clinical benefits were not perceived by the patients, and HDL levels also increased[103]. Additional trials with pioglitazone are needed.

Treatment with pioglitazone over rosiglitazone has been suggested to be preferable, especially in patients at higher cardiovascular risk[104]. TZDs, and particularly rosiglitazone, have recently been linked to edema, cardiovascular disease[104,105], and bone loss[106], side effects that may limit their therapeutic value. Specific PPARγ modulators under development, such as INT131, may have efficacy comparable to TZDs but much better side effect profiles and are greatly anticipated[107].

Management of Dyslipidemia—The goals for the treatment of dyslipidemia in lipodystrophy should follow established guidelines for those with coronary artery disease, including total cholesterol less than 200 mg/dL, HDL cholesterol greater than or equal to 60 mg/dL, LDL cholesterol less than 70 mg/dL, and triglycerides less than 150 mg/dL. Lifestyle modification is a necessary first step. In high-risk HALS patients, adjusting the antiretroviral regimen prior to starting lipid-lowering medications should be considered[108].

Statins: Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and are the first-line agents for hypercholesterolemia in the general population. They also have anti-inflammatory and antithrombotic properties and enhance endothelial function to reduce cardiovascular morbidity and mortality. Case reports of patients with generalized lipodystrophy suggest that statins may be beneficial, but perhaps insufficient if used alone, to treat hypertriglyceridemia[19]. Most research on statins and lipodystrophy has focused on HALS. Trials have shown that pravastatin and rosuvastatin decrease total and LDL cholesterol levels[109,110] and may increase subcutaneous fat in the extremities[111]. Furthermore, statins may improve endothelial function[112,113]. This is especially important in HALS patients, especially the patients on PIs, since there is a higher rate of endothelial dysfunction compared to the non-HIV-infected population[114,115]. However, statins interact with antiretroviral medications. Protease inhibitors can increase concentrations of simvastatin and atorvastatin to 30 fold and 3 fold respectively and decrease concentrations of pravastatin by half[116,117]. The concentrations of HAART medications have not been noted to be significantly altered by statins[116,118]. It is important to tailor statin therapy to the HAART regimen.

Fibrates: When hypertriglyceridemia is the primary lipid abnormality, which is common among patients with HALS, especially those on PIs, fibrates are an excellent option and have not been found to interact with HAART medications[119]. Fenofibrate may be more efficacious than gemfibrozil[119–121]; however, head to head comparisons in HALS patients are lacking. Both are well-tolerated, although rhabdomyolysis and renal failure have been reported with fibrate use[122].

Niacin: Extended-release niacin is also effective for hypertriglyceridemia; however, it may exacerbate insulin resistance in HIV-infected patients who are already prone to insulin resistance[123,124]. Acipimox, a niacin analog, may be a better option as it has been found to decrease triglyceride levels and improve insulin sensitivity in HALS[125].

Ezetimibe: Ezetimibe inhibits cholesterol absorption and may be an option for patients who are intolerant to statins. In HIV-infected patients, ezetimibe has been found to be as effective as a statin in reducing LDL cholesterol levels but does not improve endothelial function[126]. Recent trials failing to demonstrate improved cardiovascular outcomes in non-lipodystrophic patients have limited enthusiasm for this class of medications.

Management of HALS

Modification of HAART: With initiation of HAART, patients should be carefully evaluated for cardiovascular risk factors based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. If the patient is at high risk, the drug with the least metabolic complications should be selected. Specifically, PIs should be avoided as they have been associated with myocardial infarction[127]. In patients developing dyslipidemia, switching from a PI to nevirapine or abacavir may improve total cholesterol and triglyceride levels and may be preferable to starting a lipid-lowering drug[127].

Medications can also be changed if lipodystrophy develops, but the reversal of these side effects is usually slow. For lipohypertrophy, no specific antiretroviral drug has been implicated, whereas for lipoatrophy, a regimen with the thymidine analogs stavudine and zidovudine should be avoided[128]. NRTIs may inhibit mitochondrial γ-DNA polymerase as well as cause other mitochondrial defects[42], thereby contributing to lipoatrophy[2,42]. Co-administration of uridine with pyrimidines, including zalcitabine, stavudine, zidovudine, and lamivudine, may improve lipoatrophy by reversing mitochondrial toxicity and lactic acidosis[2,129]. However, the evidence is conflicting, as a subsequent randomized study found that although uridine supplementation improved mitochondrial DNA levels, there was no effect on limb fat loss[130]. Uridine supplementation also negatively affected levels of inflammatory markers and fat mitochondrial DNA[130].

Growth Hormone (GH) and Growth Hormone-releasing hormone (GHRH) analogs: Although neither GH nor GHRH analogs are FDA-approved for HALS at this time, GH replacement is a promising treatment for this population, as individuals with HALS tend to be GH-deficient[131]. Initial trials used high doses of human GH, up to 6 mg per day, and showed significant improvements in truncal obesity (up to 40% reduction) and mild improvements in limb atrophy as well as improvements in the lipid profile[132–134]. However, side effects included peripheral edema, myalgia, arthalgia, dysthesia, glucose intolerance, and diabetes, most of which were transient and reversible[132,134–137]. There is also a concern for increased risk of cancer with long-term GH therapy[136], especially since the benefits of GH therapy are generally not sustained once GH therapy is discontinued[136]. However, sustained improvements in facial lipoatrophy for up to 6 months after therapy discontinuation have been reported[138].

Given these side effects, lower doses of human GH were studied. Although higher doses may result in greater reduction of visceral adipose tissue[136], lower doses have been found to be relatively efficacious in reducing visceral fat and improving facial lipoatrophy as well as the lipid profile[134,138,139]. With lower doses, there does appear to be less side effects but glucose intolerance remains a concern[134–136].

Growth hormone-releasing factor is also efficacious and may avoid the side effect of glucose intolerance. Geref (GHRH 1-29), a GHRH analog, has been shown to increase lean body mass, decrease truncal fat, and decrease abdominal visceral fat without affecting glycemic indices[140]. Similarly, tesamorelin (TH9507), another GHRH analog, has been shown to improve anthropometric features as well as triglyceride levels and cholesterol to HDL ratio, again without affecting glycemic indices[140–142]. The overall number of patients with adverse events did not differ between treatment and placebo groups[142]. A subsequent study of longer duration confirmed improvements in anthropometric features, and decreased visceral adipose tissue in particular[143]. However, like GH, GHRH does not seem to confer any metabolic or anthropometric benefits upon discontinuation, although sustained improvements in body image have been reported[143]. Trials involving GH and GH-releasing analogs are ongoing and will further elucidate the potential of GH-based therapies.

Management of Cosmetic Appearance—Given the psychosocial implications of lipodystrophy, surgical options are attractive. Facial fillers can be used for facial lipoatrophy and have been shown to improve quality of life as well as depression and anxiety symptoms[144]. For the dorsocervical fat pad or other areas of subcutaneous fat accumulation, liposuction is successful but recurrence is a potential problem[144].

Adipokines in Lipodystrophy

Alterations in fat distribution affect levels of adipokines, including adiponectin and leptin. These hormones appear to play a fundamental role in the metabolic abnormalities seen in lipodystrophy[145], and replacement of adipokines may have considerable therapeutic value for patients deficient in adipokines, primarily those with generalized lipodystrophies and a subset of patients with HALS[3,10].

Adiponectin—Adiponectin, a 244-amino acid long protein secreted by adipose tissue, is an endogenous insulin sensitizer. Adiponectin reduces gluconeogenesis in the liver, primarily via the stimulation of adiponectin receptor 2 (AdipoR2) and activation of AMPK phosphorylation. Adiponectin also increases fatty acid oxidation in muscle via adiponectin receptor 1 (AdipoR1). Additionally, AdipoR1 stimulation in the hypothalamus may exert effects on insulin and leptin signaling, which promote increased insulin sensitivity and reduced food intake[146]. Adiponectin levels are also low in a subset of patients with lipodystrophy, including many patients with CGL1 and HALS[10,147–149]. Hypoadiponectinemia is associated with insulin resistance, hypertriglyceridemia, and fat redistribution in HIV-infected patients on antiretroviral medications[60,96,150].

In mouse studies, adiponectin administration improves insulin sensitivity, dyslipidemia, and weight[151]. Adiponectin replacement has also been shown to ameliorate ritonavir-induced hypertriglyceridemia and elevated FFA levels in mice[152]. Although adiponectin or leptin[153,154] alone improves insulin resistance in mouse models of lipodystrophy, the combined administration of both fully normalizes insulin sensitivity[155]. Although no synthetic form of adiponectin is available for treatment in humans, animal studies[151,152,155] as well as medications that increase endogenous levels of adiponectin (e.g., pioglitazone or INT-131)[102] have highlighted this adipokine's therapeutic potential. Further research is needed to elucidate the efficacy of these medications in humans and determine how long the benefits of treatment are sustained both during and upon treatment discontinuation. Nevertheless, an adiponectin analog or adiponectin receptor modulator would likely be a valuable addition to our therapeutic armamentarium for lipodystrophy.

Leptin—A significant subset of patients with lipodystrophy exhibit low leptin levels, including most patients with generalized lipodystrophy and up to 40–80% of patients with HALS[3,10]. Leptin is primarily produced by white adipose tissue and correlates positively with body fat, reflecting the amount of energy stores[156]. Via a complex neural circuit, leptin promotes satiety, leading to decreased food intake[157]. Leptin also acts peripherally to decrease gluconeogenesis in the liver and adipose tissue and to increase glucose utilization in skeletal muscle by activating signaling pathways which overlap with, but are not identical to, those of insulin[158]. Finally, leptin may protect peripheral tissues from lipotoxicity by stimulating fatty acid oxidation, as it has been shown to reduce intrahepatic and intramyocellular lipid accumulation[159].

Animal research suggests that leptin plays an integral role in certain forms lipodystrophy. Low leptin levels are a common finding in mouse models of generalized lipodystrophy, including *Pparg* knockout mice[160], *Cav1* null mice[161], *Agpat2* null mice[162], aP2-DT-A mice[163], A-ZIP/F-1 (AZIP) mice[164], and aP2-nSREBP-1c mice[153], and leptin administration favorably affects the metabolic profile in several of these mouse models[153,154,165,166]. Specifically, systemic leptin infusion was associated with improvements in insulin resistance and a reduction in hepatic steatosis in aP2-nSREBP-1c transgenic mice, which express a dominantly active form of sterol response element binding protein 1c (SREBP1c) and exhibit markedly reduced white adipose tissue stores as well as metabolic abnormalities[153]. Furthermore, chronic restriction of food intake alone did not account for all the metabolic

benefits observed, suggesting that there are other mechanisms whereby leptin improves the metabolic profile of lipodystrophic mice[153]. Similarly, low-dose intracerebroventricular leptin infusion ameliorates insulin resistance and hepatic steatosis in aP2-nSREBP-1c mice, an effect mediated by repression of stearoyl-CoA desaturase-1 (SCD-1) activity in lipodystrophic murine livers[154]. Dose-response experiments showed that peripheral subcutaneous leptin administration improved both hyperglycemia and hyperinsulinemia at a lower dose than was required to improve hepatic steatosis[154]. This lower dose was found to normalize phosphorylation of insulin-stimulated insulin receptor and insulin receptor substrate 2 (IRS-2) as well as activation of IRS-2-associated PI3K and Akt in the liver[154]. Leptin has also been shown to improve metabolic parameters in lipoatrophic A-ZIP/F-1 mice, which express a protein that inactivates (via heterodimerization) several transcription factors belonging to the basic region-leucine zipper (B-ZIP) family, in a study that crossed these mice with “skinny” mice which overexpress leptin[165]. Furthermore, surgical transplantation of normal adipose tissue in A-ZIP/F-1 mice improves insulin resistance and other metabolic factors[166], whereas adipose tissue from leptin-deficient *ob/ob* mice does not[167]. Similarly, PPARγ-deficient heterozygous mice (PPARγ$^{+/-}$) treated with leptin exhibit partial improvements in insulin resistance; when these mice are co-administered physiological doses of leptin and adiponectin, insulin resistance is completely normalized[155].

In humans, recombinant human leptin, metreleptin, has been extensively studied in the context of open-label clinical trials[168]. Pharmacokinetic and pharmacodynamic studies of metreleptin have allowed us to select appropriate doses to be administered to humans[169–171]. Physiological replacement doses of leptin (0.04–0.08 mg/kg·d) have provided tangible benefits to patients with severe leptin deficiency from congenital and non-HIV-related acquired generalized lipodystrophy. These include improvements in insulin sensitivity, fasting glucose, glucose tolerance, hemoglobin A1c, hypertriglyceridemia, and transaminitis, thus lessening the need for insulin or oral hypoglycemic agents[172–179]. Leptin replacement also favorably changes body composition (weight loss with decreased fat and lean masses)[178,180], an effect which is partially due to increased satiety[181]. Furthermore, patients with partial lipodystrophy, including syndromes associated with *LMNA* and *PPARγ* gene mutations, also gain metabolic benefits with leptin treatment[173,182,183]. Although all studies in subjects with congenital lipodystrophy have been non-randomized, open-label trials, metreleptin is currently available for difficult-to-treat patients with lipodystrophy through an FDA-approved expanded access program[168,177].

Metreleptin may provide benefits beyond improvements in metabolic parameters. Metreleptin reduces proteinuria and ameliorates glomerular injury associated with generalized lipodystrophy[184] and normalizes menstrual abnormalities, estradiol levels, and the leutinizing hormone response to gonadotropin-releasing hormone in young women with lipodystrophy and polycystic ovaries[178,185]. Leptin replacement may also have beneficial immunomodulatory effects in hypoleptinemic patients with severe lipodystrophy[186]. Although open-label trials have demonstrated benefits of metreleptin in these forms of lipodystrophy, larger, randomized, placebo-controlled trials are needed to conclusively prove its efficacy as well as safety, especially since there have been several side effects noted, including proteinuric nephropathy[184] and T-cell lymphomas[177,187] in a small number of subjects. Nevertheless, it appears as though the benefits of leptin replacement are sustained for as long as treatment continues (i.e., refractory changes in metabolic parameters and/or body composition have been largely attributed to treatment non-adherence) as patients followed for up to 8 years of continuous metreleptin treatment have continued to benefit from therapy[173]. To date, there have been only a small number of patients with CGL2 in which metreleptin treatment ceases to be efficacious, potentially from the development of leptin resistance[188].

In a randomized, placebo-controlled, double-blinded, crossover study evaluating the use of metreleptin in the most prevalent form of lipodystrophy, HALS, administration of physiological replacement doses of metreleptin to hypoleptinemic men with HALS was found to improve fasting insulin levels, insulin resistance, HDL cholesterol, and truncal obesity[189]. An independent trial of longer duration confirmed these results[190]. The improvements in visceral adiposity and lipid levels exhibited by HALS patients treated with metreleptin[189,190] were comparable to improvements reported with other therapeutics, including metformin and TZDs[78,79,97,125,132–134]. Furthermore, the improvements in insulin resistance reported in patients with HALS treated with metreleptin[189,190] provide an advantage over GH, which has been associated with glucose intolerance[135,136]. In both trials, metreleptin was well-tolerated and no side effects were observed with treatment up to 36 months[174]. It remains to be seen the extent to which patients with comparatively higher endogenous leptin levels would benefit from metreleptin therapy, but it is expected that the improvements would be less striking than those observed in patients with severe leptin deficiency[191].

Leptin's beneficial effects are mediated independently of the GH-IGF-1 system[192]. Because the GH-IGF-1 system may also play a role in HALS, it is possible that combination therapy with leptin and GH or GHRH analogs could have additive metabolic benefits without adversely affecting glucose intolerance[191], but this remains to be seen. Even more importantly, it is still not known whether the co-administration of metreleptin and adiponectin have synergistic effects on the normalization of insulin resistance in humans with lipodystrophy, as has been reported in mice[155]. Pilot studies investigating the combined administration of pioglitazone and metreleptin are underway, and preliminary data indicate that this combination further improves glycemic control (CS Mantzoros, unpublished data).

Conclusions

Recent advancements in the treatment of lipodystrophy are timely. Not only are we finding viable means to treat a severe disorder, but we are also elucidating the role of adipose tissue and gaining insight in areas of growing concern, such as insulin signaling and fatty acid metabolism, which will hopefully provide the basis for rational drug design and use. More work is needed to further explore ways to ameliorate the degree of fat loss as well as pathological fat accumulation in patients with lipodystrophy and to prevent and treat the concomitant metabolic disturbances as well as the associated long-term morbidity and mortality. These objectives are particularly relevant for the HIV-positive population. With the advent of HAART, we have observed an increase in the life expectancy[193] for HIV-positive individuals due to the efficacy of the current treatment in suppressing viral load. However, the success of medications for HIV is accompanied by adverse drug side effects and toxicity. While the ultimate goal of this field will be to prevent (via microbicides, vaccines, and/or antiviral prophylaxis) or even cure HIV-infection, more tangible future aims of this field will most likely be to manage adverse effects (including lipodystrophy and insulin resistance) and to better understand the impact of long-term use of HIV medications, given the growing number of elderly HIV-positive patients[194]. Furthermore, the increasing number of patients with HIV, due to their longer survival while on new treatments, would be expected to lead to increasing morbidity and mortality in the future. This, in turn, creates an urgent unmet need and creates pressure for the pharmaceutical industry to develop newer and safer medications that would hopefully be devoid of side effects such as lipodystrophy.

Review Criteria

All journal articles or abstracts referenced in this review were obtained using PubMed or Web of Science. The search terms, used in different combinations, were "lipodystrophy",

"congenital generalized lipodystrophy, "Berardinelli-Seip syndrome", "acquired generalized lipodystrophy", "Lawrence syndrome", "Dunnigan-Variety lipodystrophy", "acquired partial lipodystrophy", "Barraquer-Simons syndrome", "HAART-associated lipodystrophy syndrome", "HALS", "leptin", "adiponectin", and "adipokines". Reference lists from journal articles found using this search criteria as well as citing papers as reported by Web of Science were also used to obtain other relevant journal articles. All referenced journal articles were published in English.

Key Points

1. Lipodystrophy is an umbrella term used to describe a diverse group of metabolic disorders characterized by either complete or partial loss of fat (lipoatrophy), which may occur in conjunction with pathological accumulation of fat in other distinct regions of the body.
2. Patients with lipodystrophy suffer from numerous metabolic complications, indicating the importance of adipose tissue as an active endocrine organ. Not only does the total amount but also the appropriate distribution of fat deposits contribute to the metabolic state
3. Lipodystrophy can be inherited or acquired, though inherited lipodystrophic syndromes are exceedingly rare. Currently, the most prevalent type of lipodystrophy is an acquired form occurring among human immunodeficiency virus (HIV)-infected individuals treated with highly active antiretroviral therapy (HAART).
4. Circulating levels of hormones secreted by adipose tissue, such as leptin and adiponectin, are greatly reduced in distinct subsets of patients with lipodystrophy, rationalizing the use of such hormones or agents that increase their circulating levels, such as peroxisome proliferators-activated receptor gamma (PPARγ) agonists, in a subset of patients with lipodystrophy.

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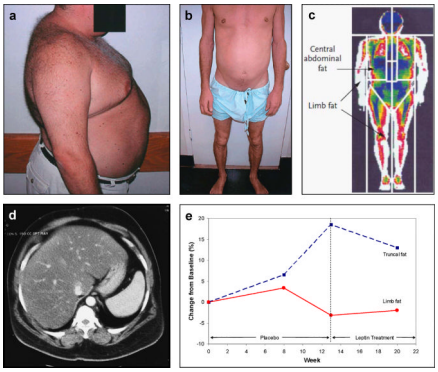

Figure 1. Fat Redistribution in HIV-infected patients on HAART

A. Buffalo hump and increased abdominal adiposity in a patient with HALS. Courtesy of A.W. Karchmer, C.S. Mantzoros, and S. Tsiodras. Image from Leow *et al*[199], *Copyright © 2003, The Endocrine Society*.

B. Loss of extremity fat and increased abdominal girth in a patient with HALS. Courtesy of A.W. Karchmer, C.S. Mantzoros, and S. Tsiodras. Image from Leow *et al*,[199] *Copyright © 2003, The Endocrine Society*.

C. Dual-energy x-ray absorptiometry (DEXA) scan indicating regions of interest for body composition analyses. Image from Grinspoon and Carr[200], *Copyright © 2005 Massachusetts Medical Society. All rights reserved.*

D. Abdominal CT scan showing hepatomegaly in a patient with HALS. Courtesy of CS Mantzoros, Beth Israel Deaconess Medical Center (Boston, MA). Image from Leow *et al*[199], *Copyright © 2003, The Endocrine Society*.

E. Change in truncal and limb fat over time in a patient with HALS. Truncal fat increases and limb fat decreases as a result of HAART. Leptin treatment commencing at week 13 begins to reverse pathological changes in fat distribution. Courtesy of C.S. Mantzoros.

Table 1

Rare Forms of Lipodystrophy.

	Type	Clinical Features	Metabolic Complications	Pathogenic Basis	References
Inherited	Kobberling-type lipodystrophy or Familial partial lipodystrophy type 1 (FPLD1)	Lack of extremity and gluteal subcutaneous adipose tissue, normal or increased adiposity of the face and neck, truncal obesity, and prominent “ledge” of fat distinguishing points of lipoatrophy and lipohypertrophy	Hypertension, insulin resistance, and severe hypertriglyceridemia	Genetic defect currently unknown; classified as inherited on the basis of family history	195
	Familial partial lipodystrophy type 3 (FPLD3)	Lipoatrophy of the extremities and increased truncal fat	Diabetes mellitus, hypertriglyceridemia, hepatic steatosis, and pancreatitis	Mutations in the *PPARγ* gene, which is a receptor involved in adipogenesis	22,84,196,197
	Familial partial lipodystrophy due to *AKT2* mutation	Lipoatrophy affecting primarily the extremities	Severe insulin resistance	Mutations in *AKT2*, which is a serine/threonine protein kinase involved in glucose homeostasis, insulin signaling, and adipocyte differentiation	23,24
	Mandiculoacral dysplasia (MAD)-associated partial lipodystrophy due to *LMNA* (type A) or *ZMPSTE24* (type B) mutation	Subcutaneous lipoatrophy affecting primarily the extremities with preserved neck and trunk fat (type A) or subcutaneous lipoatrophy affecting the face and trunk in addition to the extremities (type B)	Hypertriglyceridemia, insulin resistance, impaired glucose tolerance, musculoskeletal abnormalities, progeroid features	MAD is an autosomal recessive disorder caused by homozygous missense mutations in either the *LMNA* gene or heterozygous mutations in the *ZMPSTE24* gene	26,27
	Partial lipodystrophy due to *CAV1* mutation (only has been identified in 2 patients to date)	Lipoatrophy of the face and upper body	Diabetes, hypertriglyceridemia, recurrent pancreatitis, micrognathia, and congenital cataracts	Frameshift mutations involving *CAV1*	198
	Partial lipodystrophy due to *CIDEC* mutation (only has been identified in 1 patient to date)	Lipodystrophy of the lower limb and femorogluteal region	Insulin resistance, fatty liver, dislipidemia, acanthosis nigricans, diabetes	Homozygous nonsense mutation in the *CIDEC* gene, resulting in premature truncation of cell death-inducing DFFA-like effector C, a protein involved in unilocular lipid droplet formation	25
Acquired	Localized lipodystrophies	Loss of subcutaneous fat from a small area of the body	Metabolic abnormalities are uncommon	May be due to the use of injectable drugs (such as insulin), repeated pressure, or panniculitis.	28