Novel Forms of Lipodystrophy

Why should we care?

Lipodystrophies are a heterogeneous group of conditions in which individuals never develop or progressively lose adipose tissue in parts or all of their bodies (1,2) (Table 1). In this commentary, we will make the case that *1*) defining lipodystrophy is a work in progress; *2*) not all forms of lipodystrophy are very rare; *3*) lipodystrophy and obesity can occur simultaneously and their metabolic consequences are similar and possibly synergistic; *4*) leptin treatment can have impressive therapeutic effects; and *5*) these conditions provide useful paradigms to explore the role of the adipose tissue on metabolic homeostasis and to investigate pathways leading from distinct genetic mutations to very different clinical phenotypes.

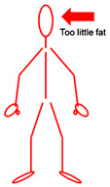
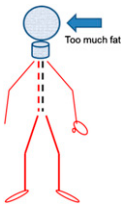
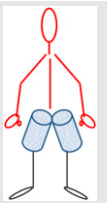
What is lipodystrophy? A recent consensus statement by the American Association of Clinical Endocrinologists acknowledges the difficulty in determining quantitative criteria and concludes that "lipodystrophy is a condition characterized by regional or total loss or absence of subcutaneous fat. This can occur either in the presence or absence of metabolic abnormalities, and with diverse clinical presentations. While generalized forms of lipodystrophy are often diagnosed during childhood or adolescence, some forms of lipodystrophy, particularly familial partial lipodystrophy, may bear some resemblance to common metabolic disorders managed by adult endocrinologists" (3). There are no specific cutoff levels for percent body fat or leptin concentrations, and it often requires time and long-term follow-up to confirm the diagnosis.

Much progress has been made in identifying the genetic etiologies of many lipodystrophy forms (1). How missing or abnormal gene products prevent adipocyte development or cause disappearance of adipose tissue in distinct regions of the human body, however, remains mostly unknown. An excellent example is familial partial lipodystrophy or Dunnigan syndrome, in which numerous mutations of the LMNA gene have been found. LMNA is expressed in a tissue-dependent manner and encodes lamin A/C, a protein, which is important for the integrity and function of the nuclear envelope. It is entirely unclear why some white adipocytes are affected and others are not. Dunnigan syndrome is characterized by accumulation of fat in the neck area and loss of subcutaneous fat only in the limbs or the gluteal region—parts of the body often not revealed on a brief clinical examination (Table 1). Thus, some patients have been misdiagnosed as having Cushing syndrome and others have suffered from delayed recognition and therapy of their marked hypertriglyceridemia and treatment-resistant diabetes associated with severe insulin resistance. Recently, it has been reported that individuals with metabolic syndrome but without classical findings of Dunnigan syndrome had a surprisingly high prevalence of mutations in LMNA and ZMPSTE24 (a gene encoding one of the lamin A processing enzymes) (4). Thus, as often in medicine, it appears that certain genetically determined conditions when associated with milder phenotypes are much more common than initially anticipated.

In this issue of *Diabetes Care*, Strickland et al. (5) describe a novel form termed "partial lipodystrophy of the limbs" (PLL). In comparison with other forms of lipodystrophy, which are extremely rare (e.g., congenital generalized lipodystrophy has an estimated prevalence of 1 in 10 million), this condition (PLL), similar to lipodystrophy associated with antiretroviral treatment of HIV (6), may affect larger numbers of individuals. The BMI of people with PLL is described to cover a wide range from normal to obese. Affected individuals have disproportionately slender forearms with or without slender calves (and at times thighs) compared with the rest of their bodies. Since huge physiological variations in quantity and distribution of body fat exist among healthy humans, it is necessary to provide evidence that a variant is harmful in order to classify it as pathological. Strickland et al. make the case that patients with PLL are more insulin resistant and have worse glycemia than others with similar degrees of obesity or type 2 diabetes, implying that this lipodystrophy has clinical significance. With greater awareness and more detailed clinical studies including laboratory testing and determination of body composition, it will become evident whether this phenotype is a circumscribed entity. Questions to be addressed are whether adipose tissue in the distal extremities is lost or never gained, whether these patients are leptin deficient or have other adipokine abnormalities, and whether affected individuals benefit from early recognition and intervention to lower their risk of developing diabetes or to more aggressively treat their overt diabetes. Thus far, the etiology, heredity, and prevalence of this condition remain to be determined.

The novel description of a presumably more common form of lipodystrophy is contrasted by the recent identification of an exceedingly rare form, part of an autoinflammatory condition: CANDLE (chronic neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome (7). Infants as young as 2 weeks of age (and at the latest by 12 months of age) present with skin rashes, accompanied by episodic fevers, anemia, and eventual development of partial lipodystrophy, predominantly affecting the face, wrists, ankles, and distal parts of fingers and toes. Joint contractures may develop early, and affected children fail to thrive. Again, incorrect diagnoses ranging from Lyme disease to cutaneous myelogenous leukemia have led to unnecessary and harmful treatments such as whole-body radiation and prolonged suffering of the affected child. CANDLE syndrome is caused by mutations in the proteasome gene *PSMB8*, which had been reported earlier by Garg et al. (8) to cause JMP syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood onset lipodystrophy) in adults (8,9). A promising treatment trial (clinical trial reg. no. NCT01724580) is underway at the National Institutes of Health to test whether the Janus kinase 1/2 inhibitor baricitinib is beneficial. Janus kinases phosphorylate activated cytokine receptors,

Table 1—*Phenotypic characterization of lipodystrophy subtypes with inclusion of genotype (if available)*

Lipodystrophy subtype	Genetic cause	Clinical presentation	Metabolic features	Associated conditions	Approximate population frequency	Fat distribution
Congenital generalized lipodystrophy (Berardinelli-Seip syndrome)	Recessive: AGPAT2, BSCL2, CAV1, PTRF	Muscular appearance with or without hepatomegaly and umbilical prominence in infancy	Severe insulin resistance/diabetes, acanthosis, hypertriglyceridemia with or without pancreatitis, PCOS/ hyperandrogenism with infertility (women), steatohepatitis	Cardiomyopathy, bone cysts, proteinuria, focal segmental glomerulosclerosis	<1 per million (1)	
Acquired generalized lipodystrophy (Lawrence syndrome)	None	Gradual loss of subcutaneous fat in childhood or adulthood; may be preceded by panniculitis	Severe insulin resistance/diabetes, acanthosis, hypertriglyceridemia with or without pancreatitis, PCOS/ hyperandrogenism with infertility (women), steatohepatitis	Autoimmune diseases (e.g., hepatitis, type 1 diabetes, juvenile dermatomyositis, Hashimoto thyroiditis), lymphoma, immunodeficiency	250 cases reported (1)	
Familial partial lipodystrophy (Kobberling and Dunnigan syndromes)	Dominant: LMNA, PPARγ, AKT2, PLIN1; Recessive: CIDEC	Unusual body fat distribution, insulin resistance, PCOS often noted during adolescence. Men have much milder phenotype and are rarely diagnosed	Insulin resistance/ diabetes, acanthosis, hypertriglyceridemia with or without pancreatitis, PCOS/ hyperandrogenism with reduced fertility (women), steatohepatitis,	Rarely myopathy, cardiomyopathy, cardiac conduction abnormalities (1)	<1 per million (1)	
Acquired partial lipodystrophy (Barraquer-Simons syndrome)	Not yet determined	Gradual loss of subcutaneous fat progressing in a cephalocaudal direction with variable lower limit with or without increased fat accumulation in lower body	Usually mild or absent	Autoimmune diseases, MPGN type 2, low complement 3 + C3 nephritic factor	<1 per million (1)	

Continued on p. 2144

Table 1—*Continued*

Lipodystrophy subtype	Genetic cause	Clinical presentation	Metabolic features	Associated conditions	Approximate population frequency	Fat distribution
CANDLE/JMP syndrome	Recessive: *PSMB8*	Loss of subcutaneous fat affecting face, wrists, ankles, and distal parts of fingers and toes	Varying degrees of insulin resistance and hypertriglyceridemia (at times severe), accumulation of visceral fat with disproportionately little hepatic steatosis	Infantile skin rashes (neutrophilic dermatitis), fever, anemia, high inflammatory markers	<100 cases reported (7)	
Partial lipodystrophy of the limbs	None known	Lack of subcutaneous fat affecting predominately forearms or forearms together with calves; occasionally thighs	Type 2 diabetes, insulin resistance, hypertriglyceridemia, elevated transaminases (indicative of hepatic steatosis)	Acanthosis nigricans, PCOS	Unknown but probably "not uncommon" (5)	
HIV/ART-associated lipodystrophy	None	Gradual loss of subcutaneous fat in face, limbs, and buttocks, with increased fat in trunk, abdomen, and dorsocervical area	Insulin resistance/ diabetes, dyslipidemia, hypertension	Increased risk with prolonged exposure to stavudine and zidovudine	13–70% of patients with HIV receiving ART (6)	

ART, antiretroviral therapy; MPGN, membranoproliferative glomerulonephritis; PCOS, polycystic ovary syndrome.

which subsequently recruit STAT transcription factors known to modulate gene transcription. Thus, it is proposed that the inflammatory cascade is interrupted.

Making the correct diagnosis may have vital consequences for patients with lipodystrophy. For familial forms of lipodystrophy, genetic counseling is essential, and in all cases, patients should be screened for known comorbidities, including but not limited to metabolic abnormalities such as diabetes, hypertriglyceridemia, and steatohepatitis, as well as cardiomyopathy (10) and kidney disease (11). Making a diagnosis of lipodystrophy may also be critical for medical management. Conventional therapies for hyperlipidemia or diabetes are often ineffective, especially in patients with extreme metabolic disturbances. Because patients with lipodystrophy have deficient adipose tissue, they also have low levels of adipocyte-derived hormones (adipokines). Leptin was the first of these adipokines to be discovered in 1994 (12) and is a major regulator of appetite and metabolism. As a result of leptin deficiency, patients with lipodystrophy have hyperphagia, which exacerbates ectopic lipid deposition and insulin resistance. In 2000, the first patient with lipodystrophy received recombinant leptin to correct leptin deficiency. Since then, between 100 and 200 patients with non–HIV associated lipodystrophy have been treated with leptin replacement worldwide, which has been shown to improve metabolic complications in numerous subtypes, including patients with profound leptin deficiency and others with "relative leptin deficiency" in partial forms of lipodystrophy (13). In these latter forms, leptin levels tend to be unexpectedly low for the degree of adiposity, suggesting that leptin may be differentially secreted by different fat depots. Unfortunately, leptin levels were not available in the patients with the newly described "partial lipodystrophy of the limbs." Presently, leptin is only available in clinical trials, but if and when it is approved by the U.S. Food and Drug Administration as an orphan drug, it remains to be seen whether it will be an effective, safe, and well-tolerated therapeutic agent for PLL and other forms of lipodystrophy. These include conditions associated with active inflammatory diseases, such as lupus erythematosus, dermatomyositis (14), or the above-mentioned CANDLE syndrome (7). Thus far, leptin treatment has been withheld in inflammatory diseases because of concerns regarding leptin's potential proinflammatory effects. These have largely

been deducted from animal and in vitro model systems and include upregulation of tumor necrosis factor-α (15). To date, leptin replacement has not been shown to promote inflammation in humans, but the number of treated subjects is too small to come to a definite conclusion. Furthermore, leptin has been successfully used in a few patients with quiescent juvenile dermatomyositis without exacerbating the underlying disease. Despite leptin's beneficial effects on metabolism, some patients express disappointment because leptin treatment does not lead to restoration of adipocytes. Fat cell transplantation and synthetic fillers have become viable options for some individuals, especially for those suffering from severe facial fat loss. Active investigation is also focusing on the potential therapeutic role of adipose stem cells (16).

In summary, greater awareness and correct diagnosis of previously described and novel forms of lipodystrophy may spare patients an arduous voyage through misdiagnoses and unnecessary treatments. Certain lipodystrophy-associated genotypes may in fact be more common in milder clinical conditions, such as metabolic syndrome. A worldwide registry of patients with lipodystrophy and lipodystrophy-related genetic mutations would certainly benefit our concerted efforts in learning about the natural history, developing better diagnostic criteria, and providing safe and effective treatment.

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