Leptin Therapy in Patients with Lipodystrophy and Syndromic Insulin Resistance

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Rebecca J. Brown and Phillip Gorden

Abbreviations

ACTH	Adrenocorticotropic hormone
AGL	Acquired generalized lipodystrophy
APL	Acquired partial lipodystrophy
BMI	Body mass index
CGL	Congenital generalized lipodystrophy
CRH	Corticotropin releasing hormone
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FPL	Familial partial lipodystrophy
GnRH	Gonadotropin releasing hormone
HIV	Human immunodeficiency
HAART	Highly active antiretroviral therapy
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
NIH	National Institutes of Health
PCOS	Polycystic ovary syndrome
PI3K	Phosphoinositide 3-kinase
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone

R.J. Brown, M.D. (✉) • P. Gorden, M.D., M.H.Sc.
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10, Room 6-5940, 10 Center Drive, Bethesda, MD 20892, USA
e-mail: brownrebecca@mail.nih.gov; PhillipG@intra.niddk.nih.gov

The discovery of the adipocyte-derived hormone leptin by Jeffrey Friedman's laboratory in 1994 was a seminal event in the history of science and medicine. Leptin acts as a signal of total body energy sufficiency. Leptin deficiency, either in the physiologic state of starvation or the pathophysiologic states of congenital leptin deficiency and lipodystrophy, leads to hyperphagia and impaired reproduction. Pharmacologic treatment with leptin reverses the hyperphagia of leptin-deficient states, but has little clinical effect in states of endogenous leptin sufficiency or excess, such as obesity. The greatest success of leptin as a pharmaceutical agent has been in patients with lipodystrophy, who have leptin deficiency as a result of deficient adipose mass. Based on the dramatic improvements in metabolic disease seen with leptin replacement, the FDA approved recombinant human methionyl leptin (metreleptin) for patients with generalized lipodystrophy in February, 2014, 20 years after the hormone was first described. Leptin remains an experimental drug for all other conditions, including partial forms of lipodystrophy. The clinical effects of leptin pharmacotherapy in both generalized and partial forms of lipodystrophy are discussed in this chapter.

Lipodystrophy Syndromes

The lipodystrophy syndromes are a heterogeneous group of disorders that are characterized by selective deficiency of subcutaneous adipose

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tissue. This deficiency of subcutaneous fat may involve the entire body (generalized lipodystrophy) or selected fat depots, most commonly the limbs and buttocks (partial lipodystrophy) (Fig. 18.1). Lipodystrophies, either generalized or partial, may be genetic or acquired in origin (Fig. 18.2). All known inherited generalized lipodystrophies are autosomal recessive, whereas the majority of inherited partial lipodystrophies are autosomal dominant [1]. Inherited forms of lipodystrophy can also be associated with other syndromic conditions, such as progeria, and may be associated with variable extent of adipose deficiency. The most common form of acquired lipodystrophy is associated with infection with the human immunodeficiency virus (HIV) combined with use of highly active antiretroviral therapy (HAART). Acquired lipodystrophies that are not due to HIV/HAART are thought to be due to autoimmune destruction of adipocytes, because they are commonly associated with other systemic or organ-specific autoimmune diseases [2].

Metabolic Disease in Lipodystrophy

The metabolic complications of lipodystrophy are shown in Table 18.1. The primary physiologic abnormality in lipodystrophy is deficient subcutaneous adipose tissue. This deficiency in adipocytes leads to low levels of adipocyte-derived hormones, including leptin, adiponectin, and others. The low leptin is sensed by the brain as a starvation signal, leading to hyperphagia. Unlike obese patients, those with lipodystrophy cannot store excess caloric intake in subcutaneous fat, and hence these excess calories are stored as triglyceride in ectopic locations, including the muscle and the liver. Ectopic lipid in the liver leads to nonalcoholic fatty liver disease, and ectopic lipid in both the liver and the muscle contributes to insulin resistance. This insulin resistance may be extreme, and frequently results in diabetes as beta-cell function declines. Despite the presence of insulin resistance, lipodystrophy patients (just like those with the obesity-associated metabolic syndrome) retain selective sensitivity to insulin at certain tissues. In the liver, although insulin fails to suppress to glucose production, insulin continues to stimulate lipogenesis, further exacerbating fatty liver disease and leading to hypertriglyceridemia. The ovary similarly maintains sensitivity to insulin, and the extreme hyperinsulinemia of lipodystrophy can lead to ovarian enlargement and hyperandrogenism, analogous to the common polycystic ovary syndrome (PCOS). In addition to subfertility from PCOS, patients with generalized lipodystrophy also have significantly reduced fertility resulting from abnormal secretion of the gonadotropin hormones, luteinizing hormone, and follicle stimulating hormone; this is a direct result of leptin deficiency.

Overall, the metabolic disease of lipodystrophy is a result of the combination of both leptin deficiency (as well as deficiency of other adipokines) plus ectopic lipid deposition. This combination results in more severe metabolic disease than that observed in patients with isolated congenital leptin or leptin receptor deficiency, who have normal adipose tissue storage capacity [3, 4]. Likewise, patients with lipodystrophy have metabolic disease that is analogous to, but more severe than that seen patients with the common, obesity-associated metabolic syndrome [5]. Patients with the obesity-associated metabolic syndrome are thought to have ectopic lipid deposition as a result of exceeding the storage capacity of their subcutaneous adipose tissue; the mechanism of ectopic lipid storage in lipodystrophy is the same, but adipose tissue stores are exhausted much sooner in lipodystrophy than in obesity.

Clinical Effects of Metreleptin in Lipodystrophy

Treatment of lipodystrophy with conventional metabolic therapies, such as insulin, oral hypoglycemic agents, and lipid lowering agents, is extremely challenging. Some patients require thousands of units of insulin per day [6], and many have severe hypertriglyceridemia leading to pancreatitis despite maximal therapy with drugs such as fibrates, statins, or even plasmapheresis [7]. Since 2000, over 100 patients with lipodystrophy have been treated with leptin, most at the National Institutes

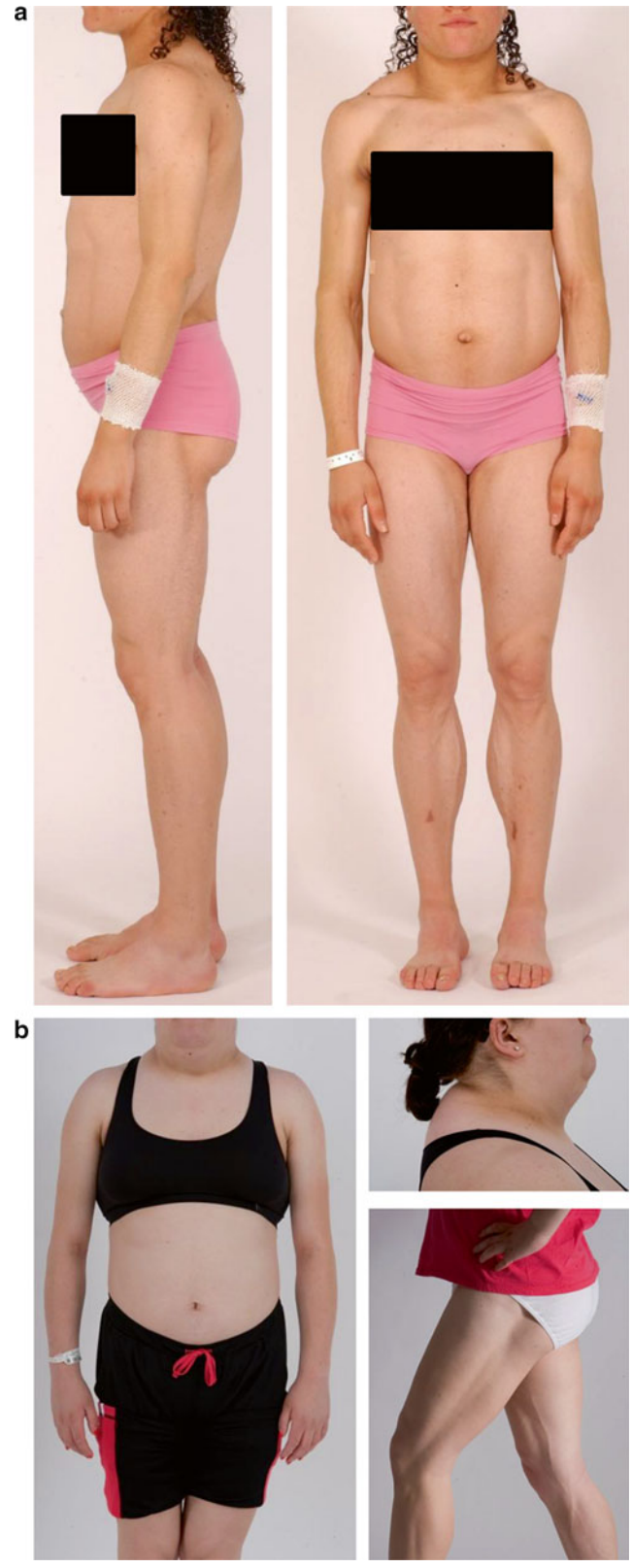

Fig. 18.1 Physical phenotype of generalized versus partial lipodystrophy. (**a**) A young woman with congenital generalized lipodystrophy due to recessive mutation in AGPAT2. She exhibits generalized deficiency of subcutaneous adipose tissue, leading to a muscular appearance with prominent veins. The increase in abdominal girth is secondary to organomegaly. (**b**) An adolescent girl with familial partial lipodystrophy due to dominant mutation in LMNA. She has absent subcutaneous adipose tissue in the legs and gluteal region, resulting in a muscular appearance with prominent veins, similar to the patient with generalized lipodystrophy. Subcutaneous fat is greatly diminished, but not absent, in the arms. There is increased fat present in the head, neck, and trunk, resulting in a Cushingoid appearance

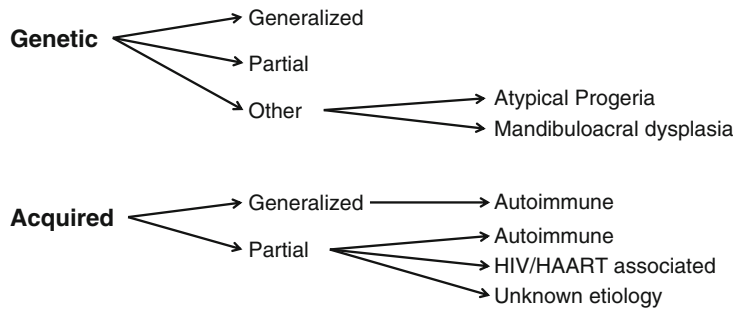

Fig. 18.2 Classification scheme for lipodystrophies. Lipodystrophies are classified according to their origin (genetic or acquired), and the distribution of body fat deficiency (generalized or partial). Lipodystrophy may also occur in patients with progeroid (premature aging) disorders, including atypical progeria and mandibuloacral dysplasia. These disorders are classified separately, as they may lead to either partial or generalized lipodystrophy. The most common form of acquired lipodystrophy arises in individuals treated with highly active antitretroviral therapy (HAART) for the human immunodeficiency virus (HIV). Most other acquired lipodystrophies are thought to be secondary to autoimmune destruction of adipocytes, as they are associated with systemic or organ-specific autoimmune conditions

Table 18.1 Metabolic complications of lipodystrophy

Glucose metabolism:
Insulin resistance
Diabetes
Acanthosis nigricans
Lipid metabolism:
High triglycerides
Eruptive xanthomata
Pancreatitis
Nonalcoholic fatty liver disease (NAFLD)
Steatosis → Nonalcoholic steatohepatitis (NASH) → Cirrhosis
Reproductive:
Polycystic ovary syndrome (PCOS)
Abnormal gonadotropin secretion

Table 18.2 Types of lipodystrophy treated with leptin at the National Institutes of Health

	Inheritance (genes)	Endogenous leptin level mean ± SD (range) (ng/mL)
Congenital generalized lipodystrophy (CGL)	Autosomal recessive (AGPAT2, BSCL2)	1.17 ± 0.8 (0.25–3.3)
Familial partial lipodystrophy (FPL)	Usually autosomal dominant (LMNA, PPARγ, unknown)	5.9 ± 3.0 (0.95–12.3)
Atypical progeria	Autosomal recessive (LMNA, ZMPSTE24, unknown)	1.08 ± 0.5 (0.33–1.8)
Acquired generalized lipodystrophy (AGL)	_	1.05 ± 0.7 (0.25–3.3)
Acquired partial lipodystrophy (APL)	_	7.5 ± 6.8 (0.61–16.9)

of Health (NIH) in Bethesda, MD. The types of lipodystrophy treated with leptin at the NIH are shown in Table 18.2. The initial investigation of leptin in lipodystrophy was designed as a proof of principle study to determine if leptin replacement in this hypoleptinemic state could act as a targeted therapy for the metabolic diseases of lipodystrophy. This uncontrolled study of nine patients with severe hypoleptinemia (leptin <4 ng/mL) showed such dramatic improvements in triglycerides and diabetes control that it was subsequently considered unethical to conduct placebo-controlled trials of leptin in this population [8]. Further studies have shown that leptin replacement in lipodystrophy leads to improvements in ectopic lipid, insulin resistance and diabetes, hypertriglyceridemia and its complications, fatty liver disease, and subfertility. While many of these effects may be mediated via reductions in hyperphagia, rodent data suggest that leptin likely has direct effects to improve metabolic disease independent of central nervous system mediated changes in food intake [9, 10].

Appetite, Weight, and Body Composition

In lipodystrophy, as in other models of leptin deficiency, leptin replacement causes a reduction in spontaneous food intake by approximately 50 % [11, 12]. The neural pathways involved in appetite regulation with leptin replacement in lipodystrophy were investigated by Aotani et al. using functional magnetic resonance imaging (fMRI) [13]. They demonstrated that leptin is most important for postprandial satiety via suppression of neural activity in brain regions including the amygdala, insulin, nucleus accumbens, caudate, putamen, and globus pallidus.

Despite the substantial reduction in food intake, lipodystrophy patients experience only modest weight loss with leptin replacement, averaging approximately 7.5 kg after 1 year, with most of the weight loss occurring during the first 4–6 months of treatment [11]. Some of this weight loss may be attributed to reduction in liver size (from 3,055 to 2,204 cm^3 after 1 year) [11]. Reductions in lean body mass occurred as well, but were not statistically significant. Some patients with generalized lipodystrophy appear to be particularly sensitive to the appetite suppressing effects of leptin, with weight loss of 20 kg or more, and the dose may need to be reduced to prevent excessive weight loss in these patients (unpublished data).

Lipid Metabolism

The most dramatic clinical effect of leptin treatment in lipodystrophy is improvement in hypertriglyceridemia. The first lipodystrophy patient treated with leptin, an adolescent with acquired, generalized lipodystrophy, had extreme hypertriglyceridemia, with serum triglyceride levels consistently greater than 10,000 mg/dL, resulting in painful xanthomata and recurrent pancreatitis. Prior to leptin treatment, this patient required weekly plasmapheresis to maintain triglycerides at ~5,000 mg/dL. After initiating leptin treatment, the patient's triglyceride level fell to ~1,000 mg/dL, plasmapheresis was discontinued, and xanthomata resolved; triglycerides improved further to ~200 mg/dL with inpatient administration of a high mono-unsaturated fat diet. This patient was one of nine patients who participated in the first study of leptin in lipodystrophy, which included eight patients with generalized lipodystrophy and one with partial lipodystrophy, all with endogenous leptin less than 4 ng/mL (mean leptin 1.3 ± 0.3 ng/mL). Thish study showed a 60 % reduction in serum triglycerides after 4 months of treatment [8]. Similar findings have been observed in subsequent, larger and more heterogeneous cohorts. In 55 patients (36 with generalized lipodystrophy and 19 with partial lipodystrophy) with endogenous leptin less than 12 ng/mL (mean leptin 2.8 ± 2.8 ng/mL), leptin treatment decreased triglycerides from 479 ± 80 mg/dL (geometric mean ± SEM) to 254 ± 40 after 4 months, and 164 ± 26 after 3 years. Among the subgroup of 41 patients who had hypertriglyceridemia (>200 mg/dL) at baseline, the change was even more dramatic, with triglyceride levels falling from 743 ± 123 mg/dL at baseline to 326 ± 59 after 4 months and 197 ± 35 after 3 years.

Ectopic Lipid

Leptin replacement in lipodystrophy leads to substantial reductions in ectopic lipid, both in the liver and in the muscle. In patients with generalized lipodystrophy, magnetic resonance spectroscopy demonstrated ~80 % reduction in hepatic triglyceride and ~40 % reduction in intramyocellular triglyceride with 2–10 months of leptin treatment [12, 14].

Nonalcoholic Fatty Liver Disease

Patients with lipodystrophy typically have a form of liver disease that most resembles the nonalcoholic fatty liver disease (NAFLD) seen in obesity. However, lipodystrophy patients appear to have a much greater prevalence of the later stages of NAFLD (nonalcoholic steatohepatitis [NASH] and cirrhosis) compared to patients with obesity-associated NAFLD (Table 18.3).

Table 18.3 Prevalence of the stages of nonalcoholic fatty liver disease in lipodystrophy versus obesity

	Obesity [49]	Lipodystrophy [15]
Nonalcoholic fatty liver disease (NAFLD)	40–90 %	90 %
Nonalcoholic steatohepatitis (NASH)	10–20 % of NAFLD	70–90 %
Cirrhosis	0–4 % of NAFLD (over 10–20 years)	17 %
Hepatocellular carcinoma	2–5 % per year in patients with cirrhosis	Not reported

Patients with congenital generalized lipodystrophy due to mutations in the BSCL2 gene (encoding the protein seipin) appear to be at particularly high risk for advanced liver disease at an early age, with 9 of 10 patients, all under 18 years of age, having bridging fibrosis or cirrhosis at the time of pre-leptin liver biopsy.

Leptin treatment reduces liver volume in lipodystrophy by 28 % after 4 months of treatment, presumably secondary to reduction in hepatic triglyceride content [8]. In 27 patients (15 generalized, 12 partial), liver biopsies were performed before and 26±4 months (median 15 months) after leptin treatment [15]. Although 86 % of patients met histologic criteria for definite or borderline NASH prior to leptin, only 33 % had NASH on biopsy after leptin. Mean NAFLD activity scores (NAS) decreased from 4.3 (out of a maximum of 8) to 2.4. This improvement in NAS was attributable to improvements in steatosis and inflammation; no changes in fibrosis were observed. Three of four patients with advanced cirrhosis at baseline remained clinically stable over 2–6 years of follow-up, and the fourth died of liver failure after 17 months of leptin treatment.

Glucose Metabolism

The original study of leptin in lipodystrophy showed a 1.9 % reduction in A1c after 4 months of treatment [8]. This effect has been reconfirmed as numbers of patients treated has grown, including not only the international NIH cohort, but also a cohort in Japan [16]. In generalized lipodystrophy patients, reductions in fasting glucose are seen rapidly after introduction of leptin treatment, with statistically significant declines (from 172 to 120 mg/dL) by day 7 of treatment [16]. Moreover, the beneficial effects on glycemia have been sustained over time [17–19]. The most recent publication based on the NIH cohort showed a 4 month reduction in A1c of 1.2 % ($n=40$), and a 2.1 % reduction after 3 years of treatment ($n=18$) [18]. Reductions were most dramatic in patients with worse glycemia control at baseline; among patients with an initial A1c>7 %, A1c decreased from 9.4 % at baseline, to 7.7 % after 4 months ($n=31$), and to 6.3 % after 3 years ($n=14$). These improvements in A1c were observed despite reductions in concomitant diabetes medications. In 32 patients with various forms of lipodystrophy, the percent taking insulin decreased from 40 to 22, and the percent using oral hypoglycemic agents decreased from 72 to 59 after 12 months of leptin treatment [6].

The beneficial effects of leptin on glycemia in patients with partial lipodystrophy are a bit more ambiguous. Park et al. reported significant improvement in fasting glucose (from 190 to 151 mg/dL) but nonsignificant change in A1c (from 8.4 to 8 %) in six patients with familial parital lipodystrophy of the Dunnigan type [20]. In two of these patients, leptin withdrawal for 3 months resulted in substantial worsening of A1c, suggesting it did have efficacy in these patients. Simha et al. did not observe improvements in fasting glucose, insulin, glucose tolerance, or A1c in 24 patients with familial partial lipodystrophy of the Dunnigan type, although some improvement in insulin sensitivity was observed in the subgroup with more severe hypoleptinemia. In a single patient with familial partial lipodystrophy due to mutation in the PPARγ gene, leptin treatment for 18 months led to a 2.7 % reduction in A1c.

The mechanisms responsible for improvements in clinical glycemic endpoints with leptin treatment in lipodystrophy have not been well explored. Reduction in food intake is likely to

play an important role, and a study to determine if leptin has effects independent of changes in food intake is ongoing (NCT01778556). In generalized lipodystrophy, leptin improves total body insulin sensitivity as measured by the hyperinsulinemic–euglycemic clamp [12, 16]. In three subjects, improvements in hepatic insulin sensitivity have been demonstrated as well [12].

Reproduction

Leptin is known to have a permissive role in pubertal GnRH secretion. Leptin replacement in patients with congenital leptin deficiency normalizes GnRH pulsatility [21] and allows normal pubertal development [22]. Lipodystrophic patients, even those with generalized lipodystrophy and very low leptin levels, appear to have sufficient leptin secretion to permit normal pubertal development in the leptin-deficient state. However, there remains some impairment of normal hypothalamic-pituitary-gonadal axis function in lipodystrophy. In the leptin-deficient state, five lipodystrophic women with severe leptin deficiency (<4 ng/mL) had attenuated LH responses to LHRH stimulation, which improved after 4 months of leptin replacement [23], but this finding was not reproduced in a larger cohort of ten women [24]. Despite the uncertain changes in gonadotropin regulation, leptin therapy clearly normalizes menstrual cyclicity in women with lipodystrophy. Eighty percent of post-pubertal women with generalized lipodystrophy are amenorrheic or have menstrual irregularity in the leptin-deficient state, and normal cycles are restored with leptin treatment [16, 23, 24]. Moreover, leptin replacement tends to increase estradiol levels in women [23, 24] and testosterone levels in men [24].

Abnormal menstrual cycles in women with lipodystrophy are not solely attributable to impaired gonadotropin secretion. The hyperinsulinemia that results from insulin resistance in these patients increases ovarian volume and androgen production, analogous to the common polycystic ovarian syndrome (PCOS) [25]. Leptin reduced free testosterone levels in ten lipodystrophic women from 40 ± 11 ng/dL to 19 ± 4 ng/dL after 1 year, although significant reductions in ovarian volume were not observed.

The combination of abnormal gonadotropin secretion and PCOS significantly impairs fertility in women with generalized lipodystrophy. In the NIH cohort, only 1 of 12 women over age 20 years became pregnant in the leptin-deficient state (unpublished data). During experimental leptin treatment, despite strong recommendations to use birth control, three additional women with generalized lipodystrophy had spontaneous pregnancies, with two live births. By contrast, fertility appears to be relatively normal in women with partial lipodystrophy, with a mean of 1.25 children (median, 1) in women over 20 years of age prior to leptin treatment. This finding is, of course, consistent with the autosomal dominant pattern of inheritance of almost all forms of familial partial lipodystrophy. Very little is known about fertility in men with congenital generalized lipodystrophy, although there have been no cases of known or suspected paternity in the NIH cohort, either before or after leptin therapy.

Thyroid

In rodent and in vitro model systems, leptin regulates the expression of thyrotropin releasing hormone (TRH), and leptin-deficient ob/ob mice have central hypothyroidism that is corrected with leptin replacement [26]. Humans with congenital leptin deficiency have a milder phenotype, with disorganized TSH pulsatility and circadian rhythm [27], but the majority do not have overt hypothyroidism [28]. Lipodystrophy patients do not appear to have an overt thyroid phenotype, although TSH pulsatility has not been studied. The initial studies of leptin on the thyroid axis in lipodystrophy patients ($N=7$) demonstrated statistically significant (but not clinically significant) declines in TSH (from 2.2 ± 1.1 to 1.2 ± 0.2 μU/mL, $P<0.001$) and total thyroxine (from 126 ± 27 to 92 ± 19 nmol/L, $P<0.001$), with no change in TSH response to TRH stimulation testing after 4 months of leptin therapy [23]. However, these findings were not reproduced in a larger cohort

($N=14$) after 8–12 months of leptin treatment [24], suggesting that leptin replacement is unlikely to have clinically important effects on thyroid function in lipodystrophy.

Adrenal

Animal and in vitro models suggest multiple (and sometimes opposing) roles of leptin in regulation of the hypothalamic-pituitary-adrenal axis [26]. However, neither humans with congenital leptin deficiency nor lipodystrophy have any measurable perturbation of adrenal function. In lipodystrophy patients, 4–12 months of leptin replacement did not result in any change in spontaneous adrenocorticotropic hormone (ACTH) or cortisol secretion, or in ACTH and cortisol responses to corticotropin releasing hormone (CRH) stimulation [23, 24].

Growth Hormone and Insulin-Like Growth Factor-1 (IGF-1)

In rodents and in vitro studies, leptin stimulates growth hormone secretion, and leptin deficiency results in impaired linear growth [26]. This does not hold true in humans. However, human models of leptin deficiency including congenital leptin deficiency, leptin receptor mutation, and starvation support the hypothesis that leptin may regulate the ability of growth hormone to stimulate secretion of IGF-1 and its binding proteins [26]. Data from lipodystrophy patients is consistent with other human conditions: leptin replacement in lipodystrophy had no effect on fasting (unstimulated) growth hormone levels, but increased IGF-1 levels by 30–53 % [24, 25]. This increase in IGF-1 may simply be a consequence of improved insulin sensitivity, as IGF-1 is lower in insulin resistant states.

Bone

Rodent models have shown that leptin impacts bone metabolism via two distinct and opposing mechanisms. Leptin increases bone mass via direct stimulation of osteoblast differentiation and proliferation, and decreases bone mass via indirect neural circuitry involving the sympathetic nervous system [29]. The phenotype of leptin deficiency in the rodent skeleton is increased trabecular bone in the vertebrae [30], and decreased cortical bone in the vertebrae and limbs [31, 32], with overall decreased total body bone mass, due to the predominance of cortical bone in the skeleton . This phenotype is reversed by leptin replacement [32, 33]. In contrast, we have found that patients with congenital generalized lipodystrophy have *increased* total body bone mass in the leptin-deficient state, and bone mass is unchanged by leptin replacement in these patients [34]. This finding suggests that pathways linking leptin to bone metabolism in rodents may not be relevant for humans.

Kidney

Kidney disease is a common manifestation of lipodystrophy, particularly among patients with generalized lipodystrophy, and typically manifests as proteinuria and hyperfiltration. Among 15 leptin-treated patients with generalized lipodystrophy, 11 (73 %) had reduction in urine protein excretion after leptin treatment [35]. This occurred in conjunction with a decrease in creatinine clearance (from over 200 to ~120 mL/min), suggesting that improvements in protein excretion may be secondary to reduced hyperfiltration.

Immune System

The leptin deficiency of lipodystrophy is not associated with overt immunodeficiency. Certain T lymphocyte subsets were lower in ten patients with generalized lipodystrophy compared to healthy control subjects, but were within the normal range [36]. Leptin replacement in these lipodystrophy patients normalized both absolute and relative T cell subsets as well as normalizing peripheral blood mononuclear cell responsiveness to stimulation [36].

Leptin Treatment in Patients with HIV/HAART-Associated Lipodystrophy

Four small studies of leptin replacement in men with HIV/HAART-associated lipodystrophy and hypoleptinemia (endogenous leptin <3 or 4 ng/dL) have been conducted, studying a total of 41 patients [37–40]. Three of the studies showed modest improvements in insulin resistance and lipids, while the fourth showed improvements in glycemia, but minimal change in fasting lipids or lipid turnover. Two of the studies also showed reductions in truncal or visceral fat.

Leptin Treatment in Patients with Insulin Receptor Mutations

Patients with mutations of the insulin receptor suffer from extreme insulin resistance and dysglycemia, and patients are at high risk for early morbidity and mortality due to microvascular complications of diabetes [41, 42]. In contrast to lipodystrophy, insulin receptor mutations do not cause NAFLD or hypertriglyceridemia, as intact insulin signaling through its receptor is required for de novo lipogenesis in the liver [43]. Hyperglycemia in these patients is very difficult to treat [44], and glucose-lowering therapies are needed that do not require signaling through the insulin receptor. The idea of treating patients with mutations of the insulin receptor with leptin arose from the discovery that the signal transduction cascades downstream of the insulin and leptin receptors overlap at the level of phosphoinositide 3-kinase (PI3K). We hypothesized that pharmacologic treatment with leptin could increase PI3K levels in patients with insulin receptors, thereby increasing post-receptor insulin signaling while bypassing the defective receptor.

The initial pilot study of leptin treatment in this population included two siblings with the Rabson Mendenhall syndrome due to homozygous mutation of the insulin receptor [45]. Leptin therapy at doses of up to 0.06–0.09 mg/kg/day for 10 months resulted in declines in fasting glucose of 62 and 139 mg/dL, and declines in A1c of 0.9 and 1.3 % in the two patients. After leptin withdrawal for 3 months, glycemia returned to the pre-leptin baseline. These two patients were subsequently followed for 10 years, and treated with escalating doses of leptin (up to 0.22 mg/kg/day), and underwent three cycles of leptin withdrawal and reinitiation. With each withdrawal, A1c rose, and it declined again with each reinitiation, suggesting a lasting effect on glycemia [46]. A total of five patients (including the original two) with this extremely rare condition were treated with leptin at doses of 0.22 mg/kg/day for 1 year, resulting in a decrease in A1c from 11.4 ± 1.1 % at baseline, to 9.3 ± 1.9 % after 6 months, and 9.7 ± 1.6 % after 12 months. This dose of leptin resulted in significant weight loss (presumably due to appetite suppression), with declines in BMI z-score from −1.4 ± 1.8 at baseline to −2.6 ± 1.6 after 12 months. The presumed reduction in food intake likely accounted, at least in part, for the reduction in A1c. Although the 1.8 % reduction in A1c with leptin still left patients considerably above glucose targets, this reduction would be anticipated to substantially reduce the risk of microvascular complications of diabetes.

Adverse Effects of Leptin Treatment

The most common adverse effects of leptin across all treatment studies (including those conducted in obese, lipodystrophic, congenital leptin-deficient, and other populations) include hypoglycemia (in insulin treated patients), weight loss, headache, and abdominal pain (http://packageinserts.bms.com/pi/pi_myalept.pdf). Two adverse events of particular concern are listed as black box warnings in the package insert: neutralizing antibodies to leptin and T cell lymphoma. Neutralizing antibodies were observed in three lipodystrophy patients in the NIH cohort. The clinical consequences of these antibodies remain uncertain, but may include loss of efficacy of the drug, as well as severe infection. T cell lymphoma has been observed in three patients in the NIH cohort, all with a diagnosis of acquired

generalized lipodystrophy. Two of these patients had preexisting neutropenia prior to initiating leptin, and were diagnosed with peripheral T cell lymphoma within a few months of starting leptin, suggesting that an active malignancy or precursor condition may have been present prior to initiation of leptin. The third patient developed anaplastic large cell lymphoma after approximately 2 years of leptin treatment. Because acquired generalized lipodystrophy is thought to be an autoimmune disorder, and patients with altered immune function are at increased risk for lymphoma, it is likely that the underlying diagnosis placed these patients at risk for lymphoma. In addition, peripheral T cell lymphoma has been reported in patients with acquired generalized lipodystrophy who never received leptin treatment [47, 48]. However, a role for leptin treatment in lymphoma development or growth cannot be entirely excluded.

Conclusions

The discovery of leptin provided a mechanism to explain how the body regulates energy balance. The fact that leptin is a circulating hormone suggested that replacement of the deficient hormone might provide benefit first in rodent models and then in humans in states of leptin deficiency. Lipodystrophy, especially in its generalized form, is a state of severe leptin deficiency and these patients, as a consequence, have severe metabolic derangements. Leptin replacement has a major effect to ameliorate hypertriglyceridemia, insulin resistance and diabetes, nonalcoholic fatty liver disease, and reproductive abnormalities, particularly in the generalized forms of lipodystrophy where metreleptin is now an approved drug. Continued studies are needed in partial forms of lipodystrophy, but at this time it seems clear that patients with more severe metabolic derangements do respond to metreleptin. Other issues remain a work in progress such as the limiting concentration of leptin in blood below which a therapeutic response can be expected, as well as further studies on optimal dosing, antigenicity, and continued safety monitoring.

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