Published in final edited form as:
Ann Intern Med. 2010 January 19; 152(2): 93–100. doi:10.1059/0003-4819-152-2-201001190-00008.

Narrative Review: The Role of Leptin in Human Physiology: Emerging Clinical Applications

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Keywords

obesity; insulin resistance; leptin; leptin deficiency; leptin physiology; hormone deficiency

Introduction

The discovery of leptin fifteen years ago generated great excitement that the treatment for obesity had been found, and thus, this prototypical adipocyte-secreted protein/cytokine was named leptin after the Greek word “leptos” for thin. It also pioneered the concept that adipose tissue is not an inert energy storage organ but an active endocrine organ. Subsequent clinical trials led to initial disappointment, however, when leptin was eventually found to be ineffective for the treatment of obesity (1). Research efforts have since expanded to elucidating leptin's role in human physiology and have resulted in a fundamentally renewed understanding of its role in regulation of energy homeostasis, neuroendocrine function, and metabolism, mainly in states of energy deficiency and not energy excess (i.e. obesity). In this review, we summarize the biology and physiology of leptin, its role in the pathophysiology of several disorders, and the emerging therapeutic applications of recombinant human leptin.

The biology of Leptin

Leptin, a 167-amino-acid product of the human leptin gene, was originally discovered through positional cloning of *ob/ob* mice, a mouse model of obesity found serendipitously at Jackson Laboratories (2). These mice were found to have a homozygous mutation of the leptin gene resulting in complete leptin deficiency, which manifested with hyperphagia, extreme obesity, diabetes, neuroendocrine abnormalities, and infertility.

Leptin is secreted mainly by white adipose tissue, and levels are positively correlated with the amount of body fat (3). Like many other hormones, leptin is secreted in a pulsatile fashion and

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has a significant diurnal variation with higher levels in the evening and early morning hours (4,5). Circulating leptin levels reflect primarily the amount of energy stored in fat and secondarily acute changes in caloric intake (4-8) (Table 1).

Leptin mediates its effects by binding to specific leptin receptors (ObRs) expressed in the brain as well as in peripheral tissues. Alternative splicing generates several isoforms of ObRs. The ObRa isoform (the short leptin receptor isoform) is thought to play an important role in transporting leptin across the blood–brain barrier (11). The ObRb isoform (the long leptin receptor isoform) mediates signal transduction and is strongly expressed in the hypothalamus, an important site for the regulation of energy homeostasis and neuroendocrine function (12-14).

The binding of leptin to the ObRb receptor activates several signal transduction pathways, including Janus Kinase-Signal Transducer and Activator of Transcription-3 (JAK-STAT3), which is important for regulation of energy homeostasis (15), and Phosphatidylinositol 3-Kinase (PI3K), which is important for regulation of both food intake and glucose homeostasis (16). Other pathways, including Mitogen-activated Protein Kinase (MAPK), 5′Adenosine Monophosphate-activated Protein Kinase (AMPK), and the Mammalian Target of Rapamycin (mTOR), have been proposed to be downstream of leptin and are under investigation (17).

Homozygous mutations of the leptin gene leading to complete leptin deficiency have been described in extremely rare cases of obese humans. The vast majority of obese humans, however, have high circulating leptin levels (3) and are either resistant or tolerant to its weight-reducing effects (18). Proposed hypothalamic mechanisms underlying leptin resistance include a) defects at or downstream of the ObRb receptor, b) induction of inhibitors of leptin signaling (e.g. Suppressor of Cytokine Signaling-3 (SOCS-3) (19)), and c) alterations in the transport of leptin across the blood-brain barrier (18,20). More studies are needed to fully elucidate leptin's signaling pathways and the mechanisms underlying leptin resistance or tolerance in humans, which in turn may lead to the development of novel treatment options for obesity and the metabolic syndrome.

The Role of Leptin in Human Physiology and Pathophysiology

The most significant roles of leptin include regulation of energy homeostasis, neuroendocrine function, and metabolism. Other effects of leptin involving regulation of immune function (21,22) and bone metabolism are under intense investigations but are beyond the scope of this clinical review.

The role of leptin in energy homeostasis

The circulating leptin level serves as a gauge for energy reserves and directs the central nervous system to adjust food intake and energy expenditure accordingly. Leptin exerts immediate effects by acting on the brain to regulate appetite (Figure 1). Via ObRb-receptor binding in the hypothalamus, leptin activates a complex neural circuit comprising of anorexigenic (i.e. appetite-diminishing) and orexigenic (i.e. appetite-stimulating) neuropeptides to control food intake. Outside of the hypothalamus, leptin interacts with the mesolimbic dopamine system, which is involved in motivation for and reward of feeding, and the nucleus of the solitary tract of the brainstem to contribute to satiety (17).

In addition to immediate effects, long-term leptin administration may result in the rewiring of the connections among hypothalamic neurons (i.e. promote synaptic plasticity) (25,26). Specifically, when administered in leptin-deficient mice, leptin has been shown to increase the number of synapses on neurons that secrete the anorexigenic neuropeptide

Proopiomelanocortin (POMC) and decrease the number of synapses on neurons that secrete the orexigenic neuropeptide Neuropeptide Y (NPY) (26).

Not only does leptin signal the central nervous system to decrease food intake, it may also increase energy expenditure. In mice, leptin increases sympathetic nerve activity (27) and activates brown adipose tissue thermogenesis (28,29), but these effects have not been confirmed in humans (30).

Clinically, patients with congenital leptin deficiency due to mutations in the leptin gene or extreme leptin resistance due to mutations of the leptin receptor gene are obese due to marked hyperphagia (31,32). For patients with leptin deficiency, administering leptin in replacement doses reduces food intake via neural circuits that diminish the perception of food reward and enhance the response to satiety signals (33) and normalizes body weight (34). However, leptin administration at pharmacologic doses to the vast majority of obese humans, who have relatively high levels of leptin and are resistant to it, induces little if any weight loss (1,35). Thus, accumulating evidence suggests that leptin is physiologically more important as an indicator of energy deficiency and as a possible mediator of adaptation to starvation.

The role of leptin in regulating neuroendocrine function

In response to fasting, leptin levels fall rapidly before and out of proportion to any changes in fat mass (6,7,36), triggering the neuroendocrine response to acute energy deprivation (7,36, 37). In mice and humans, this response includes decreasing reproductive hormone levels which prevents pregnancy (an energy-requiring process), decreasing thyroid hormone levels that slow metabolic rate, increasing growth hormone level that may mobilize energy stores, and decreasing insulin-like growth factor-1 (IGF-1) level that may slow growth-related processes (7,37,38). The interactions between leptin and the growth hormone and adrenal axes are apparently less important in humans than in animal models since patients with congenital leptin deficiency have normal linear growth and adrenal function, unlike mice (34,38-40).

We originally observed neuroendocrine abnormalities when starvation-induced falls in leptin levels reached an average of 0.27 ng/mL, and leptin administration in physiologic replacement doses restored the changes in luteinizing hormone pulsatility, decreases in testosterone levels, and decreases in thyroid stimulating hormone pulsatility (7). We then ascertained whether there is a minimum leptin threshold to allow reproduction and to maintain other neuroendocrine processes. When we induced leptin deficiency in normal-weight women, who have higher baseline leptin levels, leptin levels fell to an average of 2.8 ng/mL (36). Only modest changes in LH pulsatility were observed. Our findings suggest that a leptin threshold of ~3 ng/mL is necessary to convey to the brain the message that energy stores in adipose tissue are adequate to bring pregnancy to term. Reaching a leptin level above this threshold, as a child grows, permits the onset of puberty (41) and, in older persons, maintains reproductive and other neuroendocrine processes.

Given that women with anorexia nervosa and exercise-induced amenorrhea are chronically energy-deprived, we first hypothesized that these conditions are associated with hypoleptinemia. This was confirmed in observational studies (42-45). We then hypothesized that long-standing hypoleptinemia leads to neuroendocrine dysfunction with subsequent anovulation and osteoporosis. We conducted a proof-of-concept trial of leptin treatment in replacement doses in women with hypothalamic amenorrhea and found that it improves or fully normalizes the gonadal, thyroid, and, to a lesser degree, growth hormone axes as well as bone markers (46).

The role of leptin in insulin resistance and the metabolic syndrome

Both *ob/ob* mice and *db/db* mice, which have a leptin receptor mutation, as well as humans with congenital leptin deficiency have insulin resistance and other features of the metabolic syndrome. In the *ob/ob* mouse strain, leptin treatment improves hyperglycemia and hyperinsulinemia before weight loss is achieved (47). Leptin treatment in humans with congenital leptin deficiency has also been shown to improve not only hyperinsulinemia but also levels of low-density lipoprotein cholesterol, high-density liproprotein cholesterol, and triglycerides (39). These effects are mediated through central and peripheral actions, and the mechanisms are still being elucidated.

Similarly, mouse models of lipoatrophy, which lack subcutaneous adipose tissue, are hypoleptinemic due to lack of fat available to produce leptin and have metabolic abnormalities, including hyperglycemia, insulin resistance, and hyperlipidemia (48). Given the improvements in metabolic parameters in *ob/ob* mice after leptin administration, it was hypothesized that lipoatrophic mice may also be responsive to exogenous leptin (49). Indeed, transplantation of adipose tissue (48,50), which produces leptin, and administration of exogenous leptin (49) in lipoatrophic mice improve hyperglycemia, insulin resistance, hypertriglyceridemia, and hepatic steatosis. This has led to trials in humans with various types of lipoatrophy and associated metabolic abnormalities (51-58), described further under Clinical Applications.

In conclusion, leptin plays a pivotal role in the regulation of energy homeostasis, neuroendocrine function, and metabolism in not only states of energy excess but, more importantly, in states of energy deficiency. Thus, leptin deficiency results in distinct clinical phenotypes (Table 2) with associated neuroendocrine and metabolic abnormalities, for which recombinant human leptin is an emerging potential therapy.

Clinical Applications: Recombinant Human Leptin as a Treatment for Leptin Deficiency Syndromes in Humans

Obesity syndromes

Leptin deficiency in obesity: mutations of the leptin gene—Patients with congenital complete leptin deficiency due to homozygous leptin gene mutations develop extreme obesity very early in life and respond to recombinant human leptin treatment, which reduces appetite and food intake leading to dramatic body fat loss (32,34,40). Furthermore, these patients have distinct neuroendocrine abnormalities, including hypogonadotropic hypogonadism with failure to reach puberty, which improve with leptin replacement (34). These mutations are rare, but they should be considered in young patients with severe, early-onset obesity and hyperphagia since congenital leptin deficiency is easily treated. Leptin is currently available for congenital leptin deficiency through a compassionate use program by Amylin Pharmaceuticals, Inc.

Leptin resistance in common obesity—Since mechanisms of leptin resistance remain largely unknown, strategies to address leptin resistance in common obesity have included supra-physiologic doses of leptin and coadministration with presumed leptin sensitizers. An early trial with high, pharmacologic doses of leptin resulted in no clinically significant weight loss (1). Recently, amylin, a hormone secreted by the pancreas that also contributes to the regulation of energy homeostasis, was proposed to improve leptin responsiveness in diet-induced obesity (35). A recent study conducted by Amylin Pharmaceuticals, Inc. found that overweight and obese participants lost significantly more weight on the combination of leptin and pramlintide, an analog of amylin, than treatment with either agent alone (64). Of note, the effects appear additive, suggesting that amylin may not improve sensitivity to leptin, and the drop-out rate was high at 32%.

A more promising area of clinical interest is the potential role of leptin treatment in weight loss maintenance. It has been proposed that falling leptin levels due to weight loss activate neuroendocrine mechanisms which may drive patients to regain weight. These mechanisms may include increasing energy intake, by increasing hunger, and decreasing energy expenditure, by decreasing thyroid hormone levels and subsequently slowing metabolism (65). Thus, replacing leptin may restore these neuroendocrine abnormalities and prevent "yo-yo" dieting commonly seen in clinical practice. This is currently being investigated and, if successful, may have major implications in weight loss management.

States of energy deficiency

Leptin deficiency with generalized decrease in adipose tissue mass: Exercise- and diet-induced hypothalamic amenorrhea—Hypothalamic amenorrhea is defined as the cessation of menstrual cycles due to dysfunction of the hypothalamic-pituitary-gonadal axis in the absence of organic disease. It is associated with strenuous exercise, stress, and reduced food intake and includes patients with anorexia nervosa, female athletes with the well-recognized triad (low energy availability with or without disordered eating, amenorrhea/ neuroendocrine dysfunction, and osteoporosis), and normal-weight patients with ovulatory dysfunction.

Following our observational studies showing that women with hypothalamic amenorrhea are hypoleptinemic (42-44), our proof-of-concept study demonstrated that leptin replacement in these women not only normalizes the levels of estrogen, thyroid hormones, and IGF-1 but more importantly restores ovulatory menstruation (46). Leptin also increased markers of bone formation but did not alter bone resorption. Further randomized, placebo-controlled studies are currently elucidating the effects of longer-term recombinant human leptin treatment on neuroendocrine function, immune function, and bone metabolism in these women.

Leptin deficiency with selective decrease in adipose tissue mass: Lipoatrophy —Persons with rare syndromes of congenital lipoatrophy have severe insulin resistance, hypercholesterolemia, and hypertriglyceridemia. Observational studies have shown that these subjects have hypoleptinemia (66,67), and several uncontrolled studies have demonstrated that treatment with recombinant human leptin improves insulin resistance, suppresses hepatic gluconeogenesis, decreases hemoglobin A1c by ~3.5%, improves hyperlipidemia (57,58), and reverses hepatic steatosis (53,54). Studies have also shown that leptin treatment restores menstrual cycles in women with lipoatrophy and features of polycystic ovarian syndrome (68). Currently, leptin is available for congenital lipoatrophy through a FDA-approved, expanded access program by Amylin Pharmaceuticals, Inc.

Although congenital lipoatrophy is rare, Human Immunodeficiency Virus (HIV) lipoatrophy associated with HIV and/or highly-active antiretroviral therapy (HAART) has recently become more prevalent, currently estimated between 15% and 36% of all HIV-infected patients (63). We have shown that these patients, who also have increased cardiovascular risk (69), have relative leptin deficiency (51). Subsequently, we demonstrated in our proof-of-concept trial that treatment with recombinant human leptin in individuals with HAART-induced metabolic syndrome and hypoleptinemia improves insulin resistance, improves hyperlipidemia, and decreases central fat mass within two months (55). An independent study of six months duration confirmed these results (56). Once further clinical trials define the treatment protocols for optimal efficacy and safety, human recombinant leptin alone or in combination with thiazolidinediones, which also improves glucose homeostasis possibly through another adipocyte-secreted hormone adiponectin (70), may be able to serve this growing population.

Conclusion

Leptin regulates energy homeostasis, neuroendocrine function, and metabolism. Leptin deficiency is a clinical syndrome associated with distinct phenotypes, which encompass a very small subset of obesity (i.e. those from leptin-related gene mutations), hypothalamic amenorrhea, and lipoatrophy. Recombinant human leptin is an emerging potential therapy for these leptin-deficient conditions, since in replacement doses it normalizes neuroendocrine and metabolic functions in recent proof-of-concept clinical trials. Randomized, placebo-controlled clinical trials are currently evaluating leptin as a potential treatment for weight loss maintenance, and the development of leptin sensitizers for common obesity is greatly anticipated in the near future. Hopefully, recombinant human leptin will soon find its place in our therapeutic armamentarium.

Summary box (take home points)

- The circulating leptin level mainly reflects the amount of energy stores in adipose tissue and directs the central nervous system in regulating energy homeostasis, neuroendocrine function, and metabolism.
- Leptin deficiency results in neuroendocrine deficits, including infertility, as well as metabolic abnormalities.
- States of complete or severe leptin deficiency include rare cases of congenital leptin deficiency (due to mutations of leptin-related genes) and congenital lipoatrophy (due to lack of fat available to produce leptin).
- States of relative, acquired leptin deficiency include more prevalent conditions such as anorexia nervosa, exercise-induced hypothalamic amenorrhea, and HIV lipoatrophy.
- Recombinant human leptin treatment, in physiologic replacement doses, normalizes neuroendocrine and metabolic abnormalities in states of complete and relative leptin deficiency.

Acknowledgments

Grant support: NIDDK DK58785, DK 79929, DK 81913

Dr. Mantzoros has received grant support from Amgen Inc. through Beth Israel Deaconess Medical Center and has been utilizing leptin provided by Amylin Pharmaceuticals, Inc. for investigator-initiated studies.

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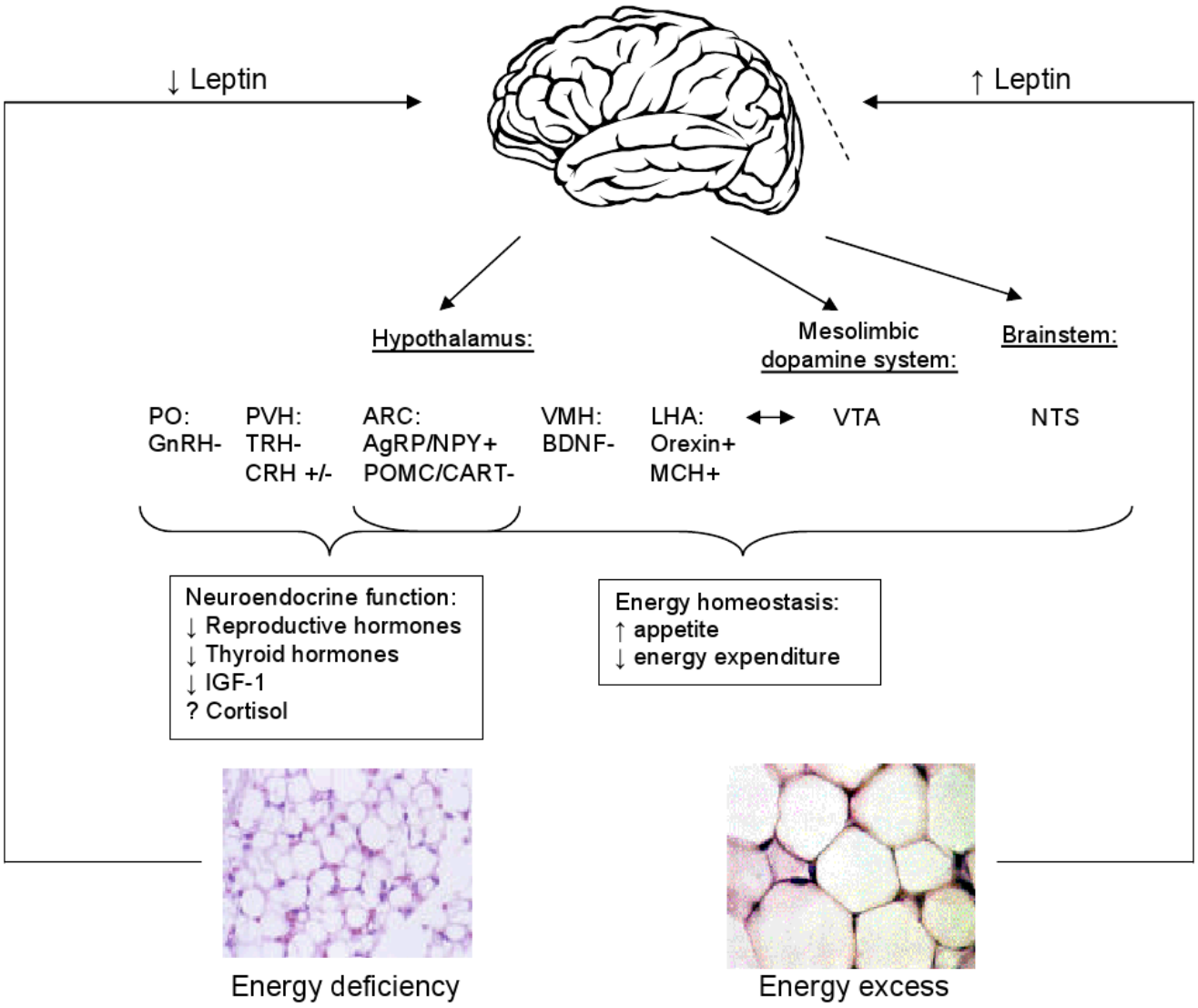

Figure 1.

The central effects of leptin in states of energy excess and deficiency. States of energy excess are associated with hyperleptinemia but the hypothalamus is resistant or tolerant to the effects of increased leptin, represented by the dashed line. Energy deficiency results in hypoleptinemia. As a result, a complex neural circuit comprising of orexigenic and anorexigenic signals is activated to increase food intake (17). There is increased expression of orexigenic neuropeptides: AgRP and NPY in the ARC (23) and orexin and MCH in the LHA. Furthermore, there is decreased expression of anorexigenic neuropeptides: POMC and CART in the ARC (23) and BDNF in the VMH. In addition to neurons that project from the LH to the VTA, leptin also acts at the VTA of the mesolimbic dopamine system to regulate motivation for and reward of feeding. Leptin activation of the NTS of the brainstem also contributes to satiety. In addition, leptin has direct and/or downstream effects on the PVN and PO that are important for neuroendocrine responses to energy deprivation, including decreasing reproductive and thyroid hormones. While leptin only acts indirectly on the GnRH-secreting neurons in the hypothalamus, it can act directly and indirectly on TRH-secreting neurons (17). The effect of leptin on cortisol levels during starvation differs in mice and humans. Unlike

in normal mice (24), leptin administration does not reverse the elevated ACTH levels associated with starvation in humans (7). The mechanism of leptin's effect on the growth hormone axis is unclear.

Abbreviations: AgRP, Agouti-related Protein; NPY, Neuropeptide Y; ARC, arcuate nucleus; MCH, Melanin-concentrating Hormone; LHA, lateral hypothalamic area; POMC, Proopiomelanocortin; CART, Cocaine- and Amphetamine-regulated Transcript; BDNF, Brain-derived Neurotrophic Factor; VMH, ventromedial hypothalamic nucleus; VTA, ventral tegmental area; PVN, paraventricular nucleus; PO, preoptic area; CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; TRH, thyrotropin-releasing hormone; ACTH, adrenocorticotropin.

Table 1
Factors that regulate circulating leptin levels

Factors promoting leptin secretion
* Excess energy stored as fat (obesity)
* Overfeeding
Glucose
Insulin
Glucocorticoids
Estrogens‡
Inflammatory cytokines, including Tumor Necrosis Factor-α and Interleukin-6 (acute effect)
Factors inhibiting leptin secretion
* Low energy states with decreased fat stores (leanness)
* Fasting
Catecholamines and adrenergic agonists
Thyroid hormones
Androgens ‡
Peroxisome Proliferator-activated Receptor-γ (PPARγ) agonists†
Inflammatory cytokines, including Tumor Necrosis Factor-α (prolonged effect)

*Denotes major factor influencing leptin levels.

†Unlike animals, in humans PPARγ agonists decrease leptin gene expression but increase subcutaneous fat mass. Thus, the net effect is null.

‡Women have higher levels than men, even after adjusting for body mass index and the effects of sex steroids, mainly due to different body-fat distribution (9,10).

Table 2

Leptin-deficient states

Syndrome	Estimated prevalence	Associated features
I. Congenital leptin-deficient states		
A. Leptin gene mutations		
Homozygous congenital leptin deficiency	Rare	Early onset morbid obesity, hyperphagia, hypogonadotropic hypogonadism, advanced bone age, hyperinsulinemia, and immune dysfunction. These manifestations are normalized by leptin treatment in replacement doses.
Heterozygous congenital leptin deficiency	Rare	Less severe obesity that may respond to exogenous recombinant human leptin though this remains to be studied in interventional studies (59).
B. Mutations leading to lipoatrophy		
Congenital lipoatrophy	Rare	Lipoatrophy, diabetes, and metabolic syndrome. Metabolic abnormalities improve in response to leptin administration but no randomized, controlled trials have been performed.
II. Acquired leptin-deficient states		
A. Generalized decrease in adipose tissue mass		
Anorexia nervosa	Up to 2.2% lifetime prevalence for women (60)	Profoundly decreased body weight and fat mass, amenorrhea/infertility, osteoporosis with stress fractures, decreased thyroid hormone levels, increased growth hormone levels, and decreased IGF-1 levels.
Exercise-induced hypothalamic amenorrhea and/or ovulatory dysfunction	Amenorrhea has been reported in 60-69% in trained female athletes and ovulatory dysfunction in up to 78% of recreational female athletes (61)	Lower percentage of body fat with or without decreased body weight, amenorrhea/infertility, osteoporosis, and neuroendocrine abnormalities listed above. Abnormalities improved in response to leptin treatment in a proof-of-concept, controlled trial (46). Larger, randomized, placebo-controlled trials are underway.
Non-athletic forms of hypothalamic amenorrhea	7.6% in women aged 15-24, 3.0% in women aged 25-34, and 3.7% in women aged 35-44 years (62)	Relatively normal or slightly decreased body weight but lower percentage of body fat, amenorrhea/infertility, and neuroendocrine abnormalities listed above.
B. Selective decrease in adipose tissue mass		
Acquired severe lipoatrophy and insulin resistance	Rare	Lipoatrophy, insulin resistance, hypercholesterolemia, and hypertriglyceridemia. These metabolic abnormalities improved with leptin replacement in both open-label (56) and randomized, placebo-controlled, cross-over (55) clinical trials.
HIV lipoatrophy	15% - 36% of all HIV-infected patients (63)	

Abbreviations: IGF-1, insulin-like growth factor-1; HIV, Human Immunodeficiency Virus; HAART, highly-active antiretroviral therapy.