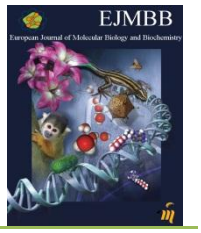
e - ISSN - 2348-2206
Print ISSN - 2348-2192

European Journal of Molecular Biology and Biochemistry

Journal homepage: www.mcmed.us/journal/ejmbb



LEPTIN AND ITS EMERGING CLINICAL APPLICATIONS IN OBESITY AND HIV

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Article Info

Received 29/07/2016
Revised 16/08/2016
Accepted 19/08/2016

Keywords :- Leptin, Obesity, Human physiology.

ABSTRACT

Leptin is a complex adiposity signal that kick started the surge of obesity research and has provided a new word 'diabeticity which means people suffering from obesity and diabetics).Probably the biggest breakthrough for the study of appetite regulation came in 1994 when the molecular geneticist Jeffrey Friedman discovered the adiposity signal leptin. Using the ob/ob mice which were thought to lack a satiety signal, Friedman and colleagues found 'ob' to code for a gene which they called leptin, after the Greek word 'leptos' meaning thin. Mice deficient in this gene are morbidly obese and this obesity can be reversed by giving the mice leptin. The leptin receptor was subsequently found in 1995 and is a member of the cytokine receptor family. Leptin has 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 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. Leptin therapy in human recombinant form has recently been used in HIV-associated lipodystrophy syndrome on experimental basis in some small short-term clinical trials

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INTRODUCTION

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. 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 like many other hormones, leptin is secreted in a pulsatile fashion and has a significant diurnal variation with higher levels in the evening and early morning hours. Circulating leptin levels reflect primarily the amount of energy stored in fat and secondarily acute changes in caloric intake (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. 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 neuro-endocrine function 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 and Phosphatidylinositol 3-Kinase (PI3K), which is important for regulation of both food intake and glucose homeostasis 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

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 and are either resistant or tolerant to its weight-reducing effects 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) and c) alterations in the transport of leptin across the blood-brain barrier. 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 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.

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. There is increased expression of orexigenic neuropeptides: AgRP and NPY in the ARC and orexin and MCH in the LHA. Furthermore, there is decreased expression of anorexigenic neuropeptides: POMC and CART in the ARC 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. The effect of leptin on cortisol levels during starvation differs in mice and humans. Unlike in normal mice leptin administration does not reverse the elevated ACTH levels associated with starvation in humans. 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;

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) 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) 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 and activates brown adipose tissue thermogenesis but these effects have not been confirmed in humans

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 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 and normalizes body weight 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 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 triggering the neuroendocrine response to acute energy deprivation 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 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. Neuroendocrine abnormalities when starvation-induced falls in leptin levels reaches 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 It is then ascertained whether there is a minimum leptin threshold to allow reproduction and to maintain other neuroendocrine processes. When induced leptin deficiency has been induced in normal-weight women, who have higher baseline leptin levels, leptin levels fell to an average of 2.8 ng/mL Only modest changes in LH pulsatility were observed. .These 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 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 It is hypothesized that long-standing hypoleptinemia leads to neuroendocrine dysfunction with subsequent anovulation and osteoporosis. A proof-of-concept trial of leptin treatment in replacement doses in women with hypothalamic amenorrhea has been done and it was found that it improves or fully normalizes the gonadal, thyroid, and, to a lesser degree, growth hormone axes as well as bone markers

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 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 lipoprotein cholesterol, and triglycerides 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 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 Indeed, transplantation of adipose tissue which produces leptin, and administration of exogenous leptin 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 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.

Physiologic variations

There could be physiological variations of leptin too as follows:

Leptin levels vary exponentially, not linearly; with fat mass Leptin levels in blood are higher between midnight and early morning, perhaps suppressing appetite during the night. The diurnal rhythm of blood leptin levels may be modified by meal-timing.

In specific conditions

In humans, many instances are seen where leptin dissociates from the strict role of communicating nutritional status between body and brain and no longer correlates with body fat levels:

- Leptin level is decreased after short-term fasting (24–72 hours), even when changes in fat mass are not observed.
- Leptin plays a critical role in the adaptive response to starvation.
- In obese patients with obstructive sleep apnea, leptin level is increased, but decreased after the administration of continuous positive airway pressure. In non-obese individuals, however, restful sleep (i.e., 8–12 hours of unbroken sleep) can increase leptin to normal levels.
- Serum level of leptin is reduced by sleep deprivation.
- Leptin level is increased by perceived emotional stress.
- Leptin level is decreased by increases in testosterone levels and increased by increases in estrogen levels.
- Leptin level is chronically reduced by physical exercise training.
- Leptin release is increased by dexamethasone.
- Leptin level is increased by insulin.
- Leptin levels are paradoxically increased in obesity

CLINICAL APPLICATIONS IN OBESITY

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). Furthermore, these patients have distinct neuroendocrine abnormalities, including hypogonadotropic hypogonadism with failure to reach puberty, which improve with leptin replacement 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 co-administration with presumed leptin sensitizers. An early trial with high, pharmacologic doses of leptin resulted in no clinically significant weight loss 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 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 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 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 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 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 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 and reverses hepatic steatosis Studies have also shown that leptin treatment restores menstrual cycles in women with lipoatrophy and features of polycystic ovarian syndrome Currently, leptin is available for congenital lipoatrophy through a FDA-approved, expanded access program by Amylin Pharmaceuticals, Inc.

LEPTIN AND HIV

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 It has been shown that these patients, who also have increased cardiovascular risk have relative leptin deficiency 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 (An independent study of six months duration confirmed these results). 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 may be able to serve this growing population.

Several small open-label clinical trials have demonstrated that patients with severe leptin deficiency from congenital and non–HIV-related acquired generalized lipodystrophy could be benefited by the physiological replacement doses of leptin (0.04–0.08 mg/kg s.c. daily) in terms of improvements in insulin sensitivity, glucose tolerance, levels of fasting glucose, and HbA1c, hypertriglyceridemia, transaminitis, and changes in body composition (weight loss with decreased adipose tissue and lean mass), and thus the need for insulin or oral hypoglycemic agents could be lessened with the help of leptin.

Similarly, trial-based recombinant human leptin therapy has been tried in hypoleptinemic patients with HIV-associated lipodystrophy, and leptin was well tolerated with marked improvement in fasting insulin levels, insulin resistance, high density lipoprotein (HDL) cholesterol, and truncal obesity. Furthermore, the improvements in insulin resistance reported in patients with HALS treated with metreleptin provide an advantage over GH replacement therapy as GH treatment is associated with glucose intolerance. But only those patients who have an absolute leptin deficiency (usually <3 ng/ml in men and <4 ng/ml in women) would enjoy the dramatic treatment benefit with leptin.

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[‡]

Factors promoting leptin secretion
Inflammatory cytokines, including Tumor Necrosis Factor-α (prolonged effect)

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
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	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	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 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	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 and randomized, placebo-controlled, cross-over clinical trials.
HIV lipoatrophy	15% - 36% of all HIV-infected patients	

Figure 1. Effects by acting on the brain

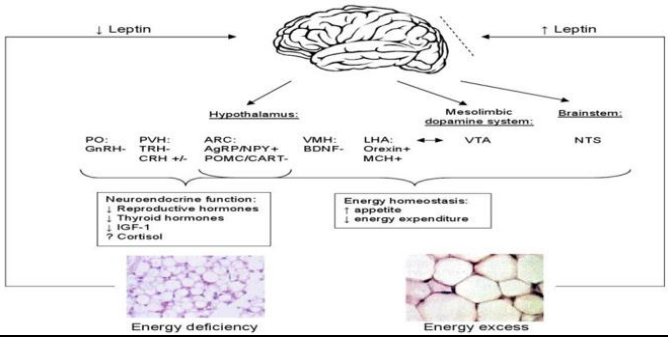
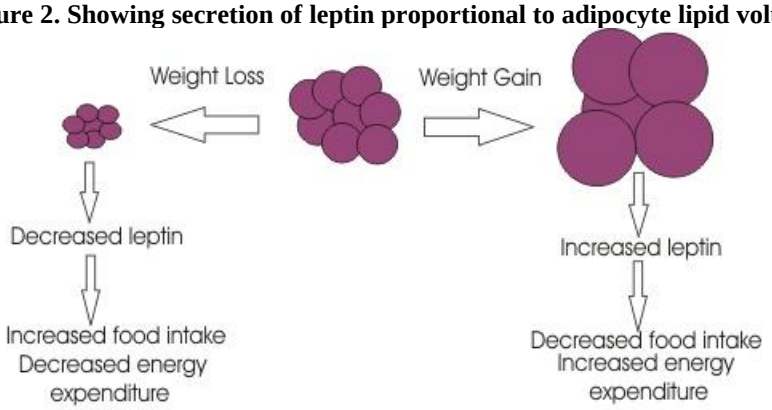


Figure 2. Showing secretion of leptin proportional to adipocyte lipid volume



CONCLUSIONS

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. Recombinant human leptin, still an investigational product, is not yet available commercially in the market for the patients suffering from HIV-associated lipodystrophy and metabolic complications. The scope for its therapeutic utility in HIV is grossly suffering from lack of longer and larger well-furnished clinical trials from many countries worldwide. Leptin levels in circulation of HIV patients under various other treatments are largely unknown, which has become a major limitation of leptin therapy.

Take home messages

- 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.

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