

Benefits of leptin therapy in HIV patients

Uma Sinha, Keshab Sinharay, Nilanjan Sengupta¹, Prasanta Mukhopadhyay

Departments of Medicine and ¹Endocrinology, Nilratan Sircar Medical College, Kolkata, India

ABSTRACT

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. It has shown its beneficial effects only in hypoleptinemic HIV-infected patients by causing definite improvement in their insulin sensitivity, glucose tolerance, lipid status, and truncal obesity. Leptin prevents lipotoxicity and activates insulin signaling pathways through several postulated mechanisms. Central leptin insufficiency with peripheral hyperleptinemia has come out to be a significant contributor to the development of obesity and metabolic syndrome. In this article, we will review the basis of leptin therapy in HIV patients, with its promises. However, further larger clinical trials are needed to prove its long-term efficacy in the control of metabolic complications related to HIV therapy.

Key words: Antiretroviral therapy, HIV, leptin, lipodystrophy, metabolic syndrome

INTRODUCTION

HIV-infected patients, especially on a long duration of antiretroviral therapy (ART), are now facing newer challenges in terms of developing pathological aberrations of fat metabolism and redistribution. The two terms, HIV-associated adipose redistribution syndrome (HARS) and HIV-associated lipodystrophy syndrome (HALS), possibly have the same connotation to describe an acquired (? iatrogenic) state of partial derangement in fat accumulation along with significant metabolic risks.^[1] Lipodystrophy (changes in fat distribution) is a clinical diagnosis and mostly subjective as standardized diagnostic criteria have not yet been defined. That is why, the exact prevalence rate of HALS has not been precisely quantified since it was first reported 13 years ago.^[2] HIV-associated lipodystrophy involves fat redistribution (lipodystrophy), fat loss from the face, buttocks, and extremities (lipoatrophy), and mixed fat disturbances

(lipodystrophy and lipoatrophy). They often have insulin resistance, type 2 diabetes, and elevated plasma lipid concentrations. The combination of hyperlipidemia, insulin resistance, and visceral fat accumulation resembles the cluster of abnormalities described in the “metabolic syndrome” associated with increased cardiovascular risk. HALS harbors endothelial dysfunction and accelerated atherosclerosis.^[3] HALS closely mimics obesity. Skeletal muscle leptin resistance can potentially contribute to muscular fatty acid accumulation in common human obesity, simulating the muscle steatosis found in lipodystrophy patients. Visceral fat accumulation in obesity also resembles lipodystrophy in HIV.

Hormone therapies in the treatment of HALS have been explored recently. Anabolic steroids, growth hormone (GH), growth hormone releasing hormone (GHRH), recombinant human leptin, and adiponectin (synthetic form unavailable) are the candidates for hormone therapy. For the last 15 years, much has been known about leptin biology. However, it is only recently that the leptin–hypothalamic axis has newly been explored which regulates insulin and glucose metabolism independent of its effect on adiposity. This article affords a comprehensive review of leptin therapy, a new strategy now in clinical trials, and its beneficial role in HIV patients in correction of metabolic complications related to HALS.

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Corresponding Author: Dr. Uma Sinha, Department of Medicine, Nilratan Sircar Medical College and Hospital, 138 A. J. C. Bose Road, 19/1C, Sil Lane, Entally, Kolkata – 15, West Bengal, India. E-mail: usinha97@gmail.com

WHAT IS LEPTIN?

Leptin is a 167-amino acid product of human leptin gene on chromosome no. 7, originally identified in 1995 through positional cloning of *ob/ob* mice, a mouse model of obesity discovered serendipitously at Jackson laboratories where these mice were found having complete leptin deficiency causing hyperphagia, severe obesity, diabetes, infertility, and other neuroendocrine abnormalities.^[4-7] This discovery led to further research works that revealed important role of leptin in energy homeostasis, weight regulation, immunity, and neuroendocrine function.

Leptin is secreted in a pulsatile fashion by white adipose tissue and is also found in circulation and cerebrospinal fluid.^[8] Its circulatory levels positively correlate with the amount of body fat and have significant diurnal variation, with higher levels in the evening and early morning hours. Leptin mediates its effects by binding to specific leptin receptors (ObRs) expressed in brain and peripheral tissues. The ObRa isoform (short leptin receptor isoform) is found to have an important role in leptin transport across the blood–brain barrier, while the ObRb isoform (long leptin receptor isoform), also known as LepR-l or LepRb, is thought to mediate signal transduction with its strong expression in hypothalamus. Leptin in brain (both in parenchyma and cerebrovascular fluid) is derived from peripheral circulation and local synthesis. Short isoform of leptin receptors on vascular endothelium and epithelium of choroid plexus transports leptin across the blood–brain barrier.^[9] It has been seen that both hypo- and hyperleptinemia are associated with reduced leptin entry into the brain.

LEPTIN AND METABOLIC SYNDROME – CLINICAL UTILITY

The discovery of leptin has advanced our understanding of metabolic diseases. Its identification has revealed a new neuroendocrine system regulating body weight. Complete leptin deficiency from mutations in leptin gene, as found in some rare genetic conditions, presents with infantile morbid obesity and associated endocrinal dysfunction including insulin resistance and hypogonadotropic hypogonadism.^[10,11] Severe lipodystrophy, both genetic and acquired (as in HALS), is another hypoleptinemic state characterized by adipose tissue loss, hypertriglyceridemia, severe insulin resistance, and even overt diabetes mellitus. Recombinant human leptin replacement therapy at physiologic replacement dose in both the situations described above has improved hormonal abnormalities, glycemic control, and dyslipidemia.^[12-14] In the management of HIV lipodystrophy and metabolic syndrome, recombinant human leptin (metreleptin) has recently

been extensively studied in the context of many open-label, clinical trials. Since no approved effective treatment exists for alleviating the major health problems associated with HALS, leptin therapy, in this context, stands out to be essentially promising which will be reviewed next.

Though most of the therapeutic trials with leptin started focusing primarily on obesity, the majority of obese subjects were proved to be leptin resistant with high serum leptin levels, which establishes that obesity is the result of hormone resistance.^[15] Leptin treatment resulted in weight loss only in a subset of obese patients, and was therefore not found to be of much help in treating obesity in general. Again, there is substantial variability of leptin levels at a given body mass index or percent fat and approximately 10–15% of obese subjects have endogenous levels of leptin that are indistinguishable from lean patients.^[16]

“Leptin insufficiency syndrome,” a concept promulgated a few years ago based mainly on strong experimental support has replaced “leptin resistance” as causal in the etiology of diabetes and obesity.^[17] The leptin insufficiency syndrome manifests due to hypoleptinemia and/or decreased leptin delivery to the hypothalamus by transport restrictions across blood–brain barrier in obese, hyperleptinemic state. Leptin receptor downregulation at the blood–brain interphase and increased binding of leptin to C-reactive protein (CRP) in peripheral circulation are the two important endogenous defense mechanisms that operate simultaneously in hyperleptinemic state to restrict leptin supply to the hypothalamus.

Leptin–hypothalamic axis has a crucial role in regulating pancreatic insulin secretion and glucose metabolism independent of its effect on adiposity. Newer experiments revealed multiple novel mechanisms whereby central leptin insufficiency and peripheral hyperleptinemia concomitantly participate in the causation of metabolic syndrome. Acute inhibition of insulin secretion by central administration of leptin has recently been reported. Enhanced leptin signaling in selected hypothalamic sites such as the medial preoptic area (MPOA), paraventricular hypothalamus (PVN), ventromedial hypothalamus (VMH), or arcuate nucleus (ARC) experimentally corrects hyperinsulinemia and averts the development of insulin resistance.^[18] Several tract tracing studies including those with microinjection of leptin transgene in hypothalamic sites imply that hypothalamus sends efferent insulin inhibiting signals to pancreas by hypothalamic neuropeptide Y NPY-ergic system bypassing the dorsal vagal neurons.^[19] Recent studies also detected insulin-independent role of leptin in hypothalamic glucose regulation possibly by accelerating glucose metabolism in brown adipose tissue, liver, skeletal muscles, and fat cells.^[20]

Various attempts to increase leptin delivery to hypothalamus and extrahypothalamic sites with daily injection or continuous infusion, both systemically and centrally (intracerebro-ventricular or intrathecal), in pharmacological doses over short periods have been quite satisfactory in animal models. Final modality of leptin delivery is central leptin gene therapy.^[21] This one-time neurotherapy with its durable antidiabetic efficacy offers a potential substitution for insulin therapy in metabolic syndrome in near future.

LEPTIN IN HIV DISEASE

It is evident that only hypoleptinemic HIV-infected patients are the actual beneficiaries and are selected for recombinant leptin treatment trials to combat metabolic syndrome. As serum leptin level varies in general population depending on age, sex, feeding status, body habitus, and circadian cycle, hypoleptinemia is usually considered when serum leptin level is <3 ng/ml in men and <4 ng/ml in women. Fasting leptin levels have been shown to correlate with total body fat concentrations in HIV-infected patients.^[22] Nagy *et al.* found that leptin levels were lowest in HIV patients exhibiting lipoatrophy, intermediate in those with mixed lipodystrophy or normal body habitus, and highest in those with lipohypertrophy.^[23] These findings suggest a reduction in leptin synthesis in those having lipoatrophy with reduced subcutaneous adipose tissue and excess circulating levels of leptin might be due to leptin resistance in those with visceral adipose tissue hypertrophy.^[24] This leptin-resistant state might also be related to metabolic syndrome and insulin resistance seen in HIV patients with lipohypertrophy. Untreated HIV infection is a progressive cellular immunodeficiency state with anorexia, weight loss, malnutrition, and opportunistic infections.^[25] Though leptin was shown to induce anorexia and augment T helper cell (Th1) population, most of the patients with HIV-associated wasting were found to have decreased serum leptin levels and that low value was proportional to the degree of fat loss.^[26]

Leptin levels in HIV patients have also been studied in the absence of antiretrovirals and irrespective of wasting. In symptomatic AIDS patients, leptin levels are shown to be depressed irrespective of wasting, possibly due to downregulation of leptin secretion by persistent inflammation, especially in the presence of secondary infections. A study on ART-naïve HIV-infected Nigerians in 2008 has shown that serum leptin levels were significantly lower in wasted HIV-infected patients compared to normal weight HIV patients from Nigeria, and leptin levels were depressed during symptomatic HIV/AIDS independent of the effect of body mass index (BMI).^[27] Grunfeld and coworkers also reported a similar BMI-independent suppression of serum leptin levels by secondary infection in

AIDS patients, contrary to the known fact that circulatory leptin level increases during sepsis and inflammation in response to bacterial endotoxins and cytokines [tumor necrosis factor- α (TNF- α)].^[28] Exhaustion of leptin production by chronic tubercular inflammation was suggested by Van Crevel and colleagues as the cause of hypoleptinemia in HIV-negative tuberculosis patients irrespective of the effect of BMI.^[29] These researchers also reported insignificant difference in leptin levels between asymptomatic AIDS patients without wasting and normal HIV-negative individuals of similar BMI.

Leptin levels have been shown to be higher in general female population than males for any given measure of adipose mass.^[30] Leptin levels also rise more rapidly in women than men with increase in proportion of body fat.^[31] In contrast, the Nigerian study revealed lower level of leptin among female HIV patients as compared to male patients.^[27] Reversal of this sex difference may contribute to more wasting in female AIDS patients as most of the HIV wasted patients were females. Most studies in humans and animal models also found a positive correlation between the number of CD4 T cells and leptin levels in healthy controls, but this correlation was blunted in HIV patients.

HIV LIPODYSTROPHY

The morphologic and metabolic changes associated with ART have led to the development of HALS characterized by peripheral lipoatrophy (fat loss in face, arms, legs, buttocks), localized fat accumulation, hyperlipidemia, insulin resistance, and hyperglycemia. Hepatic steatosis may also occur, but acanthosis nigricans seems extremely rare in contrast to congenital lipodystrophy. The prevalence of HALS in patients taking ART has been reported to be up to 80% with increased cardiovascular risks. HALS is thought to be multifactorial with complex interactions of drugs, viral and host-related factors. Although ART with protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) are said to be the most compelling risk factors, gender, altered adipose gene expression, altered adipokines, mitochondrial toxicity, HIV-1 associated protein, and genetic polymorphism are some of the important pathophysiologic mechanisms underlying its development.^[32-36] Cross-sectional studies have shown low levels of leptin and adiponectin in HALS, which are closely and inversely correlated with dyslipidemia and insulin resistance.^[37] Animal experiments also demonstrated that combined administration of both leptin and adiponectin fully normalized insulin sensitivity in hypoleptinemic and hypoadiponectinemic lipoatrophic mice.^[38]

Walker and Brinkman have shown a relation between

peripheral lipotrophy and mitochondrial toxicity in HIV patients.^[39] Mitochondrial toxicity occurs due to inhibition of mitochondrial DNA polymerase- γ by several antiretrovirals with variable affinity for the enzyme.^[40] *In vitro* studies using HepG2 human hepatoma cells showed the worst effects with zalcitabine, didanosine, and stavudine in reducing order causing marked hyperlactatemia and multiorgan toxicities involving liver, pancreas, peripheral nerves, and skeletal muscles.^[41-43]

Altered levels of adipokines and proinflammatory cytokines (as demonstrated in *in vitro* murine and human adipocyte cell lines and *in vivo* studies with NRTIs and PIs) may be responsible for insulin resistance seen in lipodystrophy.^[44,45] PIs have been found to cause reduction in lipid accumulation in adipocytes, increase in adipocyte apoptosis, inhibition of insulin-stimulated glucose uptake [inhibiting glucose transporter type 4 (GLUT4)], induction of interleukin (IL)-6, TNF- α , reduction in gene expression, and secretion of adiponectin, all thereby inducing insulin resistance.^[46,47]

Lipotrophic fat from HALS patients demonstrated reduced adipogenic transcription factors like sterol regulatory element-binding protein 1c (SREBP-1c), CAAT enhancer binding protein- α (C/EBP- α), and peroxisome proliferator activated receptor- γ (PPAR- γ) – all involved in adipocyte differentiation along with reduced mRNA expression of adiponectin and leptin.^[48] Some studies have shown similar changes in HIV patients who were not being treated with ART, suggesting that HIV may have a direct role in the mechanism of lipodystrophy. Proteasome dysfunction has been implicated in the pathogenesis of HALS. PIs have also been found to inhibit proteasome chemotryptic activity, leading to endoplasmic reticulum stress response to misfolded proteins.^[49]

HOW DOES LEPTIN BENEFIT HIV LIPODYSTROPHY?

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.^[50-52] 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.

Riddle *et al.* in the *in vitro* animal (ritonavir-treated mice) study with leptin showed reversal of raised total cholesterol, reduction in ritonavir-induced interscapular fat, and improved hepatic steatosis. Lee *et al.* observed similar beneficial effect of recombinant human leptin therapy (0.04 mg/kg s.c. daily for 2 months) in 7 men with HALS, low leptin, and hypertriglyceridemia.^[53] Beneficial response was also reported by Mulligan *et al.* with recombinant methionyl human leptin for 6 months (0.01 mg/kg s.c. twice daily for 3 months, followed by 0.03 mg/kg s.c. twice daily for 6 months) among eight hypoleptinemic male patients with HALS.^[54] Leptin treatment was associated with around 32% decrease in visceral fat, improvement in insulin sensitivity, fasting insulin and glucose levels, and HDL cholesterol, and 15–20% decrease in low density lipoprotein (LDL) cholesterol, with considerable decrease in triglyceride, whole body lipolysis, and free fatty acid levels.

It has been proposed that leptin may improve insulin resistance through several mechanisms such as: (1) activating insulin signaling pathways including skeletal muscle phosphatidylinositol 3-kinase and AMP-activated protein kinase (AMPK); (2) preventing “lipotoxicity”: decreasing intrahepatic and intramyocellular fat by activating fatty acid oxidation in skeletal muscles; (3) decreasing caloric intake; and (4) decreasing body weight and fat mass.^[55] Mulligan and Khatami *et al.* also suggested that leptin can improve hepatic insulin sensitivity possibly irrespective of its effect on peripheral insulin sensitivity and independent of reduction in visceral adipose tissue. In spite of the above-mentioned small observation-based hypotheses, the precise mechanisms underlying leptin’s beneficial role in HALS is yet to be established.

LEPTIN VERSUS OTHER AVAILABLE TREATMENT MODALITIES IN HALS

Leptin as a monotherapy or an insulin-sparing agent in controlling metabolic components of HALS is still a remote theoretical possibility. In spite of its successful placebo-controlled trials, leptin therapy has not yet been compared head-to-head with any of the many other available treatment modalities like metformin, thiazolidinediones

(TZDs) – rosiglitazone, pioglitazone, GH, or synthetic GHRH (sermorelin, tesamorelin).^[56-58] It is also not known whether a combination of leptin with any of the above-mentioned drugs can work even better than a single agent. Just like leptin, metformin and TZDs (which also increase adiponectin level) improve insulin sensitivity, but GH or synthetic GHRH is diabetogenic. Neither GH nor GHRH analogs are approved by FDA for the treatment of HALS. As individuals with HALS tend to be GH deficient, GH replacement can be a promising treatment option in this patient population. As leptin acts independent of the GH and insulin-like growth factor-1 (IGF-1) system, a combination therapy with leptin and GH or GHRH analogs could potentially have additive metabolic benefits without adversely affecting glucose intolerance.^[59,60] Adiponectin, a 244 amino acid protein, is another endogenous insulin sensitizer that reduces gluconeogenesis primarily by stimulating adiponectin receptor 2 (ADIPOR2) and activation of AMPK phosphorylation. It also increases fatty acid oxidation in muscle via ADIPOR1 whose stimulation in the hypothalamus might influence insulin and leptin signaling that promotes increased insulin sensitivity and reduced food intake.^[61,62] Adiponectin levels are also low in patients with HALS, and hypo adiponectinemia is associated with insulin resistance, hypertriglyceridemia, and adipose tissue redistribution in HIV-infected patients on antiretroviral medications. Although leptin or adiponectin alone improves insulin resistance in mouse models of lipodystrophy, the combined administration of both hormones fully normalizes insulin sensitivity in animal models. But no synthetic form of adiponectin is yet available for treatment in human beings. Adiponectin as well as its receptors ADIPOR1 and ADIPOR2 are attractive future targets for drug development in HALS.

LIMITATIONS OF LEPTIN THERAPY: QUESTIONS UNANSWERED?

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 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. Many questions regarding leptin replacement therapy have thus remained yet unanswered. Controversies and queries remain about the optimal dose, route of administration (peripheral vs. central leptin therapy), number of daily administrations, duration of therapy, need to follow-up the circulating leptin

level, scope for combination therapy, possible adverse effects after long-term usage, and last but not the least, expected benefit in patients with relatively higher leptin levels. Naturally, additional information are needed further for the basic clarity of this unclear practical scenario.

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