

Leptin in Relation to the Lipodystrophy-Associated Metabolic Syndrome

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Leptin, an adipocyte-secreted hormone, regulates energy homeostasis as well as reproductive, neuroendocrine, immune and metabolic functions. Subjects with decreased amounts of fat in their adipose tissue, i.e., lipoatrophy, have low leptin levels. In the context of open-label, uncontrolled studies leptin administration, in physiological replacement doses, has been shown to have metabolically salutary effects in the rare patients with the syndrome of congenital lipodystrophy accompanied by leptin deficiency. Much more patients with lipodystrophy suffer from lipodystrophy and the metabolic syndrome associated with the use of highly active antiretroviral therapy. In this so called highly active antiretroviral therapy (HAART)-associated lipodystrophy and metabolic syndrome, patients demonstrate fat maldistribution with dyslipidemia, insulin resistance, and other metabolic complications. Leptin administration has been shown to decrease central fat mass and to improve fasting insulin/glucose levels and insulin sensitivity in human immunodeficiency virus-infected hypoleptinemic patients with HAART induced lipodystrophy and the metabolic syndrome. By contrast, the results of leptin treatment in leptin replete or hyperleptinemic obese individuals with glucose intolerance and diabetes mellitus have been minimal or null, presumably due to leptin tolerance or resistance that impairs leptin action. In this review, we present the emerging clinical applications and potential therapeutic uses of leptin in humans with lipodystrophy and the metabolic syndrome.

Keywords: Antiretroviral therapy, highly active; Glucose metabolism; HIV; Leptin; Lipodystrophy

INTRODUCTION

Leptin plays a crucial role in the regulation of energy homeostasis, insulin action and lipid metabolism [1]. As a hormone secreted by adipocytes in quantities which mainly reflect fat mass and secondarily acute energy deprivation as well as other factors, leptin serves as an important signal of body energy stores. Leptin deficiency in mice and/or in humans is associated with neuroendocrine and metabolic [1,2] abnormalities [3,4], including insulin resistance and diabetes. All these abnormalities are corrected by exogenous leptin administration [1,2,5,6], suggesting that leptin plays a role in glucose homeostasis and possibly in the pathogenesis of other obesity-related

metabolic complications.

Interestingly, leptin-induced normalization of hyperglycemia and hyperinsulinemia in *ob/ob* mice is observed even before any alteration in body weight takes place, suggesting that leptin's effects on glucose homeostasis are, in part, independent of its weight-reducing effects [5,6]. Similar to *ob/ob* mice, other mouse models of obesity and leptin resistance or tolerance [7-9] have abnormalities reminiscent of leptin deficiency due to subnormal leptin action [7,10,11]. The importance of leptin is also evident in human physiology [3,4,7-18]. Leptin administration has been demonstrated to successfully treat obesity and its complications in individuals with congenital leptin deficiency, and thus leptin is available on a compassionate basis

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for these patients [5-7].

Recent evidence has suggested that leptin is effective in correcting neuroendocrine abnormalities and insulin resistance in patients with human immunodeficiency virus (HIV)-associated lipodystrophy [11-13,19] as well as congenital lipodystrophy [8-10].

CONGENITAL LIPODYSTROPHY

Lipodystrophy is a group of clinically heterogeneous acquired or inherited disorders characterized by complete or partial absence of subcutaneous fat that can occur in conjunction with the pathological accumulation of adipose tissue in other distinct regions of the body [10,20]. Though inherited lipodystrophies are exceedingly rare, acquired lipodystrophies (especially resulting HIV infection and its treatment) are more common. Interestingly, lipodystrophic patients exhibit insulin resistance, hyperglycemia, dyslipidemia, and hepatic steatosis [21]. The severity of these metabolic abnormalities typically correlates with the degree of adipose tissue loss (see below).

In humans, congenital lipodystrophy syndromes are rare; there have been less than a few hundred cases described in the literature and it is expected that there are less than 1,000 people suffering from this condition in North America [22,23]. The lipodystrophies are associated with partial or total leptin deficiency [24]. Leptin replacement dramatically improved dyslipidemia and insulin sensitivity and reduced HbA1c levels and intrahepatic fat content in various types of human lipodystrophy [25-32]. Fasting blood glucose and HbA1c levels decreased markedly even in patients who are not fully responsive to other antihyperglycemic medications or high doses of insulin [28]. Hyperglycemic-euglycemic clamps in three patients with lipotrophic diabetes have shown remarkable improvement in insulin sensitivity after leptin treatment [26]. This beneficial effect was seen with respect to both hepatic insulin sensitivity and whole-body insulin sensitivity. In conjunction with this, there was an 86% reduction in intrahepatic triglyceride content and a 33% reduction in muscle triglyceride content [26]. In a recently published open-label, uncontrolled prospective study in 48 patients with various acquired and inherited forms of lipodystrophy [30], leptin replacement effectively decreased serum triacylglycerol concentrations by 59% and HbA1c levels by 1.5 percentage-points within 1 year. The benefits of leptin replacement were sustained for up to 8 years of follow-up in the context of open label studies [30]. Oral

and Chan [32] collected several small, non-randomized, open-label trials in a composite study reporting on a total of more than 100 patients with severe lipodystrophy. These studies have found improvement in several metabolic parameters, including glycemic control, insulin sensitivity, plasma triglycerides, caloric intake, liver volume and lipid content, and intramyocellular lipid content, with leptin treatment [33]. In summary, all these studies have demonstrated that leptin could be an effective regimen that can be used to overcome the metabolic abnormalities characteristic of lipodystrophy, and have provided the rationale for metreleptin treatment in these patients. However, there are several issues that deserve serious consideration. Published reports are all open-label and uncontrolled; thus, a placebo-controlled trial is warranted to fully determine efficacy and safety. Given the small number of patients and the lack of firm diagnostic criteria are hurdles to perform a trial of parallel design, a cross over design should be more appropriate in this case [23]. Future trials should also allow a comparison with the current standard of care. Importantly, the side effect profile of leptin has not yet been fully characterized; although deterioration of renal function, lymphomas, and the development of antibodies to leptin have all been reported [32,34,35], it remains unknown whether these side effects are due to therapy versus the disease process *per se*. The optimal treatment regimen including dose and frequency has also not been determined. Nevertheless, metreleptin is available from the manufacturer for the treatment of leptin as part of the expanded access program, and an application for approval for this indication is under review by the U.S. Food and Drug Administration (FDA).

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)-ASSOCIATED LIPODYSTROPHY

More than 40 million people worldwide are currently living with HIV, including more than eight million individuals in Southeast Asia [36]. The widespread use of HAART has dramatically altered both the morbidity, mortality and long term outcomes but the prolonged life expectancy of patients receiving HAART, has also been associated with a dramatic increase of the incidence and prevalence of adverse effects and toxicity [37]. A frequently observed adverse effect of HAART involves metabolic abnormalities associated with lipodystrophy [38], i.e., the HAART-associated lipodystrophy syndrome (HALS).

HALS

Abnormal fat distribution, called the HALS, is associated with dyslipidemia, insulin resistance, and other metabolic complications [38,39]. The prevalence of these adverse effects depends on the HAART regimen and increases with use over time [40,41]. Patients may experience lipoatrophy, lipohypertrophy, or clinical features of both [42]. Lipoatrophy occurs in approximately 20% of patients on HAART in our experience and is typically characterized by a loss of subcutaneous adipose tissue in the face and extremities [37,41]. Other patients with HAART induced metabolic syndrome may have lipoatrophy in the extremities in the context of stable or increased visceral adipose tissue and a normal or even increased waist:hip ratio [43]. At the other end of the spectrum, lipohypertrophy is characterized by generalized or central fat accumulation [44]. The majority of the patients on HAART display a combination of lipoatrophy and lipohypertrophy, called mixed lipodystrophy, which is also closely associated with metabolic abnormalities [45].

The pathogenesis of HAART associated lipodystrophy and the metabolic syndrome is thought to be multifactorial [40]. This process involves impairment of both adipocyte differentiation and ectopic fat deposition either intra-abdominally or in areas other than the adipose tissue, such as liver, muscle, etc. [46]. This is associated with increased lipolysis [47], which in turn creates a lipotoxic environment with elevated serum free fatty acids (FFAs) and subsequent intracellular accumulation of FFAs. Ectopic deposition of FFAs in visceral adipose tissue, skeletal muscle, liver, and pancreas exacerbates dyslipidemia and insulin resistance [48] which eventually leads to metabolic syndrome and diabetes in susceptible individuals [49,50].

Among HAART, protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) have been shown to affect insulin resistance and glucose metabolism by seemingly different pathways [51]. Protease inhibitors have been suggested to stimulate lipolysis while inhibiting adipocyte differentiation and lipogenesis by interfering with peroxisome proliferator-activated receptor-gamma (PPAR- γ) [40]. NRTIs may cause lipoatrophy secondary to mitochondrial injury within adipocytes [40], and their toxic metabolic effects appear synergistic with protease inhibitors [52]. Non-nucleoside reverse transcriptase inhibitors have also been implicated in this disease process; however, the effects of this drug class are still being investigated [53]. Viral proteins and mechanisms related to HIV-1

infection have also been suggested to influence adipose tissue distribution directly [54].

THE ROLE OF ADIPOKINES IN HALS

We and others have shown that levels of adipokines leptin and adiponectin are decreased in patients with HALS, suggesting that they may play a fundamental role in the metabolic abnormalities observed in lipodystrophy [44,55,56], replacement of adipokines could be a physiological approach to the therapy of the syndrome and may provide considerable therapeutic value for HALS patients.

Adiponectin

Levels of the beneficial, adipocyte secreted hormone-insulin sensitizer adiponectin are low in obesity, diabetes, and subsets of individuals with lipodystrophy accompanied by central lipohypertrophy, including many patients with HALS [24,57-59]. Low adiponectin levels are associated with insulin resistance, hypertriglyceridemia, and adipose tissue redistribution in HIV patients receiving HAART [55]. Although adiponectin is not currently available for treatment in humans, studies in mice have demonstrated improved insulin sensitivity, dyslipidemia, and weight loss [17]. Further research is needed to determine the potential for adiponectin replacement, or the use of adiponectin receptor analogues, in humans and the extent of its effects, specifically in HALS. In the meantime, we have shown that medications that increase adiponectin levels, such as pioglitazone, improve components of HALS (see below).

Leptin

Leptin is synthesized and secreted by adipocytes and is involved in energy homeostasis, while generally reflecting the amount of energy stores within the body [17]. Leptin acts centrally to promote satiety and decreased food intake [13], while also acting peripherally to decrease gluconeogenesis in the liver and adipose tissue and increase glucose utilization by skeletal muscle through pathways overlapping with insulin [60].

A significant subgroup of patients with lipodystrophy exhibit low leptin levels, including patients with HALS [44]. In studies in congenital and non-HIV related acquired lipodystrophy, physiological replacement doses of leptin (0.04 to 0.08 mg/kg daily) have resulted in significant weight loss, improved insulin sensitivity and glucose tolerance, and reduced hemoglobin A1c levels [25,26,28].

Similar results have been demonstrated in studies of patients with HALS. We have demonstrated that in a randomized, placebo-controlled, double-blinded crossover study in seven hypoleptinemic men with HALS, physiologic metreleptin replacement doses administered for 2 months improved metabolic parameters in these patients. Leptin treatment was associated with a 14.6% adjusted decrease in central fat mass and significant improvements in fasting glucose and insulin levels, insulin resistance and high density lipoprotein cholesterol (HDL-C) levels [61].

A similar independent study of longer duration confirmed these results, demonstrating a 32% decrease in visceral fat, improved lipid profiles, and increased hepatic insulin sensitivity with metreleptin treatment [62]. The improvements in central fat mass and lipid profiles observed in these studies [61,62] were comparable to those reported with metformin and thiazolidinediones in HALS patients [63-65], and provide an advantage over growth hormone (GH) replacement because leptin has not been seen to cause glucose intolerance [66].

Recombinant metreleptin therapy was well-tolerated in both studies, and their results suggest that the benefits of leptin replacement are sustained throughout treatment in patients with HALS [61,62]. Patients with various forms of congenital, non-HIV related, lipodystrophy followed for up to 8 years have also demonstrated sustained benefit with uninterrupted metreleptin treatment [30].

FUTURE DIRECTIONS OF THERAPY

As each therapy discussed has shown some benefit to HALS patients, combination therapies are currently being studied for potential use in these patients. In a 3-month pilot study of leptin treatment in addition to pioglitazone in adult men with HALS, we observed improved insulin sensitivity and postprandial glucose levels in comparison to pioglitazone treatment alone [67]. Improvements in body fat mass and distribution were not observed during the short duration of this trial; however, it is unclear if leptin's known fat-reducing effects [61,62] were affected by the coadministration of pioglitazone.

Leptin's effects on improving lipodystrophy have also been observed to act independently of the GH and insulin-like growth factor 1 (IGF-1) system [68]. As treatment with recombinant IGF-1/IGF-binding protein-3 [69] or GH and GH releasing hormone (GHRH) analogs [70-72] have demonstrated decreases in visceral fat and improvement of lipodystrophy, a

combination therapy with leptin could potentially have additive metabolic effects [68,73,74].

TREATMENT OF IMPAIRED GLUCOSE TOLERANCE IN LIPODYSTROPHY

A variety of treatment options have been studied to control the effects of HALS, but widely accepted guidelines have not yet been established. The target of ideal treatment for HALS would aim to treat both the metabolic disturbances and pathological changes in adipose tissue distribution. Two of the most commonly used medications to treat the associated glucose intolerance include metformin and thiazolidinediones. Although metformin is recommended for treatment of type 2 diabetes mellitus it is not FDA-approved for lipodystrophy syndromes. Metformin treatment improves insulin sensitivity by decreasing hepatic gluconeogenesis and enhancing peripheral glucose utilization and thus has been shown in small, randomized controlled trials to significantly reduce weight and insulin resistance in patients with HALS [75]. However, metformin is contraindicated in states that may predispose to lactic acidosis, including states of impaired renal function, may worsen peripheral adipose tissue loss, and thus has been used with extreme caution in patients with lipoatrophy [65]. Thiazolidinediones are likewise not FDA-approved for use in lipodystrophy. They bind and activate the PPAR- γ nuclear transcription factor, which regulates adipocyte differentiation and promotes production of adiponectin [76]. We have shown that treatment with the only currently FDA approved TZD, pioglitazone, increases adiponectin and improves lipid profiles and insulin resistance over a 12-month period by decreasing triglyceride levels and increasing HDL-C levels in patients with HALS [77].

CONCLUSIONS

Leptin administration, in replacement doses, has been shown in the context of long term, uncontrolled studies, to be effective in improving the metabolic and neuroendocrine abnormalities in subjects with congenital lipodystrophy. Thus, an application by Amylin Inc. has been submitted to the FDA for approval of leptin in replacement doses for the treatment of congenital lipodystrophy. It remains to be seen whether leptin will be approved for this indication in the absence of well controlled, randomized studies that could allow a more precise

assessment of efficacy and side effects. In the meantime, leptin is available through an expanded access program for subjects with congenital lipodystrophy and leptin deficiency.

As the global epidemic of HIV and associated comorbidities continues to have a striking impact, particularly in Southeast Asia, HALS is much more prevalent than congenital lipodystrophy and still represents a significant therapeutic challenge. Much more work is needed to better understand the pathogenesis of HALS and to evaluate, in the context of large randomized phase III clinical trials, novel therapy regimens such as adipokines, including leptin administration. Additional well-designed, placebo-controlled clinical trials of sufficient power and duration are needed to further evaluate mechanisms of action of leptin alone or in combination, dosing intervals and treatment duration for leptin treatments, as well as optimal drug combinations for treatment of lipodystrophy [46,49,50].

In contrast to findings in leptin deficient lipodystrophic subjects, in subjects with garden-variety obesity or diabetes (who have high concentrations of not only insulin but also leptin presumably due to leptin tolerance or resistance) [78,79], treatment with additional exogenous leptin has not been associated with significant weight loss or reduction in metabolic complications [20,80,81]. This suggests that there is leptin tolerance or resistance in these subjects [82,83]. Hence, although great progress has been made in understanding the role of leptin in many physiological systems, much research is currently being directed toward elucidating the mechanisms and pathophysiology of leptin's effects or resistance to leptin's effects on glucose metabolism in subjects with excess adipose tissue and thus leptin excess.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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