Recombinant Methionyl Human Leptin Therapy in Replacement Doses Improves Insulin Resistance and Metabolic Profile in Patients with Lipoatrophy and Metabolic Syndrome Induced by the Highly Active Antiretroviral Therapy

Jennifer H. Lee, Jean L. Chan, Epaminondas Sourlas, Vassilios Raptopoulos, Christos S. Mantzoros


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Abstract

Context: Highly active antiretroviral therapy (HAART) for HIV-1 infection has been associated with a metabolic syndrome characterized by insulin resistance, hyperlipidemia, and redistribution of body fat (lipodystrophy). A subset of patients with predominant lipoatrophy has low levels of the adipocyte-secreted hormone leptin.

Objective: The objective of the study was to assess whether administration of recombinant methionyl human leptin (r-metHuLeptin) improves insulin resistance and other metabolic abnormalities in HIV+ leptin-deficient subjects with HAART-induced lipoatrophy.

Design, Setting, Patients, and Intervention: We conducted a randomized, placebo-controlled, double-blinded, crossover study from 2002 to 2004 in seven HIV+ men with HAART-induced lipoatrophy, serum leptin level less than 3 ng/ml, and fasting triglyceride level greater than 300 mg/dl, who were administered placebo for 2 months before or after administration of r-metHuLeptin at physiological doses for an additional 2 months.

Main Outcome Measures: Insulin resistance, lipid levels, inflammatory markers, body composition, and HIV control were measured.
**Results:** Compared with placebo, r-metHuLeptin therapy improved fasting insulin levels, insulin resistance (as expressed by the homeostasis model assessment index and an insulin suppression test), and high-density lipoprotein. Body weight and fat mass decreased on r-metHuLeptin, mainly due to a decrease in truncal fat but not peripheral fat or lean body mass. r-metHuLeptin was well tolerated, and HIV control was not adversely affected.

**Conclusions:** r-metHuLeptin replacement at physiological doses in HIV+ leptin-deficient patients with HAART-induced lipoatrophy improves insulin resistance, high-density lipoprotein, and truncal fat mass. Future larger and more long-term studies in HAART-induced lipoatrophy, including patients with more severe metabolic abnormalities, are warranted to evaluate the physiological and potentially therapeutic role of r-metHuLeptin for this condition and to fully clarify the underlying mechanisms of action.

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