Leptin is an effective treatment for hypothalamic amenorrhea

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Hypothalamic amenorrhea (HA) is associated with dysfunction of the hypothalamic-pituitary-peripheral endocrine axes, leading to infertility and bone loss, and usually is caused by chronic energy deficiency secondary to strenuous exercise and/or decreased food intake. Energy deficiency also leads to hypoleptinemia, which has been proposed, on the basis of observational studies as well as an open-label study, to mediate the neuroendocrine abnormalities associated with this condition. To prove definitively a causal role of leptin in the pathogenesis of HA, we performed a randomized, double-blinded, placebo-controlled trial of human recombinant leptin (metreleptin) in replacement doses over 36 wk in women with HA. We assessed its effects on reproductive outcomes, neuroendocrine function, and bone metabolism. Leptin replacement resulted in recovery of menstruation and corrected the abnormalities in the gonadal, thyroid, growth hormone, and adrenal axes. We also demonstrated changes in markers of bone metabolism suggestive of bone formation, but no changes in bone mineral density were detected over the short duration of this study. If these data are confirmed, metreleptin administration in replacement doses to normalize circulating leptin levels may prove to be a safe and effective therapy for women with HA.

Hypothalamic amenorrhea (HA) is characterized by cessation of menstrual cycles because of dysfunction of the hypothalamic-pituitary-gonadal axis, abnormalities in gonadotropin pulsatility, and subsequent estrogen deficiency. This disorder is associated with chronic energy deficiency, usually caused by strenuous exercise, stress, and/or reduced food intake, and accounts for more than 30% of cases of amenorrhea in women of reproductive age (1). In addition to infertility, HA is associated with other neuroendocrine abnormalities, including dysfunction of the thyroid, growth hormone, and adrenal axes (2–7) as well as bone loss (8, 9) and propensity for fractures.

Circulating leptin levels reflect the amount of energy stores in fat as well as acute changes in energy intake (10). Hypoleptinemia, signaling a state of energy deficiency, may mediate the changes in the neuroendocrine axes observed in HA. We first showed that acutely depriving mice and then healthy men of energy by caloric restriction resulted in relative leptin deficiency and neuroendocrine abnormalities affecting the gonadal and thyroid axes, and these abnormalities were prevented with recombinant methionyl human leptin (metreleptin) replacement (11, 12). Women with HA are chronically energy deficient and, in observational studies, have low leptin levels and loss of diurnal leptin variation (13–16). In our proof-of-concept, open-label pilot study, we administered metreleptin s.c. for 3 mo to normalize leptin levels in women with HA and found that metreleptin treatment resulted in ovulatory menses and significant increases in levels of luteinizing hormone (LH), estradiol, insulin-like growth factor-1 (IGF1), thyroid hormones, and bone formation markers (17). Our results indicated that hypoleptinemia may be responsible for reproductive and neuroendocrine dysfunction in women with HA, but the open-label nature of the study could not prove this notion beyond any doubt because uncontrolled confounding factors could have accounted for these findings. Moreover, the adrenal axis and the full spectrum of bone metabolism were not studied fully in the earlier study (17), and the duration of the trial was not long enough to allow the study of long-term effects of metreleptin treatment.

We therefore performed a randomized, double-blinded, placebo-controlled trial of metreleptin treatment in women with HA. End points of the study were changes in reproductive and neuroendocrine functions, markers of bone metabolism, bone mineral density (BMD), and resting energy expenditure. Compared with our previous open-label pilot study, this study was randomized, placebo-controlled, and of substantially longer duration (36 wk), permitting the assessment of study outcomes against the background rate of developing spontaneous menstrual cycles and/or neuroendocrine changes over an extended period.

Results

Baseline Characteristics. There were no significant baseline differences between the metreleptin- and placebo-treated groups in regards to age, weight, body mass index (BMI), body fat composition, duration of amenorrhea, leptin levels, LH, follicle-stimulating hormone (FSH), estradiol, and BMD (Table S1 and Fig. 1).

Subject Completion. Among the 20 participants who were enrolled in the study, 11 were assigned randomly to receive metreleptin, and nine received placebo. One participant in the metreleptin-treated group withdrew from the study because she developed injection-site reactions soon after the baseline visit. Thus, the analyses in Table 1 and Tables S1 and S2 include the results from 10 metreleptin-treated subjects. Seven of the 11 participants in the metreleptin-treated group and six of nine participants in the placebo-treated group completed the entire study (Table 2 and Table S3). Of the metreleptin-treated participants, one became pregnant at week 24, and one was discontinued from the study at week 28 because of persistent weight loss despite adjustments in study medication dose (*SI Materials and Methods*). One participant from the metreleptin-treated group at week 24 and three participants from the placebo-treated group at weeks 4, 16, and 24 decided not to continue the study because of traveling.

Weight, Body Composition, and Metabolic Rate. Except for one participant who was removed from the study because of weight loss at week 28, all participants in both the metreleptin- and placebo-treated groups maintained stable weights during the study with dose adjustments (Fig. 1*A* and Table 2 and Table S3). Four participants taking metreleptin required decreased doses because of weight loss. The BMI did not change significantly in

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