

ORIGINAL ARTICLE

## Recombinant Human Leptin in Women with Hypothalamic Amenorrhea

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### ABSTRACT

#### BACKGROUND

Disruptions in hypothalamic–gonadal and other endocrine axes due to energy deficits are associated with low levels of the adipocyte-secreted hormone leptin and may result in hypothalamic amenorrhea. We hypothesized that exogenous recombinant leptin replacement would improve reproductive and neuroendocrine function in women with hypothalamic amenorrhea.

#### METHODS

Eight women with hypothalamic amenorrhea due to strenuous exercise or low weight were studied for one month before receiving recombinant human leptin and then while receiving treatment for up to three months. Six control subjects with hypothalamic amenorrhea received no treatment and were studied for a mean ( $\pm$ SD) of  $8.5\pm 8.1$  months.

#### RESULTS

Luteinizing hormone (LH) pulsatility, body weight, ovarian variables, and hormone levels did not change significantly over time in the controls and during a one-month control period before recombinant leptin therapy in the treated subjects. In contrast, recombinant leptin treatment increased mean LH levels and LH pulse frequency after two weeks and increased maximal follicular diameter, the number of dominant follicles, ovarian volume, and estradiol levels over a period of three months. Three patients had an ovulatory menstrual cycle ( $P < 0.05$  for the comparison with an expected rate of spontaneous ovulation of 10 percent); two others had preovulatory follicular development and withdrawal bleeding during treatment ( $P < 0.05$ ). Recombinant leptin significantly increased levels of free triiodothyronine, free thyroxine, insulin-like growth factor 1, insulin-like growth factor–binding protein 3, bone alkaline phosphatase, and osteocalcin but not cortisol, corticotropin, or urinary N-telopeptide.

#### CONCLUSIONS

Leptin administration for the relative leptin deficiency in women with hypothalamic amenorrhea appears to improve reproductive, thyroid, and growth hormone axes and markers of bone formation, suggesting that leptin, a peripheral signal reflecting the adequacy of energy stores, is required for normal reproductive and neuroendocrine function.

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N Engl J Med 2004;351:987-97.

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