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Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women

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ABSTRACT

Strenuously exercising young women with hypothalamic amenorrhea are hypoleptinemic and have low bone mineral density (BMD) and content (BMC), which predispose them to increased fracture risk. Short-term leptin replacement in these women corrects many neuroendocrine abnormalities and increases circulating levels of bone formation markers. Whether treatment with recombinant methionyl human leptin (metreleptin) for a long period improves BMD and BMC remains unknown. We studied 20 strenuously exercising young women with hypoleptinemia (leptin concentration <5 ng/mL) and hypothalamic amenorrhea of at least 6 months' duration. Eleven were randomized to metreleptin (initial dose, 0.08 mg/[kg·d] for 3 months; altered thereafter to 0.12 mg/kg for lack of efficacy or 0.04 mg/[kg d] for more than 5% weight loss) and 9 were randomized to placebo for 9 months. After a 3-month washout period, subjects were reexamined at the 1-year time point. Six subjects elected to continue on open-label metreleptin treatment for another 12 months. Two subjects dropped out after 18 months, and 4 completed the entire 2-year study. The BMD and BMC of the total body, lumbar spine (L1-L4), hip, and radius were assessed by using dual-energy x-ray absorptiometry at baseline and at 3, 6, 9, 12, 18, and 24 months of treatment. Metabolic and hormonal parameters and bone markers were measured in blood and urine. Metreleptin significantly increased BMC ($P = .034$) and tended to increase BMD ($P = .069$) at the lumbar spine at 9 months in the entire study group (intention-to-treat analysis). In subjects who completed the entire 2-year study (n = 4), metreleptin significantly increased BMD ($P = .024$) and BMC ($P = .049$) at the lumbar spine by 4% to 6%. Changes were not significant at the whole body, hip, and radius. Changes in hormonal and metabolic

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