

# Leptin effect on bone: Is it ethnic specific?

**Abbreviations:** BMD = bone mineral density; BMI = body mass index; OPG = osteoprotegerin

**O**steoporosis is a worldwide public health issue with considerable morbidity and mortality. Obesity, another serious public health problem, protects against bone loss and osteoporotic fractures. Several studies have shown that this protective effect of obesity on bone mass is related in part to the increased fat mass. Factors contributing to this protective effect may include mechanical loading and hormonal factors, such as estrogen aromatization and insulin. Recently, the hypothesis that leptin, an adipocyte-derived hormone, may be a mediator of the protective effects of fat mass on bone tissue has been widely discussed in the literature.

Leptin, a member of the cytokine family, is a 146–amino acid polypeptide hormone secreted primarily by extramedullary adipocytes in humans and in small amounts by the gut and the placenta.<sup>1</sup> Plasma levels correlate with body weight and body fat content. Sexual dimorphism in plasma levels has been described, with women having higher levels than men.<sup>2</sup> When leptin was discovered in 1994, it was described as a hormone acting on the hypothalamus as an appetite regulator. However, since the identification of widely distributed leptin receptors, leptin has been recognized as a mediator of many biological processes, including hematopoiesis, immune regulation, brain development, and reproduction. Some *in vitro* evidence indicates that leptin stimulates cancer cell proliferation.<sup>3</sup> Recently, leptin has emerged as a potential regulator of bone metabolism.

Leptin receptors are expressed on bone cells. Findings from *in vitro* studies have suggested that leptin enhances osteoblastic differentiation and inhibits osteoclastic generation via local mechanisms.<sup>4,5</sup> Both osteoblasts and adipocytes share the same precursor: bone marrow stromal cells. Thomas et al<sup>4</sup> reported that conditionally immortalized human stromal cells express leptin receptors. They showed that leptin administration enhanced differentiation of these hMS cell lines into osteoblasts and inhibited their differentiation to adipocytes. In contrast, osteoclasts differentiate from hemopoietic precursors of monocytes/macrophage lineage.

Holloway et al<sup>5</sup> showed that leptin inhibits *in vitro* osteoclastic differentiation of peripheral blood mononuclear cells and mouse spleen cells. It is thought that osteoprotegerin (OPG), a potent inhibitor of osteoclastogenesis, mediates this effect because leptin increases mRNA OPG expression.

As a result of leptin's demonstrated effects on osteoblastic and osteoclastic generation, higher leptin levels would be expected to be associated with higher bone mass. This has been shown in some, but not all, animal studies. Cornish et al<sup>6</sup> reported that 4-week systemic administration of leptin increased bone strength in male mice by > 20%. This was confirmed by another study demonstrating that leptin administration led to a significant increase in femoral length, total body bone area, bone mineral content, and bone density in ob/ob mice as compared with vehicle-treated controls.<sup>7</sup> Burguera et al<sup>8</sup> reported that leptin administration reduces bone loss after ovariectomy in rats. But this was not the conclusion of other studies. Ducy et al<sup>9</sup> found that despite hypogonadism, the leptin-deficient ob/ob mice are "high bone mass" phenotype, and intraventricular infusions of leptin led to rapid bone loss. Thus, in animals leptin is thought to regulate bone metabolism by 2 different mechanisms: an indirect negative effect via the hypothalamic pathway when administered centrally and a direct positive effect when administered peripherally. As in animals, in humans the findings are not consistent. In one study, 1 of 4 subjects who were homozygous for leptin deficiency had decreased bone mineral density (BMD) despite obesity.<sup>10</sup> Interestingly, females with anorexia nervosa have very low leptin levels and have lower BMD than what would be expected in patients with hypothalamic amenorrhea.<sup>11</sup>

Nevertheless, cross-sectional studies in humans have yielded contradictory results, varying from no association between leptin and BMD<sup>12,13</sup> to a positive relationship that persisted<sup>14</sup> or did not persist<sup>15,16</sup> after adjustment for body mass index (BMI) or fat mass. Other studies found negative associations.<sup>17,18</sup> Thomas et al<sup>19</sup> found sexual dimorphism in this relationship with positive association in women but not in men. The reasons behind these discrepancies remain unclear.

In this issue of the *Journal of Laboratory and Clinical Medicine*, Jen et al report a study of a large population of 2 different ethnic groups and raise an interesting issue that may, at least in part, explain the

J Lab Clin Med 2005;146:7–8.

0022-2143/\$ – see front matter

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doi:10.1016/j.lab.2005.04.009

contradictory results of studies in humans. They demonstrate that leptin correlated with BMD after adjustment for BMI in white and postmenopausal women but not in black or premenopausal women. Thus the relationship between leptin and BMD differs across ethnic groups. Because white and postmenopausal women have lower BMD than black and premenopausal women, the authors concluded that leptin may be a predictor for BMD in a population that is prone to have low BMD. There was no difference in leptin levels between breast cancer cases and controls in either ethnic group. This study has some limitations, however. Leptin is secreted by fat tissue, but the authors did not adjust for fat mass. BMI may reflect the fat mass but does not necessarily reflect its characteristics, and thus may not reflect fat mass function. The relationship between leptin and BMD was assessed at only the forearm, a site rich in cortical bone. It has been previously suggested that the effect of fat mass on humans varies with age, gender, and skeletal site.<sup>20</sup> It would have been interesting to assess whether the findings extend to other sites.

In conclusion, the effect of leptin on bone metabolism may not be the same across ethnic groups. Whether the ethnic difference is present at all skeletal sites, and if so, whether it is due to differences in the expression of leptin receptors on bone cells or to differences in leptin action in the brain, remain to be investigated.

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