Perspective
Leptin, Bone Mass, and the Thrifty Phenotype

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INTRODUCTION

THE CYTOKINE-LIKE HORMONE leptin has emerged as a significant factor in the regulation of bone metabolism. Leptin is produced by fat cells (adipocytes) and is thought to regulate bone mass through alternate pathways: one involving a direct, stimulatory effect on bone growth when administered peripherally, and another that is indirect, involving a hypothalamic relay that suppresses bone formation when administered centrally. It is therefore unclear whether leptin should be considered an anti-osteogenic factor or an anabolic agent for bone formation. The role of leptin in bone metabolism has, however, rarely been considered within the broader context of leptin’s role in regulating growth, fertility, and energy expenditure. Periods of food shortage and/or nutritional stress lead to rapid drops in leptin levels, which in turn lower metabolic rate, reduce energy expenditure, and promote the partitioning of energy toward fat. Increased food intake increases leptin production, which in turn increases growth hormone secretion, restores fertility, and promotes energy expenditure. An osteogenic function for leptin is consistent with the broader role(s) of this factor in human physiology, because periods of leptin deficiency in humans are associated with infertility, bone loss, and cessation of bone formation, whereas increased leptin production accompanies the adolescent growth spurt and the onset of menarche. This indicates that leptin action has evolved to preserve the “thrifty phenotype,” in part, by synchronizing periods of bone growth, mineral accretion, and fertility with periods of food availability while restricting growth and reproduction during periods of nutritional stress. This perspective highlights the role of leptin as an important osteogenic factor in human growth, development, and evolution.

THE THRIFTY PHENOTYPE AND BONE METABOLISM

The discovery of the obese (ob/ob) mouse mutant by Douglas Coleman at the Jackson Laboratory in the 1960s inspired a search for the satiety factor that might regulate food intake and body weight. This search culminated in the discovery of the obese gene, and its protein product leptin, by Jeffrey Friedman’s laboratory at Rockefeller University in 1994. Numerous studies on the role of leptin in human physiology have followed, but one consensus has emerged; namely, that a primary function of leptin is to set in motion a starvation response involving decreased energy expenditure and increased energy intake when leptin levels begin to fall (Fig. 1). This starvation response is now known to include heightening of appetite, reduction of fertility, lowering of metabolism, and suppression of growth. Although many studies have focused on the role of leptin as a factor in the development of obesity, obesity is a very recent phenomenon in human evolution. As others have noted, the primary challenge to our species over evolutionary time has been food shortage, not food surplus. Thus, it has been suggested that natural selection has favored strategies such as a finely tuned starvation response that enable individuals to survive these periods of food scarcity and nutritional stress. Specific physiological adaptations related to this heritage of feast or famine have often been referred to as the “thrifty” genotype or phenotype.

Congenital leptin deficiency in humans is exceptionally rare, and leptin deficiency most often occurs with decreased food intake and availability. Studies of fasting humans and food-restricted laboratory animals show, not surprisingly, that these individuals have very low serum leptin levels as well as low levels of leptin in their cerebrospinal fluid (CSF). The low CSF levels are especially significant, because leptin signals through its receptors located in the hypothalamus. Nutritionally stressed, food-limited individuals are therefore leptin-deficient, as we would expect given the fact that leptin deficiency is an important starvation signal. Coincident with the leptin deficiency of fasting individuals is a fall in plasma osteocalcin, loss of bone mass, density, and strength, reduction in bone formation rate, and reduction and/or cessation of long bone growth. Hence, an important component of the starvation response initiated by leptin deficiency is bone loss as well as decreased bone formation (Fig. 1). This is to be expected, given that there is no consistent source of dietary mineral or protein from which...
Fitness, in evolutionary terms, is measured by reproductive success. Reproductive success has two components: the probability of a genotype’s survival from birth to reproduction and the average fecundity of a particular genotype. It is apparent from the previous discussion that leptin signaling plays a major role in the first component, survival, particularly during times of nutritional stress and caloric restriction. It is now known that leptin signaling is also a major player in the second aspect of reproductive success, fecundity, or the quantity of gametes produced by an individual. A study by Frisch and Revelle and a study by Frisch showed a strong link between adipose tissue mass and human fertility by showing that, on average, ~24% of a woman’s body mass should be comprised of fat in order for menarche to occur. It has since been found that the onset of menarche in human females depends not only on “critical fat” but also on a significant increase in serum leptin, because leptin levels indicate to the brain whether adequate energy reserves are available for reproduction. (35) Leptin deficiency directly affects fertility not only by delaying sexual maturity in girls but also by inducing amenorrhea in premenopausal women. (35) Treatment of prepubertal mice with leptin advances the onset of puberty, and leptin levels are elevated at puberty even after levels are normalized for body mass index (BMI). (37) The hypothalamic-pituitary axis is impaired with leptin deficiency, but leptin treatment restores fertility as well as growth hormone secretion in fasting rats and leptin-deficient mice. (38, 39) Delayed menarche is a major risk factor for osteoporosis, and there is a strong, inverse relationship between peak BMD and age at menarche. (40, 41) Age at menarche is inversely related to serum leptin, so that age at menarche is lowered by 1 month for every 1 ng/ml increase in serum leptin. (37) Leptin signaling therefore represents an important pathway linking fatness, fertility, and maturation (Fig. 1). (42)

It is well known that there is a very rapid accrual of bone mineral during adolescence as well as an accelerated rate of skeletal growth (the pubertal growth spurt). (43) In fact, 25% of the total mineral content in the skeleton at maturity is acquired in just 2 years of the adolescent period. (44) As noted above, leptin levels remain high during adolescence, precisely when rates of bone growth and bone mineral accretion are at their peak, and leptin levels are higher in pubertal girls than boys. (45, 46) Leptin therefore seems to link mineral storage with periods of fertility and food availability. At the molecular level, this linkage may be direct, through leptin’s positive effects on chondrocyte and osteoblast proliferation (2, 47) and its inhibitory effects on osteoclastogenesis (2, 48, 49) or it may be indirect, through leptin’s activation of growth hormone secretion. (50, 51) As Hofbauer has noted “these actions of leptin” link the regulation of energy balance to fertility and have probably been important in the context of evolution.” These actions of leptin during puberty may also augment mineral storage in anticipation of pregnancy and lactation, an important function that also has been assigned to estrogen by Albright et al. (50) and more recently by Jarvinen et al. (51) Thus, leptin signaling and its actions during adolescence preserve the thrifty phenotype by (1) restricting fertility, reproduction, and skeletal growth to periods when adequate food resources are available (and body fat and serum leptin are high) and (2) suppressing reproduction and growth during those times when food resources are scarce (and body fat and serum leptin are low).

EVIDENCE FROM LEPTIN-DEFICIENT RODENTS

The numerous studies showing a role for leptin signaling in the onset of puberty, maintenance of fertility, and stim-
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ulation of skeletal growth together indicate that leptin is an important osteogenic factor early in life. However, a series of recent studies has suggested that leptin-deficient rodents actually have high bone mass(3–5) and that intracerebroventricular infusions of leptin led to rapid bone loss.(6) This has led to the suggestion that leptin is a powerful inhibitor of bone formation.(52,53) The question is therefore how to reconcile these apparently contradictory findings. First, leptin-deficient ob/ob mice have significantly lower whole body BMC and BMD than normal mice.(6) Leptin-deficient mice also have lower bone mass and density in their femora compared with normal mice, which is caused by a significant reduction in cortical thickness and trabecular density (BV/TV).(54) And leptin treatment increases femur length and BMD in these animals.(6) Trabecular bone mass and density are also lower in femora of leptin receptor–deficient db/db mice(55) and in femurs and tibias of leptin receptor–deficient fa/fa Zucker rats(56,57) compared with those of wildtype controls. These findings are all consistent with the view that leptin is an osteogenic factor.

Leptin-deficient ob/ob mice do, however, have greater trabecular density (BV/TV) in their spine compared with normal mice.(54) Thus, whether or not leptin-deficient animals are considered to have high or low bone mass depends in part on which region of the skeleton is being referenced. The increased trabecular BMD in the spine and decreased BMD in the limbs of leptin-deficient rodents is significant because a similar pattern is also observed in mice with caloric restriction. A recent study showed that 30% caloric restriction over a period of 6 months, between the ages of 2.5 and 8.5 months, significantly retarded growth in three different inbred strains of mice as measured by changes in body length, body mass, and fat mass.(58) Caloric restriction reduced femur BMC in all three strains, a pattern also observed in rats with caloric restriction,(59) but vertebral BMC actually increased with caloric restriction in all three mouse strains examined.(58) The result was a net decrease in whole body BMC in two of three inbred strains, but the data highlight the fact that caloric restriction, which reduces fat mass and leptin production, also reduces bone mass in the limb skeleton but stimulates trabecular bone formation in the spine.

Why trabecular bone formation would increase in mouse vertebrae with leptin deficiency and/or caloric restriction is unclear. It is possible that the effects of leptin deficiency on bone metabolism that are thought to involve central nervous system signaling(3–5) are restricted to bones of the spine, perhaps because of regional differences in either sympathetic innervation or adrenergic receptor types. It is also possible that increased trabecular bone formation in the axial skeleton of leptin-deficient animals reflects an increased demand for hematopoietic stem cell populations in the spine. Leptin deficiency increases bone marrow adipogenesis in the limb bones of ob/ob mice, leading to the replacement of hematopoietic tissue with adipocytes,(57) but increased marrow adipogenesis is not observed in the spine of these mice. It is tempting to speculate that if hematopoietic stem cell populations decline in the limbs, their numbers must increase in the axial skeleton to maintain a steady supply of hematopoietic stem cells (HSCs). Osteoblastic cells have recently been shown to regulate hematopoietic stem cell number in bone marrow,(60,61) and increased trabecular number is associated with increased HSC numbers in mice.(60) The increased trabecular bone mass and density in the spines of leptin-deficient and calorie-restricted rodents may therefore reflect an increased demand for hematopoiesis in marrow of the axial skeleton as hematopoietic tissue in the limbs is replaced by fat.

A PROVISIONAL SYNTHESIS

Considerable debate has surrounded the role of leptin in regulating bone metabolism, but much of this confusion can be resolved if the primary function of leptin signaling is viewed within the broader context of leptin’s role in human physiology and evolution. Leptin deficiency will normally occur in humans with loss of food supply, and the resulting effect is a fall in energy expenditure, fertility, and growth. When food supplies return to normal, leptin levels increase and fertility is restored, energy expenditure increases, and skeletal growth resumes. Thus, leptin is an osteogenic factor that couples periods of growth and reproduction with food availability. Caloric restriction and the starvation response triggered by leptin deficiency may also mobilize mineral reserves in the limb skeleton while increasing bone formation and hematopoietic stem cell numbers in the axial skeleton.

It has been suggested that leptin action may explain the protective effects of fat mass on bone in postmenopausal women.(62) While some studies(63,64) support a correlation between leptin and bone mass in postmenopausal women, others do not.(65,66) This is not surprising, because the primary function of leptin is to initiate a response when leptin levels are low rather than when they are elevated.(67) It should also be emphasized that the link between leptin, fat mass, and bone formation is one that is most critical before puberty and throughout adolescence. Thus, the importance of leptin signaling in the prevention of osteoporosis derives mainly from its role as an osteogenic factor early in life, during the accretion of peak bone mass, rather than later in life when bone is being lost. Finally, it is estimated that ~60% of the variation in fracture risk is explained by the peak bone mass reached at skeletal maturity, and reduced peak bone density is known to be an important factor in the development of osteoporotic fractures.(68,69) Therapeutic strategies that focus on the role of leptin signaling in mineral accrual and osteogenesis during the first 20 years of life may therefore have a greater impact on bone health than those that focus primarily on leptin signaling interactions in adults and the elderly.

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REFERENCES


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