

# Bone, Fat, and Body Composition: Evolving Concepts in the Pathogenesis of Osteoporosis

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## ABSTRACT

Disorders of body composition, including obesity and osteoporosis, have reached record proportions. Coincidentally, our understanding of the mechanisms controlling body mass also has greatly improved. Shared regulation at the hypothalamus and the bone marrow highlight major bone-fat interactions. The hypothalamus modulates fat and bone via the sympathetic nervous system by regulating appetite, insulin sensitivity, energy use, and skeletal remodeling. In the bone marrow, fat and bone cells arise from the same stem cells. Insights from disorders such as anorexia nervosa provide a new rationale for examining the mechanisms that link bone to fat. This article explores these relationships in the context of a new paradigm with implications for obesity and osteoporosis.

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**KEYWORDS:** Adipokines; Anorexia nervosa; Bone marrow stromal cells; Hypothalamus; Sympathetic nervous system

Two disorders of body composition, obesity and osteoporosis, have increased in prevalence during the last 3 decades. At the same time, there has been a sea change in our understanding of the homeostatic mechanisms controlling body mass. Shared regulation at 2 levels, the hypothalamus and bone marrow, highlight major bone-fat interactions.<sup>1</sup> The hypothalamus centrally modulates fat and bone via the sympathetic nervous system by regulating appetite, insulin sensitivity, energy use, and skeletal remodeling. In the bone marrow, osteoblasts and adipocytes arise from the same precursor. New insights from genetic engineering in mice and clinical disorders such as anorexia nervosa provide an important rationale for reexamining the physiologic mechanisms that link the acquisition and maintenance of bone mineral density (BMD) to energy use and ultimately fat mass.

## A COMMON ORIGIN FOR FAT AND BONE CELLS

Bone marrow surrounds trabecular elements in the skeleton and is composed of pluripotent stromal cells and red and white blood cells, platelets, and their progenitors. Stromal cells are regulated by endocrine, paracrine, and autocrine signals, and enter bone, cartilage, or fat lineages depending on their mode of activation. The allocation of stem cells into bone-forming osteoblasts, some of which may enter the circulation, is accelerated after skeletal injury and during the rapid growth phase of puberty. Runx2/Cbfa1 and osterix are 2 of several bone-specific transcription factors required for this process. In contrast, entry of stromal cells into the fat lineage occurs through activation of the nuclear receptor peroxidase proliferator-activated receptor- $\gamma$ 2 by endogenous fatty acids or exogenous ligands.<sup>2</sup> Until recently, stem cell specification was considered as an either/or paradigm; that is, commitment is exclusive to one lineage or the other. For example, the peroxidase proliferator-activated receptor- $\gamma$ 2 complex is activated by the thiazolidinediones (TZDs: rosiglitazone or pioglitazone). These agents improve insulin sensitivity but also promote stromal cell entry into the fat lineage. TZD results in improved glucose tolerance, associated with modest weight gain and increased marrow adiposity at the expense of the skeleton, but marrow fat cells can coexist with active osteoblasts.<sup>3</sup> Thus, the “switch” of stem cells into either the fat or bone lineage may

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not be mutually exclusive, and genetic determinants are likely to be important in both physiologic and pathologic states.

Although much of what we have learned about the “switching mechanism” in mesenchymal stromal cells has come from basic investigations, clinical experiences have been illustrative. For example, glucocorticoids are remarkable for their ability to enhance marrow adipogenesis at the expense of osteoblast differentiation.<sup>4</sup> In glucocorticoid-induced osteoporosis, bone loss is rapid at a time when fat mass is enhanced, particularly in central depots. The TZDs reduce bone mass and increase the risk of peripheral fractures because stem cells switch into the adipocyte lineage.<sup>5</sup> Another example of switching occurs during aging when fatty infiltration of the vertebral marrow replaces bone and can be recognized on magnetic resonance imaging scans.<sup>6</sup> Thus, bone and fat cells share a common origin, and their fates are interwoven in a context-specific manner. Pharmacologic manipulation of stem cells to reduce adipogenesis or increase osteogenesis is a promising new avenue of therapeutic investigation.

**SHARED CONTROL OVER BONE REMODELING AND BODY COMPOSITION**

Bone and energy also are functionally related through a complex neuroendocrine circuit that features leptin (an adipokine produced by fat cells), the hypothalamus, and the sympathetic nervous system. Leptin regulates appetite, reproduction, and

energy use by crossing the blood–brain barrier and binding to a receptor in the hypothalamus. In the ventromedial nucleus, leptin triggers activation of the sympathetic nervous system. Deficiencies of, or resistance, to leptin cause obesity, impaired fertility, and changes in appetite in both rodents and humans.<sup>7,8</sup>

Surprisingly, the absence of leptin also results in high bone mass, even though estrogen concentrations are markedly suppressed. Animal studies have demonstrated that the high bone mass of leptin deficiency is a result of reduced sympathetic tone innervating  $\beta_2$  adrenergic receptors in osteoblasts. Not surprisingly, the system is more complex than originally perceived and includes other hypothalamic networks, such as the neuropeptide CART, melanocortin 4 receptors, Y receptor system, and neuromedin U.<sup>1,9</sup> Cannabinoid receptors that regulate appetite and energy balance also modulate bone turnover centrally and peripherally, principally by blocking sympathetic innervation.<sup>10</sup> An investigative group recently reported that a bone-specific protein, osteocalcin, regulates insulin secretion in mice. If validated in humans, this connection provides another step in a complex integrative circuit that modulates body composition and bone turnover (Figure 1).

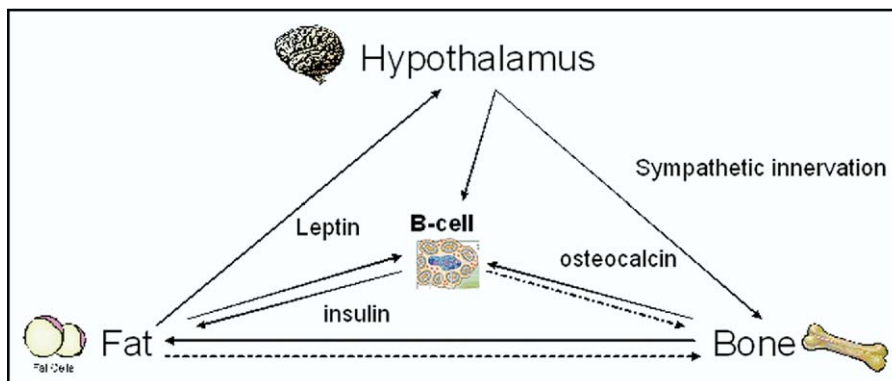
**CLINICAL SIGNIFICANCE**

- The hypothalamus regulates bone turnover and fat distribution.
- Fat and bone cells originate from the same bone marrow stem cell.
- Anorexia nervosa is a psychiatric disease that adversely affects bone remodeling by changes in gonadal steroids and release of adipokines.
- Obesity and osteoporosis can coexist, and excess visceral fat might contribute to bone loss.
- New therapies for osteoporosis target stem cells into the bone lineage.

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**ANOREXIA NERVOSA: A MODEL FOR STUDYING THE BONE–FAT–BRAIN CONNECTION**

Abnormalities in fat metabolism associated with clinical states of extreme under- and overnutrition enable a global



**Figure 1** The neuroendocrine circuit that ties body composition to the hypothalamus through several interconnecting networks. The hypothalamus processes incoming signals from fat, primarily leptin. Several nuclei integrate signals through neuropeptides releasing sympathetic activity, which in turn regulates insulin secretion and skeletal remodeling. Osteocalcin, a bone-specific protein, can regulate insulin secretion and sensitivity. The negative feedback signals to bone from the islets and fat tissue have not been defined.

**Table 1** Changes in Body Composition and Hormonal Mediators in Anorexia Nervosa

Variable	Increased	Decreased
<i>Body Composition</i>		
BMI		↓ ↓
Fat mass		↓ ↓
Bone density		↓
Bone formation		↓ ↓
Bone resorption	↑ ↑	
Bone marrow fat	↑	
<i>Hormones</i>		
Estradiol		↓ ↓
Testosterone		↓
IGF-1		↓ ↓
Growth hormone	↑	
Insulin		
Cortisol	↑	
<i>Appetite regulatory mediators</i>		
Leptin		↓ ↓
Adiponectin	↑	
Ghrelin	↑	
PYY	↑	

BMI = body mass index; IGF = insulin-like growth factor; PYY = peptide YY.

consideration of the relationship between fat and bone. The most extreme and well-studied disorder of low body fat and its effects on bone is anorexia nervosa. A primary psychiatric disorder affecting up to 1% of young women, anorexia nervosa is characterized by self-induced starvation, severe decreases in body fat and muscle mass, functional hypogonadotropic hypogonadism, and substrate shunting to preserve vital functions.<sup>11</sup> Additional physiologic adaptations to starvation that affect bone metabolism and fat mass include hypercortisolemia and growth hormone (GH) resistance. Rapid and significant bone loss in adults and inadequate acquisition of bone during the peripubertal period in children is a hallmark of the disorder. In a community-based outpatient study of 130 young women with anorexia nervosa, 92% were osteopenic and 38% met criteria for osteoporosis.<sup>12</sup> Bone formation is markedly reduced, whereas bone resorption is increased in this disorder, and paradoxically, marrow fat is increased. Weight recovery causes increases in bone formation and decreases in bone resorption.<sup>13</sup>

### Hormonal Mediators in Anorexia Nervosa

Several hormonal mediators have been linked to low bone mass in anorexia nervosa, and among these are estrogen, an inhibitor of osteoclast-mediated bone resorption (Table 1). In the setting of severe undernutrition, suppressed GnRH pulsatility results in gonadotropic hypogonadism and subsequent estrogen deficiency. However, the increased severity of bone loss in this disorder compared with that seen in other young amenorrheic women, as well as the failure of estrogen replacement to improve bone mass, implicates other nutritional factors, such as insulin-like growth factor 1.<sup>14-18</sup>

The strongest predictor of bone mass restoration in anorexia nervosa is weight recovery.<sup>19,20</sup> In a longitudinal study of women with anorexia nervosa, a 0.6% increase in hip bone mass was seen with weight gain compared with losses of 2.4% during active disease. However, return of ovarian function also is a key factor because greater improvement in bone mass is seen in women who regain both weight and menses. Biochemical measures in such patients show that markers of bone formation increase with weight gain but that decreases in bone resorption markers occur only in those women who regain menses and have adequate endogenous production of estrogen.<sup>20</sup>

Hypercortisolemia, thought to be caused by activation of the corticotropin-releasing hormone–adrenocorticotrophic hormone–adrenal axis, occurs in anorexia nervosa, and elevated cortisol secretion and loss of diurnal rhythmicity occur and are determined by low levels of insulin and fat mass.<sup>21-23</sup> Because hypercortisolemia is known to suppress bone formation and increase marrow adiposity, this effect may contribute to low bone mass in patients with anorexia nervosa. Despite cortisol excess, central adiposity has not been seen, presumably because of a generalized decrease in fat mass.

In children with anorexia nervosa, baseline cortisol levels predicted increases in body fat with disease recovery.<sup>24</sup> During weight recovery in adults, truncal fat also is disproportionately increased. This is hypothesized to occur because of new substrate availability.<sup>25</sup> In such patients, assessment of body composition and fat distribution by anthropometry, dual-energy x-ray absorptiometry, and whole-body magnetic resonance imaging demonstrated that waist-to-hip ratios, total truncal, visceral, and intramuscular adipose tissue were significantly greater than that of healthy controls of comparable weight.<sup>26</sup> Anorexia nervosa also is characterized by GH resistance with elevated GH levels and decreased hepatic production of insulin-like growth factor 1.<sup>27</sup>

The development of anorexia nervosa during adolescence is of particular concern because pubertal delay may occur.<sup>14,28</sup> Because adolescence is a time of rapid bone accretion and pubertal changes in body composition, the onset of disease during this critical window in development can dramatically affect peak bone mass accrual with consequences that may endure throughout life. Seeman et al<sup>29</sup> showed that the development of anorexia nervosa in childhood can lead to a reduction in bone size and volumetric BMD. Of note, the site and severity of specific deficits in both these parameters showed a maturational dependency on the age of onset of anorexia nervosa, as well as disease duration.<sup>29</sup> In sum, the skeletal components of this disease are directly related to changes in body composition and energy metabolism.

### ADIPOKINES AND MEDIATORS OF APPETITE AND BONE TURNOVER

Another link between fat and bone has emerged from the characterization of a family of adipokines, including leptin and adiponectin (Table 1). In addition, leptin is an anorex-

igenic hormone. Anorexigenic and orexigenic hormones affect food regulation, energy expenditure, and bone mass, and vary with total body fat. In humans, serum leptin is an excellent surrogate marker of body mass index, is highly correlated with fat mass, is consistently shown to be low in anorexia nervosa, and increases with weight gain.<sup>30</sup> Although weight loss typically precedes amenorrhea, an interesting observation has been that reproductive function can be maintained in some women, despite very low weight.<sup>31</sup> This might be due to several factors, including fat mass and leptin levels.<sup>24,32</sup> Low percent body fat and decreases in adipokine secretion, specifically leptin, might be a key mediator of reproductive function and bone mass.<sup>33</sup> Although low in both groups, spine BMD is higher in eumenorrheic than amenorrheic women with anorexia nervosa, despite similar weight.<sup>32</sup> As expected, eumenorrheic women were found to have higher mean estradiol levels than amenorrheic women. Of importance, mean percent body fat, total body fat mass, and truncal fat were higher in eumenorrheic than amenorrheic patients. This increase in body fat was associated with higher leptin levels in the eumenorrheic women than in the amenorrheic women. Therefore, increased fat mass may protect bone in a subset of women with anorexia nervosa, despite low body weight, by preservation of normal menstrual function through increased leptin secretion. Indeed, fat mass emerges as an independent predictor of bone density in regression models, including other variables such as multiple body composition and gonadal function.<sup>28</sup>

Other appetite-regulating hormones that may mediate bone loss in anorexia nervosa include peptide YY (PYY), an anorexigenic hormone, and ghrelin, which is orexigenic. Produced in the intestinal L cells in response to caloric intake, PYY acts via the Y2 receptor, which when deleted in the hypothalamus causes increased bone formation in rodents.<sup>34</sup> Obesity is associated with low levels of PYY, and these correlate inversely with body mass index.<sup>35</sup> PYY levels have been reported to be elevated in anorexia nervosa compared with lean or obese controls.<sup>36</sup> In a study of girls with anorexia nervosa, PYY levels were higher compared with controls and PYY predictors included body mass index, fat mass, and resting energy expenditure.<sup>37</sup> In addition to the inverse association between fat mass and PYY levels, there was a negative association between fasting PYY levels and fat intake. In that study, PYY levels predicted markers of low bone turnover consistent with hypothesized effects of PYY increases on bone metabolism. This finding also is consistent with the enhanced osteoblastic activity noted in Y2 receptor knockout studies. In adults with anorexia nervosa, mean overnight PYY levels are strongly and inversely correlated with BMD at the spine, total hip, femoral neck, and radius, and PYY was the primary determinant of spine BMD.<sup>38</sup>

Another appetite hormone linked to both bone and fat in anorexia nervosa is ghrelin. The orexigenic stomach-derived peptide hormone ghrelin is secreted in response to fasting, peaks before meals, and stimulates secretion of both GH and adrenocorticotrophic hormone. Ghrelin levels have

been consistently reported to be elevated in anorexia nervosa, and positive correlations are found between the ghrelin/obestatin ratio and body mass index.<sup>39,40</sup> Ghrelin also affects adipogenesis. Thompson et al<sup>41</sup> infused ghrelin, des-octanoyl ghrelin, or synthetic GHS-R<sub>1a</sub> agonists into GH-deficient rats of varying severity and demonstrated that a major circulating form of ghrelin, des-octanoyl ghrelin, has a direct adipogenic effect.<sup>41</sup> Chondrocytes have been shown to synthesize and secrete ghrelin in human cell lines and rat cartilage.<sup>42</sup> Ghrelin administration increases osteoblast proliferation in vitro.<sup>43</sup> In a prospective observational study of adolescents with anorexia nervosa, ghrelin was an important predictor of changes in spine and whole-body bone mass.<sup>44</sup>

Most, but not all, studies have found increased adiponectin levels with anorexia nervosa.<sup>45</sup> In women with the restrictive subtype of anorexia nervosa, body mass index, body fat content, and serum leptin levels were significantly decreased. Of note, an inverse relationship was found between adiponectin levels and body mass index, such that the elevated adiponectin levels compared with normal subjects was thought to reflect the marked decrease in body fat in anorexia nervosa.<sup>46</sup> In a study of adolescents with anorexia nervosa, Misra et al<sup>47</sup> found that adiponectin levels contributed significantly to bone density variability of the lumbar spine and femoral neck. Although the mechanisms whereby adiponectin might affect bone mass are unclear, changes in fat mass and insulin sensitivity in anorexia nervosa clearly play a central role. In 1 study,<sup>48</sup> plasma adiponectin levels were elevated in young women with anorexia nervosa compared with controls in the setting of reduced fat mass and impaired insulin-stimulated glucose disposal. Therefore, markedly reduced fat mass increases adiponectin secretion that may then affect bone mass directly or through changes in insulin sensitivity. In sum, multiple changes in hormones and adipokines contribute to the pathogenesis of low bone mass in patients with anorexia nervosa. Most importantly, this disorder highlights the intimate relationship between fat mass and BMD.

## BONE MINERAL DENSITY, FAT MASS, AND SKELETAL INTEGRITY

Obesity is protective for the skeleton, whereas low body weight, particularly in elders, is a major risk factor for fractures. In the 10-year fracture risk algorithm, now widely used in clinical practice, body mass index can be freely substituted for BMD to define absolute fracture risk. This relationship can be attributed to greater skeletal protection from falls, excess loading on the skeleton, and the extraovarian contribution of estradiol from aromatase activity in fat tissue. On the other hand, osteoporosis and obesity can coexist in syndromes of fat redistribution, such as Cushing's disease and the drug-induced lipodystrophies. Type II diabetes mellitus is actually associated with a greater number of fractures, and TZDs, highly effective drugs for diabetes, increase the risk of peripheral fractures.<sup>49</sup> Furthermore, the extent of fat deposition in vertebral bone marrow correlates

negatively with bone mass and indicates a greater fracture propensity.<sup>50</sup> In some cohorts, the percent of total fat mass, when body weight is kept constant, is strongly but inversely associated with BMD.<sup>51</sup> A disturbing picture also has emerged from the ongoing obesity epidemic. The prevalence of radial fractures in young adults has increased dramatically during the last decade, and one of the strongest predictors of fracture in this population is excess body weight.<sup>52</sup> The mechanism(s) responsible for this relationship is unknown but likely to be multifactorial and related to lifestyle, nutrition, and genetic determinants.

## CONCLUSIONS

Fat and bone are inexorably linked in mammalian physiology by their reciprocal needs. Skeletal remodeling, as a finely tuned means of replenishing calcium and maintaining bone integrity, evolved over millions of year but demanded a sustainable energy source from adipose tissue. On the other hand, fat tissue, via signaling through the hypothalamus, can regulate bone mass as a means of controlling energy use and modulate insulin secretion and sensitivity. The clinical correlates of this intimate relationship are profound and translatable to clinical practice. For example, the use of glucocorticoids or TZDs cause bone loss principally by shifting the marrow equilibrium toward adipocyte differentiation. As noted previously, BMD increases in anorexia nervosa only when body weight is restored. Similarly, the metabolic syndrome characterized by obesity and lipid abnormalities has long been associated with multiple cardiovascular complications; however, recent studies would suggest that fracture risk also might be increased in this syndrome. Bariatric treatment of obesity is associated not only with weight loss but also with a profound decrease in bone mass. Thus, the evaluation and treatment of obesity must also include an assessment of skeletal status.

In the future, therapeutic manipulation of marrow stem cells could conceivably improve bone mass, at the expense of excess fat. Studies by Rubin and colleagues<sup>55</sup> have been illuminating in that regard, who demonstrated that individuals standing on a vibration platform that emits low-magnitude but high-frequency sound waves (ie, laser microprobe mass spectrometry), for just 10 minutes per day for 2 years, have significant increases in bone mass.<sup>53</sup> More intriguing, when laser microprobe mass spectrometry is applied to young mice for just 10 minutes per day for 16 weeks, intraabdominal fat is lowered and stem cell allocation into the bone lineage is enhanced, even after the mice are placed on a high-fat diet.<sup>54,55</sup> In sum, there is a shifting paradigm regarding body composition. No longer can it be said that obesity per se protects against osteoporosis. Rather, as we learn more about bone and fat, it will become more accurate to conclude that these 2 complex diseases are indeed connected through multiple hormonal, neuronal, and environmental pathways.

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