Minireview: The Link Between Fat and Bone: Does Mass Beget Mass?

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Osteoporosis is less common in individuals with high fat mass. This putative osteoprotection is likely an adaptive mechanism that allows obese individuals to better carry their increased body mass. Recent studies have focused on hormones that link fat to bone. Adipokines, such as leptin, modulate bone cells through both direct and indirect actions, whereas molecules activating peroxisome proliferator-activated receptor γ drive mesenchymal stem cell differentiation towards adipocytes away from the osteoblastic lineage. There is emerging evidence that bone-derived osteocalcin regulates insulin release and insulin sensitivity and, hence, might indirectly affect fat mass. Despite these molecular connections between fat and bone, animal and human studies call into question a primary role for body fat in determining bone mass. Mice devoid of fat do not have a skeletal phenotype, and in humans, the observed correlations between bone and body mass are not just due to adipose tissue. An improved understanding of the integrative physiology at the fat-bone interface should allow us develop therapies for both osteoporosis and obesity. **(*Endocrinology* 153: 2070–2075, 2012)**

Obesity and osteoporosis are two leading causes of morbidity in the United States. However, it is widely accepted that obese individuals are less likely to develop osteoporosis (1), probably the only clinical benefit of obesity. Consistent with epidemiological observations, genetic studies have identified candidate molecules, including IGF-I, IGF-II, leptin receptor, neuropeptide Y, vitamin D receptor, estrogen receptor α, androgen receptor, TGF-β1, IL-6, TNF-α, tumor necrosis factor receptor 2, apolipoprotein E, and peroxisome proliferator-activated receptor (PPAR)γ, that affect both bone mass and body fat. More recently, six single nucleotide polymorphisms in a strongly associated obesity gene fat mass and obesity associated protein have been linked to bone mineral density (BMD) (2, 3). Mice lacking the fat mass and obesity associated protein gene are thus protected from obesity but have low BMD (4, 5).

One hypothesis to explain the relationship between body mass and bone density centers on increased mechanical demand in obese individuals. These individuals accrue more bone as a compensatory mechanism to better support their high body mass. Mechanical stimulation of bone causes increased osteoblast proliferation and matrix deposition (6), whereas absent or reduced gravity, as experienced in space or upon immobilization, results in acute, rapid, and severe bone loss (7, 8).

Increased mechanical demands due to increased body mass arise mostly from two tissues: fat and muscle. Attention has nonetheless been directed mostly to fat, not to muscle. However, in premenopausal women, femoral neck BMD increases linearly with muscle mass and nonlinearly with fat mass (9). Thus, women with high muscle/low fat mass have higher BMD than those with low muscle/high fat mass, suggesting that fat mass is protective only when associated with substantial muscle mass (9).

Several clinical studies, however, challenge the notion that mechanical strain, fat, or, indeed, muscle is a critical determinant of bone mass. For example, during weight

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Abbreviations: BMD, Bone mineral density; CNS, central nervous system; ECM, extracellular matrix; MSC, mesenchymal stem cell; PPAR, peroxisome proliferator-activated receptor.

loss of 14 kg, consisting of an approximately 1.8-kg loss in muscle mass and approximately 11-kg fat mass, BMD increased, rather than decreased, by 0.004 g/cm^2 (10). This means that the association between bone density and body mass is not always linear. It could nonetheless be explained by reduced adipose tissue dysfunction, as opposed to an effect of reducing fat mass *per se*. A similar profile has been noted in women during the menopausal transition, during which time fat mass increases, whereas bone density drops (11). All of these changes occur without a reduction in muscle mass (11), suggesting that interactions between bone, muscle, and fat are at best complex.

Exemplifying this complexity further, but in contrast to simple weight loss, patients with anorexia nervosa suffer from severe osteoporosis characterized by rapid bone loss at both trabecular and cortical sites (12–16). Women with anorexia nervosa therefore have three times the risk of fracture (15), and one in two women will have at least one fracture before age 40 (15, 17). In addition to the possible direct contribution of reduced fat and muscle mass to the bone loss, it is very likely that other factors, such as hypogonadism, inflammation, glucocorticoid excess, and malnutrition, play permissive roles (18). Leptin levels are also dramatically decreased in anorexia nervosa patients (19). Although reduced central leptin signaling would be expected to increase bone mass (see below), anorexic patients are also likely to be hypersensitive to leptin, a phenomenon that could oppose a positive bone mass effect.

The Adipokine Leptin Acts through the Central Nervous System (CNS) to Regulate Bone Mass

Although increased mechanical stimulation underlies, in part, the osteoprotective effect of high fat mass, recent studies have focused on the interplay between fat, bone, and the nervous system. Both adipose tissue metabolism, such as lipolysis, and bone remodeling are subject to endocrine and neural control.

Leptin provides an example of an adipokine that regulates both bone mass and fat mass via a CNS relay (20). Serum leptin levels directly correlate with fat mass. As a key adiposity signal, leptin gauges the availability of peripheral energy reserves and relays this information to the CNS. In turn, it suppresses appetite and controls nutrient partitioning (21–23). Humans with congenital leptin deficiency and knockout mice for either leptin (denoted *ob/ob*) or its receptor (*db/db*) develop morbid obesity (23, 24). The mice also have a high bone mass (25). Likewise, reducing serum-free leptin level by overexpressing a soluble receptor increases bone mass (26). Importantly, the high bone mass phenotype of the *ob/ob* mouse is reversed by intracerebroventricular leptin infusions (25, 27, 28), a maneuver that also restores metabolic control and improves adipose tissue function, besides decreasing adiposity *per se*. Unfortunately, obese patients are not responsive to leptin injections (29). This leptin resistance is a hallmark of obesity.

Impaired CNS leptin signaling is likewise thought to underlie the high bone mass in receptor-deficient *db/db* mice, despite elevated circulating leptin (25). Leptin acts through the sympathetic nervous system to regulate bone formation. The ablation of adrenergic signaling thus results in high bone mass that is resistant to correction by icv leptin (30). Notably, none of the aforementioned adrenergic manipulations affect fat or muscle mass (30), suggesting that the leptin/adrenergic pathway for bone mass regulation is dissociable from the leptin pathway controlling adiposity. It is important to note, however, that leptin is also a major regulator of nutrient flux, such as free fatty acid release from adipose tissue through lipolysis. This action will alter adipose tissue function but may not necessarily reduce total fat mass (31, 32). One therefore cannot exclude that the bone actions of leptin are completely independent of its overall effect on fat metabolism.

Paradoxical to high bone phenotype of *db/db* mice, the administration of recombinant leptin to women, who have become hypogonadal due to strenuous exercise, increases bone mass by approximately 5% (33). However, because the increase in bone mass is accompanied by a restoration of estradiol levels, an indirect action of leptin via estrogen cannot be excluded. There is also evidence that leptin acts peripherally by stimulating osteoblast proliferation and inhibiting osteoclastogenesis, which promotes bone formation, although these effects of leptin on osteoprogenitor cells have not been clearly established *in vivo* (34–36). These peripheral effects of leptin may counteract the central leptin effects and may account for the beneficial effects of leptin in hypogonadal women.

Adipokines Directly Regulate Mesenchymal Stem Cell (MSC) Differentiation into Osteoblasts or Adipocytes

In addition to a fat-bone axis that requires the brain as a relay mechanism, fat cells can interact with osteoblasts and their precursors in a paracrine loop. When MC3T3-E1 osteoblasts are exposed to adipocyte-exposed culture media, the expression of PPARγ and runt-related transcription factor 2 is increased and decreased, respectively (37). Increased PPARγ/decreased runt-related transcription factor 2 is permissive to increased adipogenesis and reduced osteoblastogenesis. In fact, PPARγ selectively

promotes adipogenesis from MSC, and ligands that activate PPARγ, such as rosiglitazone, result in the accumulation of fat cells with a concomitant reduction of osteoblast numbers in bone marrow (38). Together, these findings suggest that PPARγ activation commits MSC to become adipocytes, away from the osteoblastic lineage.

Indeed, MSC differentiation can be provoked to increase one cell lineage at the expense of another. For example, TSH enhances chondrogenesis (39) while increasing or reducing osteoblastogenesis depending on the conditions (40, 41). Furthermore, FSH receptors have been shown to exist on human MSC (42). Admittedly speculative, their stimulation might divert osteoblastogenesis to adipogenesis during early menopause, thus partly explaining the increased fat and reduced bone density noted during the menopausal transition (42). Likewise, glucocorticoids inhibit osteoblastogenesis and increase bone marrow fat, in part, by up-regulating cannabinoid receptor-1, which, in turn, modulates PPARγ2 signaling. Pharmacological inhibition of cannabinoid receptor-1 thus reverses glucocorticoid-induced alterations in osteoblast and adipocytes differentiation (43). Overall, therefore, there is a strong neuroendocrine connection in the reciprocal regulation of adipogenesis and osteoblastogenesis.

Finally, Wnt signaling in the osteoblast is critical to bone formation. Noncanonical signaling in MSC can either promote or inhibit adipogenesis depending on the ligand (Fig. 1). Wnt5B promotes and Wnt5A inhibits adpiogenesis. As with canonical signaling, noncanonical Wnt signals, although inhibiting adipocyte differentiation, stimulate osteoblast differentiation in MSC cultures. Thus, Wnt5A, as well as its hormone inducers, such as TSH, are known to promote osteoblastogenesis (42, 44).

MSC commitment to osteoblasts or adipocytes is also determined by extracellular matrix (ECM) components. MSC grown in a soft gel matrix preferentially differentiate into adipocytes, whereas those grown in a stiff collagen gel become osteoblasts (45, 46). Integrins likely mediate the signaling effects on MSC differentiation into osteoblasts. Integrin signaling from stiffer ECM induce Rac and Rho to trigger osteogenesis while suppressing adipogenesis (46). Ligands, such as Wnt 5A, can also be activated by ECM signals. For example, the treatment of human MSC with Wnt 5A increases integrin expression (47). Furthermore, integrin expression induced by ECM is abrogated with loss of Wnt5A in human mesenchymal stem cells (47). Overall, therefore, Wnt5a appears to increase osteogenesis through a positive feedback with the ECM (47).

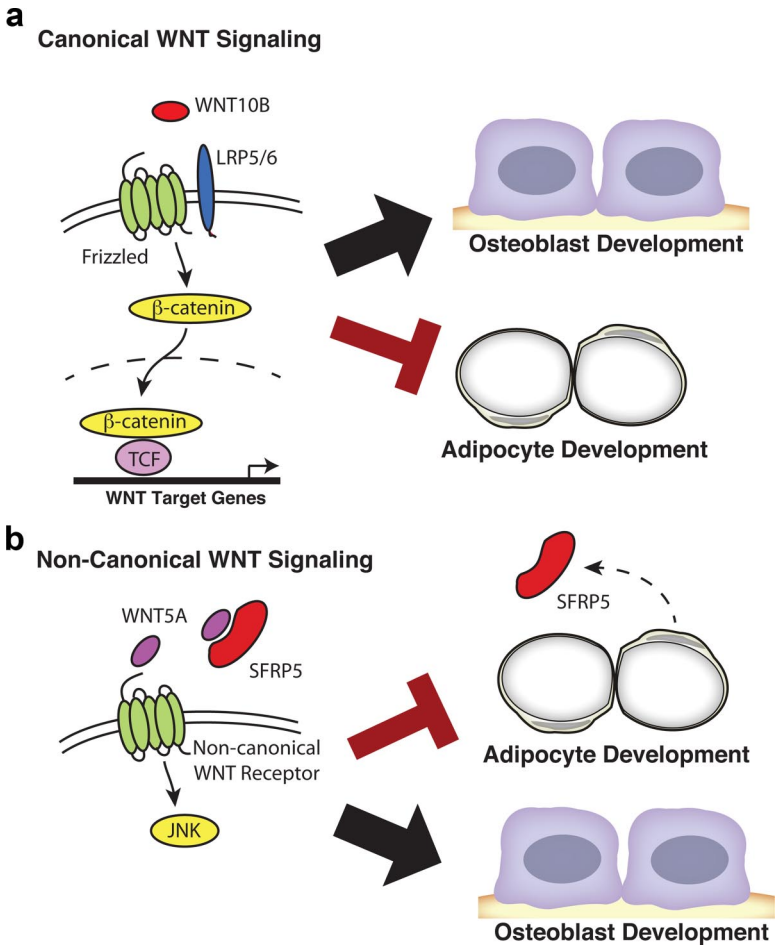

FIG. 1. The role of Wnt signaling in osteoblast and adipocyte differentiation. A, Canonical Wnt signaling resulting in β-catenin activation plays a critical role in mediating the fate of MSC. Wnt10B has been shown to signal through Frizzled and LRP (low-density lipoprotein receptor-related protein) 5/6 to cause β-catenin accumulation and downstream transcription of Wnt target genes. The resulting genetic program impairs adipocyte development while simultaneously augmenting osteoblast development. B, Similar to canonical Wnt signaling, noncanonical Wnt signaling also controls the fate of MSC. Wnt5A signals through JNK (Janus-N-terminal kinase) to promote osteoblastogenesis at the expense of adipocyte differentiation. In a negative feedback loop, adipocytes secrete SFRP5 that acts as a decoy for Wnt5A, thereby preventing signaling. Similar to many other adipokines, SFRP5 (secreted frizzled related protein 5) secretion can alter the extracellular signals nearby MSCs are exposed to, and reinforce differentiation into, similar cell types (*e.g.* produce more adipocytes). Through this mechanism, clusters of fat, or alternatively, rows of osteoblasts reinforce their own differentiation while inhibiting differentiation into other cell types.

It Is Not Just "Mass Begets Mass"

Although abundant mechanistic data support a bone-fat axis, its true physiologic meaning comes into ques-

tion on three grounds. First, obese and nonobese women lose bone at similar rates during the late perimenopause, suggesting that bone loss is independent of body mass and that it is driven by hormonal mechanisms involving estrogen, FSH, and inhibins (48, 49). Second, caloric restriction increases rather than decreases bone mass, despite the dramatic reduction in fat mass. The high bone mass is associated with increased osteoblastogenesis and reduced osteoclastogenesis, likely arising from up-regulated sirtunin-1 expression (49). Further supporting a role of sirtunin-1 is the finding that its deletion in mice leads to osteopenia and prevents bone mass accrual during caloric restriction (50).

Finally, there is controversy regarding the bone phenotype of lipoatrophic A-ZIP/F1 "fatless" mice (51). With undetectable adipokine levels, fatless mice represent a valuable model for studying the effect of fat-derived hormones on bone. Their use is, however, confounded by the profound alterations in overall metabolic control and organ cross talk (31). Although these mice were shown to have high bone mass (20), others have failed to find a bone phenotype (52). Interestingly, however, fatless mice exposed to irradiation display an increase in osteogenesis (52). This augmented osteogenesis has been attributed to enhanced osteoblastogenesis and appears to be related to decreased PPARγ and reduced bone marrow adiposity in fatless mice (52).

Whether or not there is a high bone mass in fatless mice, the fact that these mice do not have low bone mass proves that, at least under lipodystropic conditions, fat mass and bone mass do not correlate or may indeed be regulated in a more complex manner than has been previously anticipated. Toward this notion of complexity in the relationship between fat and bone mass, numerous epidemiologic studies have demonstrated that fat mass may negatively impact bone mass and strength (53–55). For example, Hong *et al.* (53) demonstrated recently that the percent fat mass was inversely correlated with bone mass regardless of age.

Closing Thoughts

In closing, the simplistic notion that fat mass regulates bone mass has been called into question. Although fat can secrete hormones, such as leptin, that act to limit osteoblastogenesis and stimulate adipogenesis *in vitro*, the mechanisms regulating body fat and bone mass *in vivo* are more complicated. Straightforward hypotheses on the connections between bone and fat fail to account for situations such as the elevated bone mass seen with caloric restriction in humans, or the absence of osteopenia in fatless mice. The integrative physiology at the interface of bone and fat may therefore be multipronged and, even perhaps, disease specific. Mouse genetics has unraveled some, but not all critical regulators, whereas clinical studies tend often to counter data from mouse models.

Several key issues nonetheless arise. It would be important to differentiate the effects of fat mass *vs.* fat functionality on bone. For example, it would be meaningful to separate any contributions to bone mass of *de novo* lipogenesis *vs.* lipolysis, both of which produce biologically active lipokines. Second, emerging evidence that bone-derived molecules, such as osteocalcin, can regulate insulin sensitivity and insulin secretion, begs the question as to whether osteocalcin can also act directly on fat cells (56, 57). Finally, the role of muscle mass as a separate and critical modifier of bone mass is just beginning to glean (58). Particularly in the ever-increasing elderly and very elderly population, a declining muscle mass may independently affect bone mass and *vice versa*. This would beg the need for novel agents that could reverse both sarcopenia and osteoporosis in concert.

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