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Body Composition and Skeletal Health: Too Heavy? Too Thin?

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Abstract

The relationship between body composition and skeletal metabolism has received growing recognition. Low body weight is an established risk factor for fracture. The effect of obesity on skeletal health is less well defined. Extensive studies in patients with anorexia nervosa and obesity have illuminated many of the underlying biologic mechanisms by which body composition modulates bone mass. This review examines the relationship between body composition and bone mass through data from recent research studies throughout the weight spectrum ranging from anorexia nervosa to obesity.

Keywords

Obesity; Anorexia nervosa; Osteoporosis; Bone density; Growth hormone; IGF-1; Estrogen; Adipokines; Body composition; Skeletal health

Introduction

Osteoporosis is characterized by an increased risk of fracture resulting from reduced bone mass and abnormal microarchitectural parameters compared to a normal cohort. The economic burden of skeletal fractures is considerable. Worldwide, 9 million osteoporotic fractures are estimated to have occurred in 2000, and these events represented approximately 0.83% of the global noncommunicable disease burden (5.8 million disability-adjusted life years). The disease burden associated with osteoporotic fractures in Europe exceeded that associated with virtually all common cancers [1].

Health care expenditures attributed to osteoporotic fractures in the United States for adults aged 45 years and over were an estimated $19 billion in 2005 and are projected to be $25.3 billion in 2025 [2].

Although the prevalence of osteoporosis is higher in older age groups, fractures remain a significant health burden in younger populations. Approximately 25% of children are injured on an annual basis [3, 4], and fractures account for a quarter of these events [5]. Up to half of children experience at least one fracture by the age of 18 years [6].

Pathologic deviations from a normal body weight are increasingly prevalent. The World Health Organization estimates that global obesity has increased more than twofold over the

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past 30 years. According to the 2009–2010 National Health and Nutrition Examination Survey, the prevalence of obesity among US adults was 35% [7]. Worrisome rates of obesity have also been observed in children. Ten percent of children ages 5 to 17 years of age are estimated to be overweight [8]. At the opposite end of the weight spectrum, anorexia nervosa (AN), a frequent cause of low weight in developed nations, affects approximately 0.3% of young females and is among the most common chronic illness in this population. The incidence and prevalence of AN appear to be increasing [9].

A majority of individuals with AN have significantly decreased bone mineral density (BMD) [10] and an increased risk of fracture [11, 12]. Traditionally, obesity has been regarded as a protective factor for bone, although recent studies have shown the importance of fat depots at specific sites in determining this effect. The relationship between body composition and bone metabolism has been the subject of intensive research, and recent investigations have explored the complex links between bone, adipose tissue, muscle, the nervous system, neuroendocrine axes, and the gastrointestinal system. Elucidation of the pathways for communication between these systems has enhanced our understanding of skeletal regulation and helped identify new potential biologic targets for therapeutic intervention. In this review, we discuss these relationships in the context of altered body composition and their impact on bone health.

Bone Strength, Fracture Risk, and Body Composition

The assessment of an individual's fracture risk is a complex evaluation that incorporates bone quality and strength, the degree of mechanical strain applied to bone, and the likelihood or frequency of these events. Although higher body weight produces a greater momentum during a fall, fat mass can cushion the area of impact and significantly decrease the effective forces applied to underlying bone. In a study of postmenopausal women, assessment of trochanteric soft tissue thickness reduced estimates of fall forces by as much as 50% at the hip, and incorporation of this parameter alongside areal BMD may better predict fracture risk [13, 14]. In regard to fat depots, both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) contribute to total body mass, but SAT may attenuate bone impact forces in a site-specific manner.

Obese individuals may be at higher risk for fall-related bone injuries. A large adult dataset from the Medical Expenditure Panel Survey suggested that the incidence of fall injuries is higher in obese individuals compared to the normal weight population [15]. Obesity-associated pathologies such as diabetes mellitus and various arthropathic conditions may partially explain an increased risk of fall. More fundamentally, it appears that obese individuals, similar to the elderly, require greater attentional resources to maintain postural stability [16].

Low body weight is a well-known risk factor for fracture and is incorporated into the FRAX and Garvan algorithms, calculations aimed to predict an individual's prospective fracture risk [17]. Studies in adolescents and adults with AN have consistently shown reduced bone mass and an increased fracture incidence and prevalence [10–12, 18–21]. Studies investigating the relationship between bone structure parameters and obesity have produced conflicting results, and a comprehensive discussion of those studies is beyond the scope of this review. The interpretation and comparison of the studies' results can be complicated by lack of group homogeneity (in regard to gender, age, ethnicity, and metabolic profile) and variations in bone measurement technique (eg, dual-energy x-ray absorptiometry [DXA] and peripheral quantitative computed tomography [pQCT]), bone site, and method of analysis (including bone mineral content [BMC]; areal BMD, volumetric BMD, microarchitecture, and algorithm-based analyses such as the Hip Structure Analysis program). Studies have

also utilized varied measures to assess adiposity. These strategies include indirect methods such as body mass index (BMI) and waist circumference or direct measurement by DXA, CT, or magnetic resonance imaging. The presence of multiple compartments of adipose tissue such as SAT, VAT, and bone marrow fat and their potential distinct metabolic characteristics add to the complexity of analysis. Limitations imposed on statistical models by colinearity between highly related variables have not routinely been addressed in a consistent manner in studies seeking to isolate the impact of fat mass on BMD and bone structure. Misleading data and potentially erroneous conclusions can result from treating highly related covariates as independent variables [22•, 23]. The cross-sectional nature of many bone imaging studies is an additional limitation. Recent large longitudinal fracture studies in postmenopausal women suggest that the relationship between obesity and fracture is site-dependent [24•, 25]. Similar results were observed in a recent near-nationwide medical record review in Spain [26]. Comparatively large longitudinal studies are not available in pediatric populations.

Mechanical Stimuli

Mechanical stimuli linked to body weight have been thought to underlie differences in bone mass and fracture risk in patients. The hypothesis that bone adapts to mechanical forces was first postulated by J. Wolff in 1869 and later refined into the “mechanostat” proposal by H. Frost [27]. Experiments have demonstrated that dynamic, rather than static, loads promote bone formation [28, 29], and that the response of bone is governed by the amplitude and frequency of these stimuli [29, 30]. Body mass and composition influence the amplitude of mechanical forces exerted on bone, and the frequency of forces is defined by an individual’s physical activity. Adipose tissue predominantly applies a static load on bone (although it can also indirectly affect the amplitude of dynamic forces). Muscle use creates dynamic strains on bone, and these forces greatly exceed the static gravitational loads resulting from body mass [31, 32].

Because individuals with AN have reduced amounts of lean and fat mass, their skeleton encounters diminished mechanical stimuli. Moreover, exercise does not appear to benefit BMD in individuals with active AN [33]. Obese individuals have excess fat mass and generally also have an increased amount of lean mass. From a biomechanical viewpoint, the excess mass associated with obesity should benefit bone strength, although perhaps less than initial expectations due to the fact that excess fat mass primarily exerts static loads on bone.

Nutrition and Diet

Adequate micronutrient intake, especially calcium and vitamin D, are important factors to maintain normal BMD and prevent fractures. Studies in adults with AN suggest that a significant portion do not meet the recommended intake levels of calcium and vitamin D, although the percentages were comparable to healthy controls [34, 35]. Interestingly, data in adolescent girls showed that those with AN had significantly higher intake of calcium and vitamin D compared to healthy controls, often through the use of dietary supplements, and that a higher percentage of girls with AN met the Dietary Reference Intake for these nutrients [36].

Obesity is often described as a high-caloric state of malnutrition. Micronutrient deficiencies, including vitamin D, are prevalent in obese populations [37, 38]. Studies show an inverse correlation between serum levels of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D and BMI [39, 40]. Proposed etiologies for this correlation have included poor dietary intake, limited sun exposure, decreased hepatic production of 25-hydroxyvitamin D, or reduced bioavailability due to storage in adipose tissue. A study by Wortsman et al. [41] showed decreased serum 25-hydroxyvitamin D levels in obese subjects and concluded that obese

subjects had decreased bioavailability of vitamin D from cutaneous and dietary sources, possibly due to deposition in adipose tissue. Parathyroid hormone (PTH) levels are also elevated in obese populations, and PTH appears to positively correlate with BMI [40, 42]. Although relative vitamin D deficiency is likely contributive, a recent study utilizing citrate-calcium clamps revealed that the PTH-calcium set point is altered in obese subjects. Specifically, the results were consistent with enhanced PTH production in obese individuals [43].

Neuroendocrine Function

Hypothalamic-Pituitary-Gonadal Axis

Reproductive function is typically impaired in extreme states of over- and undernutrition, and amenorrhea is a part of the current *Diagnostic and Statistical Manual of Mental Disorders*-IVR (fourth edition, text revision) diagnostic criteria for AN. Amenorrhea associated with AN is hypothalamic in origin due to impaired gonadotropin-releasing hormone (GnRH) pulsatility and reflects an adaptive response to a negative energy state. In individuals with AN, levels of gonadal steroids are reduced, and gonadotropin secretion patterns mimic those observed in prepubertal or early pubertal children [44, 45]. Administration of exogenous GnRH is able to restore gonadal axis function [46].

Lumbar BMD is lower in adults with the onset of AN during adolescence compared to adult onset and reflects the impact of the disease on attainment of peak bone mass [47]. Bone mass is lower in amenorrheic women with AN compared to eumenorrheic women with comparable body mass [48]. Women have elevated markers of bone resorption after menopause, a physiologic state of hypoestrogenism. A similar pattern of enhanced bone resorption is observed in women with AN [49]. However, oral estrogen administration does not improve BMD in adults with AN [50, 51]. A recent study by our group has demonstrated improvement in BMD in adolescent girls after treatment with physiologic transdermal estradiol [52••]. The dissimilar outcomes may be the consequence of the effects of oral versus transdermal estradiol on levels of insulin-like growth factor 1 (IGF-1) [53], and/or age-dependent skeletal responses to estrogen in undernutrition.

GH-IGF-1 Axis

Impairment of the growth hormone–insulin-like growth factor type 1 (GH-IGF-1) axis can be seen in both under- and overnutrition. Although the mechanisms of impairment differ, a relative state of decreased GH action may be present at both extremes. The anabolic effects of IGF-1 on bone have been well described [54]. Typically, serum levels of IGF-1 are reduced, and levels of GH are elevated in AN, consistent with a state of acquired GH resistance [55, 56]. In adults with AN randomized to placebo or supraphysiologic doses of recombinant human GH, GH did not significantly increase levels of IGF-1, implying a resistance of GH at the level of the liver [57•].

Serum levels of bone formation markers are reduced in AN [44,49], consistent with the loss of an endogenous anabolic factor, and levels of IGF-1 correlate with bone microarchitectural parameters [58]. Administration of recombinant human IGF-1 (rhIGF-1) increases serum markers of bone formation in adolescents and adults with AN [49, 59], and treatment with the combination of an oral contraceptive and rhIGF-1 significantly improves BMD in adult women with AN compared to placebo [52••]. Levels of IGF-1 peak during adolescence and decline with age [60]. The relative contribution of IGF-1 with regard to bone formation is likely to be most profound during adolescence.

Visceral adiposity is associated with reduced GH secretion, and IGF-1 may be lower [61–63]. Hypoactivation of the somatotropic axis appears limited to individuals with increased

visceral fat [64]. Levels of IGF-1 positively correlate with markers of bone formation and BMD in obese premenopausal women and inversely correlate with visceral adiposity [65].

HPA Axis

Hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and enhanced cortisol secretion are observed in AN. Serum and urinary measures of cortisol are elevated compared to healthy weight controls, and pooled serum cortisol levels inversely correlate with BMD [66–68]. Excess cortisol has well-defined direct deleterious effects on bone mass and may indirectly influence bone via effects on sex steroids, GH, muscle mass, intestinal calcium absorption, and renal tubular calcium excretion [69–72].

Visceral Fat and Subcutaneous Fat

VAT and SAT compartments may exert distinct effects on bone. VAT is generally considered to be metabolically unhealthy; compared to SAT, VAT exhibits increased immune cell infiltration and a more proinflammatory cytokine/adipokine profile. VAT secretes lower levels of adiponectin and higher levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which stimulate osteoclastogenesis and bone resorption [73]. Higher levels of preadipocyte factor 1 (Pref-1) may promote the development of a proinflammatory environment [74]. Levels of Pref-1 are elevated in the VAT and SAT of metabolically unhealthy obese individuals compared to healthy obese adults and correlate with parameters of metabolic dysfunction [75]. Furthermore, VAT inversely correlates with serum levels of IGF-1 in obese women [76] and is a negative predictor of insulin sensitivity [74].

In a study of obese women, VAT (but not SAT) correlated with marrow adiposity, and marrow fat content inversely correlated with lumbar trabecular BMD [77]. Similar results were observed in a study of normal weight women [78]. Several studies have shown inverse correlations of VAT, but not SAT, with measurements of bone structure and strength [76, 79–81]. Skeletal muscle adipose tissue accumulation is considered pathogenic and shares similar metabolic characteristics with VAT. A large study in girls showed an inverse association of skeletal muscle fat with volumetric BMD and bone strength indices [82]. Similar results were observed in men [83]. Therefore, consideration of the effects on adipose tissue on BMD is likely dependent on specific fat depots.

Adipokines

Leptin is a fat-derived hormone, primarily made in subcutaneous fat, whose concentration is proportional to total body fat mass. Serum levels of leptin are reduced in conditions of low weight, such as AN [84, 85], and are elevated in obesity [86]. Leptin-deficient mice have reduced total bone mass, but the effects of leptin vary according to the bone site examined. Leptin deficiency in mice results in greater BMD in the axial skeleton but reduced values at appendicular locations [87, 88], and its effects are mediated through central and peripheral pathways [89–92]. In patients with the rare condition of congenital leptin deficiency, BMD and BMC appear largely normal, and treatment with leptin did not affect BMD in most of these individuals [93, 94]. Studies examining the relationship between serum leptin levels and BMD in humans have been inconsistent likely due to differences in bone sites examined, gender, and leptin resistance. A recent meta-analysis of studies in nonobese adults indicated that leptin is positively associated with BMD in men and women, especially in postmenopausal women [95]. Serum leptin levels also predict bone microarchitectural parameters in women with AN [58]. In addition to its central and peripheral actions, leptin may influence bone metabolism by its effects on the gonadal, GH, and HPA axes and glucose metabolism/insulin sensitivity [85, 96–98].

Although adiponectin is produced by adipocytes, serum levels inversely correlate with BMI and visceral fat [99, 100]. Studies have shown high, normal, or low levels in patients with AN [101–103], and one study showed an inverse association between adiponectin values and bone density parameters in adolescents with AN [104]. Adiponectin levels are inversely associated with BMD in children and adults [95, 100, 105, 106]. Adiponectin receptors are expressed on osteoblasts and osteoclasts [107, 108]. In vitro experiments with human cell cultures demonstrate that adiponectin promotes osteoclastogenesis through osteoblast production of receptor activator of nuclear factor-κB ligand (RANKL) and inhibition of osteoprotegerin [109]. Other studies suggest that adiponectin enhances osteoblast proliferation and activity and suppresses osteoclast function [110–112]. Low adiponectin levels are predictive of greater insulin resistance [113]. Other adipokines, including visfatin, resistin, and Dickkopf-1, interact with bone but are outside of the scope of this paper [114–116].

Gut-Derived Hormones and Neuropeptides

The gastrointestinal system secretes a variety of factors that participate in appetite regulation and the maintenance of energy homeostasis in conjunction with the nervous system. Several of these factors have direct effects on bone mass or may impact bone metabolism by their interaction with hormones thus far discussed.

Peptide YY (PYY) is an anorexigenic hormone principally secreted by intestinal endocrine cells, and two forms predominate in the circulation: PYY_{1-36} and PYY_{3-36} [117, 118]. Serum levels of PYY are elevated in AN compared to lean or obese groups [119, 120], and mean overnight PYY levels in women with AN inversely correlate with BMD at multiple sites [121]. PPY and neuropeptide Y (NPY) bind to Y2 receptors with an approximately equal affinity, and PYY_{3-36} is a selective agonist of the Y2 receptor [117]. Central activation of Y2 receptors appears to inhibit osteoblast activity, and hypothalamus-specific adult-onset Y2 receptor deletion in mice results in an anabolic bone phenotype [122]. PYY also displays significant affinity for Y1 receptors, and deletion of Y1 receptors in bone marrow stromal cells enhances osteoblast proliferation and activity [117,123]. Studies in rodents suggest that PYY may regulate the gonadal axis [124, 125].

Ghrelin is an orexigenic peptide secreted by the stomach and is a potent GH secretagogue [126]. Levels of ghrelin are elevated in AN and are reduced in obesity [127, 128]. Ghrelin levels predict BMD parameters in healthy girls and elderly men [129, 130]. In vitro experiments in rats demonstrate that ghrelin stimulates osteoblast proliferation [131]. Like PYY, ghrelin modulates the gonadal axis. In rat models, ghrelin regulates the gonadal axis at the level of the hypothalamus and pituitary, and ghrelin administration to men suppresses luteinizing hormone secretion [132, 133]. Additionally, ghrelin influences β-cell survival, insulin secretion, and insulin sensitivity [134].

Insulin integrates effects of many of the hormones thus far discussed. In rodents insulin exerts anabolic effects on bone in vivo [135, 136]. Insulin stimulates osteoblasts directly and may participate in a regulatory loop between the bone and pancreas in conjunction with osteocalcin [137, 138]. Serum insulin levels are often elevated in obese individuals and are reduced in girls with AN compared to healthy controls. Insulin levels correlate with markers of bone turnover in AN and predicts BMD in elderly men and women [139, 140]. Consistent with these findings, patients with type 1 diabetes, a state of insulin deficiency, have an increased risk of fracture [141].

NPY is emerging as a significant intermediary between fat, bone, and the nervous system. NPY is an orexigenic hormone produced in the central and peripheral nervous system, with particularly high expression in the hypothalamus [142, 143]. Recent studies have also shown

that NPY is expressed by subcutaneous and visceral fat in rodents and humans and by osteocytes and osteoblasts in mice [144–147]. Peripherally, NPY receptors are expressed on mesenchymal stem cells (MSCs), osteoblasts, preadipocytes, and adipocytes in mice [123, 144, 147]. Current evidence suggests that NPY acts centrally in the hypothalamus and peripherally to inhibit osteoblast activity. Central and peripheral NPY also promote lipogenesis [148]. In a small study, serum levels of NPY were increased in women with AN compared to healthy controls [149]. In a study of lean, overweight, and obese adults, serum NPY correlated positively with BMI, although this association appeared to be present only among hypertensive subjects [150].

Bone Marrow Adiposity

The regulation of bone marrow MSC differentiation has been the focus of extensive research. Osteoblasts and marrow adipocytes differentiate from MSCs [151]. Regulation of MSC differentiation into these lineages may influence bone formation [152]. Studies have demonstrated an inverse correlation between marrow fat content and BMD in adolescents and adults and linked age-related bone loss to increased marrow adiposity [153–157]. Higher marrow fat content has also been observed in prolonged immobilization and women with AN [158, 159]. Hormones implicated in the regulation of MSC differentiation include estrogen, IGF-1, and glucocorticoids [160–162]. More recently, Pref-1 has been shown to inhibit adipocyte and osteoblast differentiation [163–165]. Serum levels of Pref-1 are elevated in women with AN compared to healthy controls, and levels of Pref-1 correlated positively with bone marrow fat content and inversely with BMD [166]. The role of bone marrow adiposity as a factor in bone mass regulation is under active investigation.

Conclusions

Body composition influences bone directly via mechanical stimuli and adipokine secretion and more obliquely through the communication with and modulation of various central and peripheral pathways. The metabolic characteristics of adipose tissue are not uniform, and different depots may exert distinct effects on the regulation of bone mass and structure. The effect of body composition on clinical outcomes, namely fracture risk, integrates the metabolic effects of energy balance, lean mass, and adipose tissue mass on bone and the frequency and severity of mechanical “challenges” that the skeleton encounters. Enhanced understanding of the pathways that govern skeletal metabolism will support the identification of therapeutic strategies to maximize skeletal strength.

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