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Bone Metabolism in Obesity and Weight Loss

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Abstract

Excess body weight due to obesity has traditionally been considered to have a positive effect on bone; however, more recent findings suggest that bone quality is compromised. Both obesity and caloric restriction increase fracture risk and are regulated by endocrine factors and cytokines that have direct and indirect effects on bone and calcium absorption. Weight reduction will decrease bone mass and mineral density, but this varies by the individual's age, gender, and adiposity. Dietary modifications, exercise, and medications have been shown to attenuate the bone loss associated with weight reduction. Future obesity and weight loss trials would benefit from assessment of key hormones, adipokine and gut peptides that regulate calcium absorption, and bone mineral density and quality by using sensitive techniques in high-risk populations.

Keywords

body weight; bone; caloric restriction; hormones; calcium; nutrients

INTRODUCTION

Obesity and osteoporosis are growing concerns worldwide, and both are attributed to a poor diet, excess caloric intake, and/or lower physical activity. An estimated 1.5 billion people were obese in the year 2008 worldwide (191), and in the United States, 34% of the population is obese, and 68% is either overweight or obese. This has led to an increased risk for several comorbidities, including cardiovascular disease (CVD), type 2 diabetes, and certain cancers (48). Osteoporosis is often referred to as a silent disease and therefore contrasts the high visibility of obesity. In the United States, osteoporosis affects 55% of the population over 50 years of age (116). One out of three women will suffer a fracture compared to one out of five men, but mortality afterward is greater in men. Neither obesity nor osteoporosis is considered to be a part of normal aging, and both conditions have common hormonal alterations and are associated with increased proinflammatory cytokines and oxidative stress. These factors contribute to increased fat acquisition and loss of bone mass.

Body weight is directly associated with bone mineral density (BMD). A low body mass index (BMI) has been identified as an important risk factor for lower BMD and predicts greater bone loss in older age (118, 138) and in younger persons in the absence of menses and/or an eating disorder (113). On the other hand, a high body weight can be due to increased physical activity or obesity, and both will increase BMD, but there is increasing

evidence that excess weight due to adiposity is detrimental to bone and fracture risk. In addition, although weight reduction is recommended to reduce comorbidities related to obesity, it also induces bone loss and increases risk of fracture in older individuals. Dietary factors, exercise, and some medications will attenuate bone loss due to weight reduction. This review addresses how obesity due to greater adiposity and weight reduction separately and together influence bone quality, bone turnover, and bone loss and examines how interventions influence bone metabolism during weight reduction.

OBESITY AND BONE

Cellular Relationship of Adiposity and Bone

The pluripotent stromal cell differentiates into mature cell types—adipocytes, osteoblasts, and chondrocytes. Because the stromal cell can differentiate into an osteoblast or adipocyte, this can eventually determine the balance between bone and adipose tissue. This is further evident in multiple clinical conditions that show a relationship between bone marrow fat and BMD. Both osteoporosis and aging-related bone loss are associated with an increase in marrow adipogenesis (108), which may suggest a conversion of stromal cells to adipocytes rather than osteoblasts. It remains unclear whether adipocytes and osteoblasts respond in a unique and possibly opposite manner to the same factor that is regulating differentiation to ultimately affect the bone and fat relationship.

The peroxisome proliferator–activated receptor-δ (PPARδ) plays a central role in initiating adipogenesis and inhibiting osteoblastogenesis (145). Several drugs act as ligands for PPARδ. These include the thiazolidinedione class of antidiabetic drugs (i.e., rosiglitazone) that increase insulin sensitivity (175) and have also been shown to increase adiposity, reduce bone mass, and increase fracture risk (68). Another example of drugs that increase adiposity, especially visceral fat, at the expense of osteoblast differentiation are glucocorticoids. In addition, low-density lipoprotein oxidation products promote osteoporotic bone loss by directing progenitor marrow stromal cells to undergo adipogenic instead of osteogenic differentiation (127). Furthermore, skeletal unloading due to immobilization or inactivity increases adipocyte differentiation and inhibits osteoblast differentiation (1). There is also evidence that the higher adiposity in obesity is associated with a lower rate of bone formation (126). Overall, a further understanding of the cellular connection between adipocytes and osteoblasts could result in drugs to inhibit marrow adipogenesis and attenuate age-related bone loss.

Factors Influencing Bone in Obesity

Hormonal and mechanical loading—The higher BMD and bone mineral content (BMC) in obesity are attributed to multiple factors (153). These include a greater mechanical loading on bone (53, 198) and the altered hormonal milieu and higher serum levels of adipokines associated with obesity (41, 153, 197). Other genetic and environmental factors such as smoking, dietary intake, and lifestyle also play an independent role in influencing bone mass in obesity.

In comparison with leaner individuals, in obese persons higher levels of serum estrogen and parathyroid hormone (PTH), lower 25 hydroxyvitamin D (25OHD) and sex hormone–

binding globulin (SHBG), and possibly lower 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) are found (95, 153, 197), and all have specific actions on bone. Higher levels of serum estrogens in obese postmenopausal women and men in comparison with leaner individuals are largely derived from the metabolism of circulating androstenedione by adipose tissue. The lower serum levels of 25OHD in obesity are likely due to storage in adipose tissue (193). In contrast, it is not clear why excess body fat is associated with higher PTH (16, 131), but PTH affects calcium metabolism and proinflammatory cytokines (65, 164), which would have a detrimental effect on bone.

Obesity is also associated with higher levels of pancreatic hormones such as insulin, amylin, and preptin (86) that are anabolic to bone (21, 30, 35). Levels of several adipose-derived peptides and enzymes, such as aromatase, hydroxyl steroid dehydrogenase, leptin, and resistin are higher in obesity and have specific anabolic or catabolic actions on the osteoblast (87, 129, 130). Adiponectin is reduced in obesity (5), and in vitro observations show it increases osteoblastic activity (104), yet clinical studies do not necessarily support a positive effect on bone (6, 7, 85, 100) or fracture risk. Obesity is also associated with higher circulating concentrations of inflammatory cytokines, such as interleukin-6 (IL-6), monocyte chemoattractant protein-1, and C-reactive protein (CRP) (67). In leaner populations, higher inflammatory cytokines have been associated with higher bone turnover (11, 83, 93, 114), and their role in regulating bone in obesity is likely also important (159) but is not clearly understood. It is possible that the low level of chronic inflammation in obesity is counterbalanced by adipose-derived estrogen and/or other factors such as weight bearing activities to prevent bone loss that occurs in leaner populations.

Mechanical loading—The skeletal tissue is highly responsive to its mechanical environment, and strain will maintain mineral homeostasis (52). In addition, mechanical loading also stimulates bone formation by decreasing apoptosis and increasing the proliferation and differentiation of osteoblasts and osteocytes (43). Mechanical loading, in fact, favors osteoblastogenesis at the expense of adipogenesis by downregulating PPARδ in bone marrow stromal cells (37). It is well established that dynamic loads due to muscle contraction are more anabolic to bone than are static loads (177) induced by excess adipose tissue and relates to the differential mechanostatic sensitivity of these tissues (52, 156). Thus, obesity may not confer a mechanical advantage to the bone if not accompanied by greater lean mass and a physically active (nonsedentary) lifestyle.

Body Composition and Bone

Lean and fat masses are both independent determinants of bone mass. Lean mass is a reflection of physical activity, whereas adipose tissue acts as an endocrine organ with an important influence on the bone, as described above (41, 153, 197). In premenopausal women, low muscle mass is associated with low BMD (162), and the positive effect of a higher body weight on bone occurs only when it is primarily composed of lean mass (149). The excess weight in obesity is primarily attributed to excess adipose tissue, yet in general, there is also higher fat-free soft tissue to support the weight. The positive effect of a higher lean mass on BMD may be attributed to lifestyle factors including exercise and diet, estrogen sufficiency, genetic influences, or a combination of these factors (152). Also,

greater muscle mass has an independent effect on better balance and therefore reduces frailty and falls associated with osteoporotic fracture. Fat mass shows a direct correlation with bone in some studies of postmenopausal women (26, 42, 102), but not necessarily in children and young adults (63, 80), and may differ by skeletal site and amount of trabecular/cortical bone (89). At least some of these studies have corrected for muscle mass, so the independent effect of fat on bone could be determined, which can explain some of the different conclusions in these studies. In addition, the location of fat accumulation, including visceral adipose tissue (VAT) compared to subcutaneous tissue, may differentially influence bone. For example, studies in postmenopausal women suggest a positive relationship between VAT and bone, but not in children or men, and again findings may depend on the specific bone site that is measured (56, 96, 105, 187). However, many of these studies measure trunk fat using dual-energy x-ray absorptiometry (DXA), which includes both subcutaneous and visceral depots, unlike quantitative computed tomography (QCT), which can distinguish between fat depots. Higher VAT is associated with greater dyslipidemia, insulin resistance, and inflammatory cytokines, which would be expected to have a detrimental effect on bone. Nevertheless, a decrease in VAT due to weight loss has been shown to decrease BMD (18), suggesting that other factors unrelated to VAT are regulating bone during caloric restriction (CR). Besides white adipose tissue, increased bone marrow fat tissue has been shown to be associated with lower BMD (157), whereas brown adipose tissue may be important in maintaining bone (20). Understanding how lean tissue and the type and amount of adipose tissue influence BMD in different populations is important to better estimate fracture risk under conditions where body composition is altered.

Bone Mass, Quality, and Fracture

There is greater calcium retention during growth in obese children (74) and higher bone mass in obese adults (197). Not surprisingly, the higher BMD in obesity is not proportional to the increase in body weight because adiposity is the major component of excess weight gain. Therefore, BMD per unit BMI is lower in obesity (38). Indeed, studies suggest that excess adipose tissue may have a negative impact on bone quality in adults and children (80, 132, 165, 198). Also, studies show lower bone formation relative to resorption markers in obese compared with leaner populations in adults (27, 126) and children (40). Excess adiposity and a high-fat diet may be particularly detrimental to BMD and bone quality during growth, as demonstrated in rodent studies (24, 128, 190).

Bone quality is a composite of BMD (cortical and trabecular), bone geometry, and bone strength and is considered a major determinant of fracture risk. Several techniques are used to measure BMD (19) and other aspects of bone quality. DXA is the gold standard method of measuring areal BMD (aBMD), BMC, and soft tissue composition. Low aBMD predicts fractures, but the sensitivity and specificity of the prediction are low since more than half of all fractures occur in persons without osteoporosis, as defined by aBMD. Newer noninvasive imaging techniques, including volumetric assessments of bone density (vBMD) and geometry, bone compartments (trabecular and cortical), and microarchitecture, and measurements of bone strength such as finite element analysis, provide estimates of bone fragility (19). These in vivo high-resolution bone-imaging techniques, such as QCT and high-resolution magnetic resonance imaging assessed at axial (hip and spine) or peripheral

(radius and tibia) sites, combined with DXA can improve estimates of bone strength and fracture risk in the future.

There is evidence that bone quality is altered in obesity. The obese have lower cortical BMD, as measured by peripheral QCT in comparison with age-matched leaner individuals (132, 165, 169, 188). Serum PTH, which is elevated in obesity (16, 165), has known catabolic actions on cortical bone, with less evidence for an effect on trabecular bone (25). Other obesity-induced factors may also affect bone quality and may contribute to the higher-than-expected fracture risk for a given BMD in this population (133). The extent to which an altered bone quality and/or balance contribute to fractures in the obese is not known and should be addressed in prospective studies.

There is consistent evidence for a higher fracture risk in the obese pediatric population that may be explained by an altered bone quality or mineralization (40). It is not clear why obese children have a higher fracture risk, but it could be related to abnormal bone mineralization (39, 40), poor balance (62), or force upon falling creating a greater risk for injury and fracture (62, 137). In older women, there is a higher site-specific fracture risk with higher BMI at the humerus, and in both men and women at the ankle (58, 78, 32, 134), and the higher fracture risk occurs in the presence of normal BMD (119, 133) (Figure 1). In contrast, there is a lower risk of hip, vertebral, and forearm fractures with higher BMI (58, 78). In addition, BMI adjusted for BMD is associated with a higher risk of hip fracture when BMI is greater than 35 kg/m^2 (38). The high BMI–fracture link in obesity may be influenced by altered bone quality, different patterns or forces upon falling, or the greater padding by adipose tissue at specific bone sites.

WEIGHT REDUCTION AND BONE

A weight loss of ~10% will have a positive effect on the comorbidities associated with obesity. However, this also results in a 1% to 2% bone loss at the hip and total body and a 3% to 4% loss at highly trabecular sites such as the trochanter and radius (143, 163, 182). The weight-loss-induced BMD reduction has been found in peri- and postmenopausal women and older men (14, 45, 98, 118, 148, 153, 184) and is more than double the annual rate of bone loss in weight-stable individuals. In addition, it is unclear whether the rate and amount of weight loss influence the loss of bone, since in the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) trial, middle-aged individuals on a very-low-energy diet who rapidly lost 15% of their body weight did not show a greater bone loss than did individuals in a slower, moderate weight loss intervention (139). Furthermore, the long-term effect of weight loss continues, based on one-year follow-up studies (75, 182). Short-term (less than six months) weight loss studies are not reported in this review because bone remodeling requires a minimum of four to six months and may continue for one to two years (72).

Several epidemiological studies have addressed the influence of voluntary or involuntary weight loss on bone over a long period of time. In one study, approximately 1,500 men were followed up for 30 years to assess the influence on bone with a 5% to 10% weight loss or regain (109). The prevalence of osteoporosis in the lowest quartile of baseline BMI was 31%

in persons losing weight compared with 4% in those who gained weight (109). In another study, men who lost greater than 5% of body weight had a 1.7% total hip BMD loss/year compared with 0.1% loss in men who were weight stable (45). A recent study in elderly women identified risk factors for hip BMD loss over four years and concluded that women who gain weight show attenuated BMD loss at the trochanter, femoral neck, and total hip (66). Importantly, high rates of BMD loss, weight loss, and weight fluctuation are also predictors of all-cause mortality in elderly men and women (117).

Fracture Risk

Weight loss of only about 5% is associated with bone loss and increased fracture risk in both men and women (36, 97, 98, 110, 111). The risk of fracture also increases in individuals of low body weight and in those who have a history of weight loss (44, 76, 97, 115). In community dwelling older women (98) and men (115), those who lost greater than 10% of body weight had the highest risk of hip fracture. In a study examining ~11,000 men and women, a 10-year reduction in BMI (-2 kg/m^2) compared to an increase (1 kg/m^2) was associated with an elevated nonvertebral fracture risk of about 1.7 (hazard ratio) in nonsmokers (189). Another longitudinal study with a 17-year follow-up period in over 7,500 postmenopausal women who lost 5% or more of their weight showed a 33% increased risk of distal forearm fractures compared with those who lost less than 5% of their weight (123). Both voluntary and involuntary weight reduction result in loss of BMD and increase fracture risk in older men and women at several bone sites.

Gender, Age, and Initial Body Weight

Bone loss and increased fracture risk due to weight reduction occur in both older women and men, but neither has been demonstrated in younger individuals (139, 144, 156, 179). The absence of bone loss may be due to the well-maintained muscle in men and young women (180). In a controlled six-month weight loss trial, 38 obese (average age 44 years; BMI of 35 kg/m^2) premenopausal women lost 8% of their body weight without significant BMD loss (156). Because a lower initial body weight could result in bone loss, another study was conducted in 44 overweight premenopausal women (average age 38 years; BMI of 28 kg/m^2) (144). In this study, six months of weight reduction resulted in 7% loss of body weight and no loss of BMD at any site (144). Others also found that bone is preserved in younger men and women with adequate calcium intake during moderate weight loss (139), yet bone is not spared under conditions of extreme weight loss (see Bariatric Surgery and Extreme Weight Loss section below). In rodents, biomechanical properties of bone are reduced more in older compared with younger energy-restricted rats (171). This is consistent with evidence of a higher fracture risk in the older populations that lose weight (36, 97, 98, 110, 111).

Studies show that initial body weight is not only a predictor of bone loss due to aging (76, 118), but that weight reduction also causes greater loss of bone in leaner populations. In a large study of older women and weight loss (≤5%), thinner women (<60 kg) lost more femoral neck BMD (3%/year) compared with heavier women (>70 kg) who lost <1%/year (118). There is also some evidence that initial body weight results in a greater loss of trabecular than cortical bone in rodent studies (71). Multiple mechanisms may influence a

differential response of bone to energy restriction in obese compared with leaner individuals, such as a greater decline in serum estrogen and other sex steroids.

Both obesity (132, 165) and weight reduction (69) are associated with reduced cortical bone density, and the combination may pose a unique risk to cortical bone. Randomized clinical trials have assessed how dietary or exercise interventions during CR or surgical interventions influence bone, and findings are discussed below.

Factors Leading to Bone Loss During Weight Loss

Hormones, cytokines, and peptides influencing bone during CR—Several bone-regulating hormones are altered during CR and with weight reduction. A reduction in adiposity decreases circulating estrogen and other sex hormones (121) and increases sex hormone–binding globulin. These changes negatively influence bone osteoblastic (46) and osteoclastic activity directly or indirectly (73) due to increased levels of cytokines (i.e., IL-1, IL-6, and tumor necrosis factor-α). Weight loss studies show that a decline in estradiol correlates with BMD loss (141, 151). Even small decreases in estradiol and other sex steroids lead to a rise in bone resorption and loss in both older women and in men (47, 90), so small changes due to loss of adiposity are important in older individuals.

There is a rise in the Ca-PTH axis during CR in women consuming low Ca, which would increase bone resorption (141, 153). Serum 25OHD rises with weight loss (106, 143) due to its release from adipose tissue (22), but this should not have a detrimental effect on bone. Short-term CR also increases serum levels of cortisol (143, 174), and this may be linked to bone loss (9). Also, during CR there is a decrease in serum insulin-like growth factor-1 (IGF-1) (125). Serum IGF-1 increases osteoblast differentiation and BMD (120), and hence a decrease in IGF-1 associated with CR would negatively influence bone.

The adipocyte-derived hormones may also play a role in bone metabolism during weight reduction. Leptin is an anorexic hormone with both central and peripheral effects to inhibit bone formation, possibly through sympathetic signaling (170), and direct effects on osteoblasts (172) and osteoclasts (77). The role of reduced leptin on bone in clinical weight loss trials is likely complicated due to its varied peripheral and central effects and leptin resistance in the obese population. For example, leptin administration does not prevent a rise in bone resorption and decrease in formation due to weight reduction in obese patients (34), yet it increases BMD in amenorrheic women in energy-deficient states (158). Adiponectin, the anti-inflammatory adipokine, is low in obesity and increases with 10% or more weight loss (92), but its role in the regulation of bone mass is not clear (6). Because adiponectin suppresses osteoclast number and activates osteoblastogenesis (124), it is possible that a rise due to weight reduction would have a beneficial effect on bone mass. Other adipokines such as resistin and visfatin that are altered due to weight reduction do not consistently show an association with BMD (12).

Several gut peptides [i.e., ghrelin, incretins, cholecystokinin (CCK), peptide YY (PYY), and pancreatic polypeptide (PPY)] that regulate satiety are altered during CR and also regulate bone. Ghrelin, an appetite-regulating hormone, increases in response to weight reduction (91, 166) and modulates the proliferation and differentiation of osteoblasts (54). However, a

recent systematic review examining 59 studies concluded that there is a lack of convincing data to support an association between ghrelin and BMD or fractures (12). The incretin hormones, gastric inhibitory polypeptide and glucagon-like peptide-1 and -2, which are released upon meal ingestion and decrease with weight loss, appear to have an anabolic effect on bone (195). PYY and PPY are neuropeptides implicated in the regulation of energy balance and bone mass. For example, PYY-deficient mice show a reduction in trabecular bone mass and deficit in bone strength (192), and PYY levels decrease following weight reduction (166). Serum levels of amylin and CCK are both reduced due to weight reduction (166). Amylin is a peptide hormone cosecreted with insulin from pancreatic beta cells and has been shown to stimulate bone formation and decrease bone resorption (21), whereas the role of CCK on bone is not well understood. Currently, there is no clear link between the change in gut peptides during CR and its influence on bone metabolism and loss.

Calcium absorption and other factors influencing bone during CR—Energy restriction also reduces calcium absorption efficiency (28, 29), and it is another mechanism whereby weight reduction could regulate bone loss. Several of the endocrine changes due to CR may also be regulating the decrease in calcium absorption. For example, reduced estrogen levels (29, 71, 122, 141) and a rise in cortisol may have a direct detrimental effect on calcium absorption (28). Consistent with these observations, the high serum PTH that has been shown to occur with weight reduction (141, 153) may be a response to decreased calcium absorption. In addition, the reduced weight bearing and the loss of lean mass due to CR may contribute to bone loss (see Exercise-Induced Weight Loss section). Insufficient micronutrient intake during CR could contribute to bone loss yet cannot explain it entirely because micronutrient replacement in clinical trials (143, 163) and in rodent studies also resulted in bone loss (69, 171). The loss of mass resulting from weight reduction would decrease mechanical loading to bone, especially if the loss consisted of lean soft tissue in addition to adipose tissue.

Overall, the interaction between hormones, growth factors, and cytokines and their effects on calcium absorption and bone during caloric restriction are complex (Figure 2), and this is influenced by other factors such as initial body weight/composition, the amount of weight loss, gender, age, and ethnicity. A change in the endocrine profile due to energy restriction can affect bone both directly and indirectly. Targeting the primary regulators and/or organs that respond to energy restriction and influence calcium metabolism are approaches to minimize or prevent bone loss.

Intervention Studies: Strategies to Reduce Bone Loss During Caloric Restriction

Dietary and clinical interventions can help attenuate bone loss with weight reduction, such as increasing a specific micro- or macronutrient and/or physical activity.

Calcium—Randomized controlled trials (RCTs) have shown that calcium supplementation will attenuate the increased activity of the calcium-PTH axis and decrease bone turnover and loss at multiple sites in post-menopausal women who reduce their weight. One study in obese postmenopausal women showed that 1g Ca/day compared with placebo suppressed bone turnover and total body BMD loss (140). In another double-blind RCT study, 66

overweight postmenopausal women (age 61 years) reduced body weight by 9% over six months (143). This resulted in 4% loss of trochanter BMD when consuming 1 g Ca/d but not in women consuming a higher Ca intake of 1.7 g/d (143). Even with supplementation of calcium (1.7 g/d), postmenopausal women with moderate activity level continue to lose trochanter and spine BMD. In another six-month randomized CR trial, 52 women (14 postmenopausal) were assigned to Ca supplement or no treatment (81). A loss of 5.5% of body weight resulted in 2.2% total body BMC loss and 4% loss of hip BMC only in the untreated group of women (81). In contrast, double-blind RCT studies of premenopausal women showed no bone loss over a six-month period irrespective of Ca intake (<0.8 g–1.8 g/d) (144, 156). In one of these weight-reduction studies, 1 g of Ca supplementation tended to increase lumbar spine BMD by 1.7% compared with the placebo. However, this was likely due to low Ca intake before the study and filling of resorptive space (156). In studies of extreme weight loss and bariatric surgery, calcium and vitamin D supplementation is less effective in suppressing bone turnover and loss (see Bariatric Surgery and Extreme Weight Loss section below). The effect of Ca intake in men during CR has not been specifically examined, but it is hypothesized that older men losing weight would also benefit from supplemental Ca intake.

Protein—The positive effect of a higher protein intake on bone has been established in several epidemiological and clinical studies (33). A higher-protein weight loss diet may preserve bone mass during caloric restriction by various mechanisms such as attenuating the decrease in IGF-1 or Ca absorption or by other physiological changes accompanying a higher protein intake. Caloric restriction leads to a decrease in serum IGF-1 and IGF-1/IGF binding protein (BP)-3 ratio, whereas a higher protein intake raises these levels. Additionally, a higher protein intake increases Ca absorption (88), which thus may attenuate the decrease in Ca absorption associated with caloric restriction. There are reports showing that a higher-protein diet will decrease bone turnover and loss during CR (154), but these studies failed to control for Ca or other nutrients (161, 173). In a one-year randomized controlled trial in our laboratory, 47 postmenopausal women either received a higher-protein (24% of total calories) or a normal-protein (18% of total calories) diet with a controlled Ca intake totaling 1.2 g/day in both groups (163). After one year, women lost 7% of body weight. The higher-protein (86 g/d) compared with the normal-protein (60 g/d) diet attenuated (*a*) the loss of BMD at the ultradistal radius and lumbar spine, (*b*) total hip and trabecular volumetric BMD, and (*c*) BMC of the tibia. This was attributed to the higher final values of IGF-1 and IGFBP-3 and lower bone resorption in the higher-protein diet. Thus, a dietary protein intake of up to 24% of total calories, even without higher Ca intake than recommended, will attenuate bone loss due to weight reduction.

Vitamin D—The effect of vitamin D on BMD in combination with Ca is well established (79). To address the 10% reduction in calcium absorption caused by caloric restriction (29), we conducted a double-blind RCT in 82 overweight/obese women who were assigned to 2,500 IU of vitamin D/d (Hi-D) compared to 400 IU/d. We used dual stable isotopes of calcium and measured true fractional calcium absorption (TFCA) at baseline and after six weeks of CR. Our preliminary results showed a greater rise in 25OHD (+8 ng/ml) and no reduction in TFCA in the Hi-D group, whereas the 400 IU/d vitamin D group showed no

change in 25OHD (+1 ng/ml) and the expected CR-induced reduction in TFCA (155). The results of this study indicate that CR is not associated with a decline in Ca absorption with higher vitamin D, and the possibility that this will attenuate bone loss due to weight reduction is currently being addressed.

Other nutrients and foods—The role of several other nutrients on bone has been examined in long-term clinical or animal studies. Studies consistently show a positive influence of dairy on BMD (107). Other foods, such as dietary amylase-resistant starch (15), also attenuate bone loss associated with weight reduction (and cycling) in rodents. Phytoestrogens and functional foods such as dried plum, flaxseed, and garlic have shown some positive effects on bone yet have not been studied specifically during CR. In addition, other vitamins and minerals have smaller effects on bone health. Overall, with the exception of vitamin D and calcium, there is little or no evidence for a role of other foods or nutrients in attenuating bone loss during CR.

Exercise-induced weight loss—The mechanical load on the skeleton may contribute to the higher bone mass in obesity and the bone loss due to weight reduction. Exercise training in adults reduces BMD loss in the presence of adequate calcium (135). The types of physical activity most likely to have beneficial effects on reducing fracture risk are those that include impact forces that generate both gravitation and muscle loading (94).

Exercise added to weight loss regimens attenuates bone loss at the hip or femoral neck compared with diet alone (147, 159, 184). Yet as compared with a weight-stable group, weight reduction with exercise in older individuals (148, 151, 167, 185) is associated with bone loss, suggesting that it can be attenuated but not prevented. When CR is combined with exercise, a few factors may attenuate the bone loss, including an increase in IGF-1 and a reduction in inflammation in adults (159) and children (10). In addition, exercise attenuates lumbar spine bone loss with 8% weight reduction in relatively lean (BMI of 25 kg/m^2) perimenopausal women (148). It is possible that the improvement in physical function associated with exercise during dieting (150, 183) is just as important as increasing BMD to prevent falls and fractures. In children, weight loss may slow bone growth (146), and although it would be expected that exercise would have a positive effect, this has not been specifically addressed.

The mechanical loading advantage of excess body weight on bone may be reduced with weight reduction. However, weight loss resulting primarily from loss of fat rather than lean tissue (such as with exercise) should maintain this mechanical advantage on bone. Overall, exercise attenuates bone loss during conditions of weight stability and loss in older individuals, but some bone loss will occur nevertheless. Hence, factors in addition to reduced weight bearing are also contributing to the loss of bone associated with weight reduction.

Medication and other factors—Medications to treat osteoporosis, such as estrogen and raloxifene, during weight reduction will prevent bone loss (64), and a study in rodents shows that low-dose PTH can maintain normal bone formation during rapid weight loss (178). Several herbal supplements (194) have also shown a positive influence on BMD; however,

use of medications or herbal remedies to prevent bone loss during caloric restriction remains an experimental approach.

Bariatric Surgery and Extreme Weight Loss

An increasing number of individuals with severe obesity are undergoing bariatric surgical procedures that are associated with substantial weight reduction and amelioration of obesity-related comorbidities. Bariatric surgery also increases the risk for development of metabolic bone disease (59, 60). The malabsorptive procedures [Roux-en-Y gastric bypass (GB) and duodenal switch] compared with those that only reduce stomach size (gastric banding) induce greater weight reduction as well as bone loss, persistence of high serum PTH, and a rise in 25OHD (60, 142, 160, 181). One study also found a rise in serum levels of 1,25OHD (160). A 27% to 35% weight loss six to 18 months after GB surgery results in BMD loss of 9% to 10% at the hip and 3% at the lumbar spine, despite adequate calcium intake of 1.2 g/d or more (31, 49, 57, 84, 181). In a longer (three-year) study, GB individuals lost 30 kg body weight, and BMD decreased by 13.6% and 5.5% at the femoral neck and lumbar spine, respectively (181), suggesting that bone loss continues but at a less rapid rate after weight stabilizes. The amount of bone lost from different sites may differ: Four years after GB surgery, women have higher lumbar spine BMD and lower femoral neck BMD in comparison with weight-matched controls who never had surgery (60). The differential bone loss in GB women may be attributed to the high serum PTH (60) or the presence of spinal osteoarthritis that overestimates BMD and is more common in patients with a history of severe obesity (103). The bone loss due to extreme weight reduction is not simply proportional to the loss in body weight. For example, BMD loss at the hip is two to three times greater than expected after GB compared with 1% to 2% BMD loss found with 10% weight loss. This may be partially related to the 33% reduction in Ca absorption due to GB surgery (142). However, because absolute absorption (24%) is not especially low after GB, other factors are also contributing to bone loss, such as the potential incidence of other micronutrient deficiencies (4), hormonal factors, and/or reduced weight bearing.

It does not appear that serum 25OHD influences bone loss, at least during the first year, since 25OHD levels rise after Roux-en-Y GB or gastric banding (49, 84, 160). In addition, supplementing with higher vitamin D does not further raise serum 25OHD (49, 160), although this has not been examined in a controlled trial. Although the American Society for Metabolic and Bariatric Surgery recommends high levels of Ca (1.5–2 g/day) and vitamin D intake (2,000 IU/day) following surgery (2), exact levels associated with beneficial outcomes are not known due to the lack of RCTs.

Weight Cycling

Weight cycling, defined as weight loss followed by regain (one or more times), is a concern because lean body mass is not typically regained as much as fat is with weight regain (8, 99). For example, Fogelholm et al. (51) found that women with a history of weight cycling have lower spine and distal radius BMD in comparison with those who are not weight cyclers. Importantly, Meyer et al. (111) showed that greater weight variability was associated with increased hip fracture incidence in women and men over a 12-year period (ages 50–62 years). Restrained eaters who chronically diet or who weight cycle may be at

greater risk of low bone mass or osteoporosis (3, 15, 111). Other researchers have not found an effect of weight cycling on bone, such as a cross-sectional study in younger pre-menopausal women (50, 55). After successful weight reduction in the obese individual, maintaining the reduced body weight over a longer duration may result in further bone loss even after weight stabilizes (182, 186) or when preserving muscle mass with the addition of exercise (75). In addition, individuals with lower compared with higher body weight who weight cycle would be expected to lose more bone (118).

Bone Measurement Concerns: Obesity and Weight Loss

Excess fat tissue surrounding the bone in obesity may result in DXA measurement errors for BMD (13, 17, 70, 176). The lack of homogeneity of the adipose tissue and fat overlying a specific bone site will affect the amount of error. Furthermore, measurement of sites with less surrounding fat thickness (for example, a peripheral site such as forearm or leg rather than axial sites such as spine) may reduce BMD artifacts in the obese (70). In addition, QCT, which measures true volumetric bone density (mg/cm^3) and uses the density of fat tissue as zero, can reduce artifacts associated with a two-dimensional measurement of areal bone density (g/cm^2) by DXA (196). Reporting BMC (g) is helpful because it is not an areal measurement, as is BMD; BMC (g) is typically reported in children due to its higher reproducibility (61). In general, measurement error in the lumbar spine (196) due to excess abdominal fat in the obese makes this site less desirable than the hip or other sites. In addition, obese individuals are at greater risk of spinal osteoarthritis and osteophytes (103), which contribute to the overestimation of bone mass. In our experience, the prevalence of spinal osteoarthritis in post-menopausal obese women is ~43% (140, 141). The International Society for Clinical Densitometry established criteria for vertebral exclusion to increase precision in patients with spinal deformities (101). An additional concern about BMD measurements in the obese is the difficulty of positioning them within the scan area on the DXA bed (23).

Weight reduction also alters the precision of DXA because of changes in the soft tissue surrounding the bone (136, 168, 176), but it does not cause systematic errors in longitudinal results in DXA studies (13). Experiments that simulate increases in body fat by sequential fat layering on bone show that this overestimates BMD measurements by DXA (82, 112, 196). In general, the accuracy of DXA measurements in extreme obesity (BMI >40 kg/m^2) is reduced, and studies examining extreme weight loss (typically about 35 kg) after gastric bypass would be expected to overestimate the decrease in BMD. Importantly, a reduction in BMD as a result of weight loss is not questioned because of the evidence in animal models and the higher risk of fracture, but there remain concerns about precision and the intrinsic limitations of measuring bone due to the varying amounts of excess soft tissue over time. However, this would primarily affect the interpretation of studies examining bone changes after *extreme* weight loss or studies of very lean individuals with weight gain because the errors are greater in individuals at the extremes of body weight. There is less concern about measurement error in studies with moderate weight loss or in studies with a control group. Instruments such as QCT, peripheral QCT, and magnetic resonance imaging can also reduce measurement error while addressing bone quality and the location of fat and should be considered for future trials.

CONCLUSION

Obesity and weight loss are both associated with alterations in bone metabolism. With a significant percentage of the population being either obese and/or undergoing weight reduction, the influence of these conditions on bone metabolism requires attention. The poor bone quality and higher fracture risk in obese individuals are only beginning to be understood, and well-designed prospective trials are required to address these issues and to explicate the mechanisms that regulate the effect of excess adiposity on bone. The use of additional sensitive imaging techniques to measure bone quality and the interaction of bone with the amount and location of adipose tissue will improve our understanding of fracture risk in different populations. Several clinical trials have investigated the effect of nutrient supplementation on bone during CR, and nutrients such as calcium, protein, and vitamin D alone or in combination have shown positive results. However, bone loss is not completely attenuated with nutrient supplementation during CR. The use of weight reduction and/or lifestyle changes to reduce the comorbidities associated with obesity needs to be encouraged, but it should be balanced with methods to prevent the risk of osteoporosis. Overall, understanding the mechanisms regulating bone in obesity and during CR should help address concerns about declining bone health with aging and in achieving peak bone density and strength in children.

Glossary

BMD	bone mineral density
BMC	bone mineral content
PTH	parathyroid hormone
25OHD	25 hydroxyvitamin D
DXA	dual-energy x-ray absorptiometry

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SUMMARY POINTS

1. Adipogenesis and osteoblastogenesis share a common cellular relationship.
2. Endocrine factors and body composition influence bone mineral density in obesity.
3. Bone quality is compromised in obesity.
4. Caloric restriction leads to changes in calcium metabolism, resulting in bone loss. Endocrine and other physiological changes during weight reduction regulate bone loss.
5. Nutrient, exercise, and drug interventions partially attenuate bone loss associated with caloric restriction.

FUTURE ISSUES

1. Well-designed prospective trials are required to investigate mechanisms regulating bone in the presence of excess adiposity.
2. The mechanisms regulating bone during caloric restriction can only partially explain the bone loss during and after weight loss and require further study.
3. Our understanding of fracture risk in different populations will be improved with the use of additional sensitive techniques to measure bone quality and its interaction with the amount as well as type of fat.

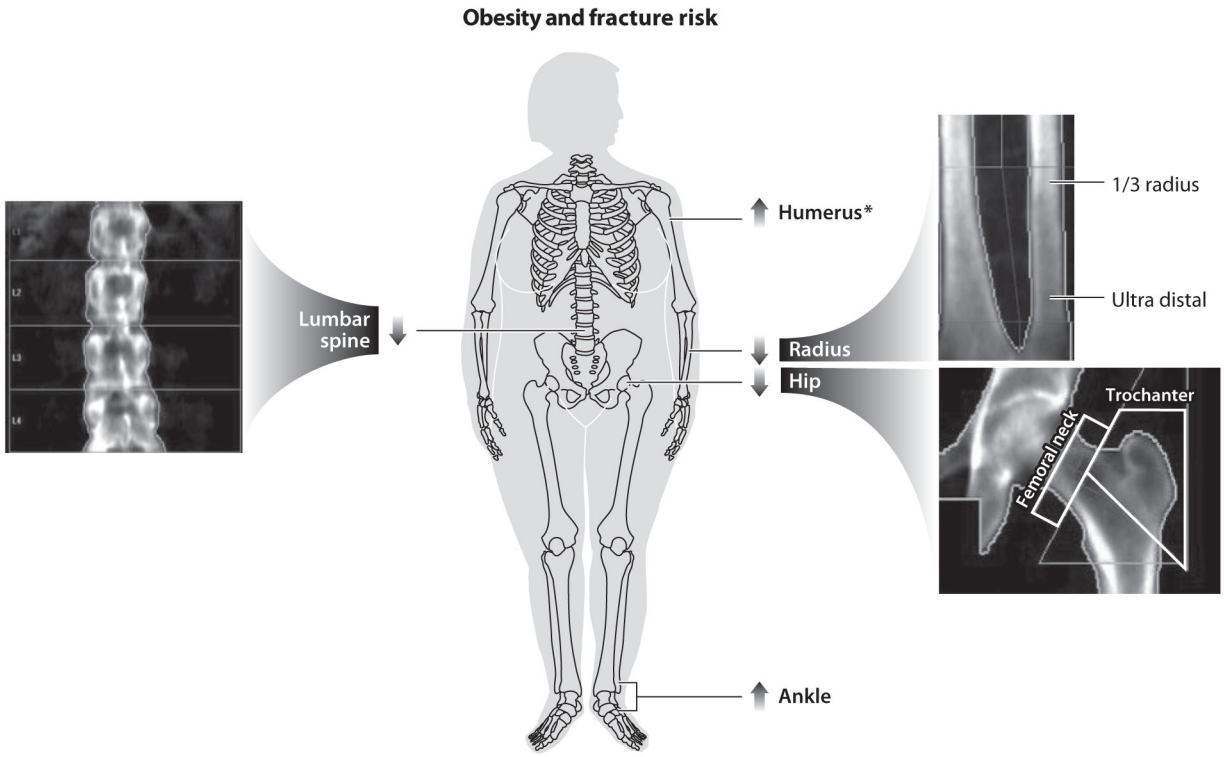

Figure 1.

Arrows indicate direction of fracture risk at bone sites measured by dual-energy x-ray absorptiometry showing axial (lumbar spine and hip) and peripheral sites (humerus, radius, and tibia/ankle) due to increased body mass index (obesity). *Higher humerus fracture due to obesity is found in women but not in men (32, 58, 78, 119, 134).

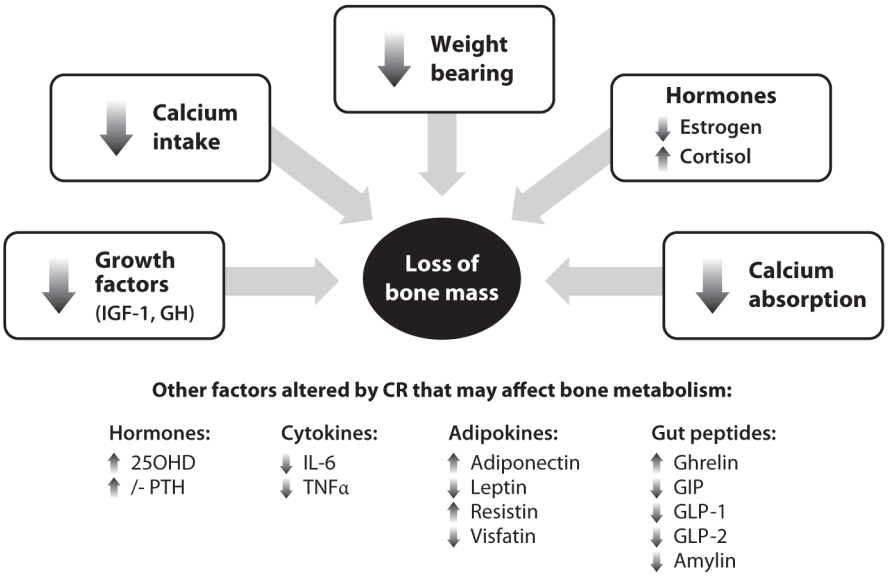

Figure 2.

Mechanisms leading to bone loss due to caloric restriction (CR) and weight reduction. 25OHD, 25 hydroxyvitamin D; GIP, gastric inhibitory polypeptide; GLP, glucagon-like peptide; IL-6, interleukin 6; PTH, parathyroid hormone.