The Hormonal Milieu in Obesity and Influences on the Trabecular, Cortical, and Geometric Properties of Bone

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Abstract

Obesity is associated with alterations in several endocrine factors, some of which are involved in regulating bone metabolism. The higher serum concentrations of parathyroid hormone (PTH), estradiol, pancreatic hormones, and adipokines such as leptin, resistin, and cytokines and the lower 25-hydroxyvitamin D (25OHD) have specific actions on the skeleton and regulate cortical and trabecular bone differently. Recent evidence suggests that bone quality is altered in obesity with a higher trabecular volumetric bone mineral density (vBMD), while cortical vBMD is lower. Also, the obese are at greater risk of fracture for a given BMD compared to normal weight individuals supporting the evidence that bone quality is altered due to excess adiposity. Higher concentrations of serum PTH have a catabolic effect on cortical bone and may play a role in reducing cortical vBMD in obesity. The lower serum 25OHD, higher leptin and resistin, and lower adiponectin may also independently contribute to the lower cortical vBMD in obesity. There is little evidence to show that higher pancreatic hormones and cytokines influence trabecular and cortical bone in obesity. The altered hormonal milieu in obesity is one important factor that explains bone architectural changes that occur due to excess adiposity. However, other factors such as diet, genetic factors, altered mechanical loading, and/or other environmental factors may also contribute to bone quality and site-specific fracture risk in obesity.

Keywords

Obesity • Hormones • Trabecular • Cortical • Volumetric bone mineral density • Body composition

Introduction

Obesity is a worldwide epidemic and the World Health Organization reports that at least 2.8 million people die each year as a result of excess body weight [1]. Obesity is considered a true epi-

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P. Burckhardt et al. (eds.), *Nutritional Influences on Bone Health*,
DOI 10.1007/978-1-4471-2769-7_4, © Springer-Verlag London 2013

demic because while rates are disparate across different socioeconomic and racial/ethnic groups, the rise in obesity is similar [2]. It is associated with an increased risk for several comorbidities, including cardiovascular disease, type 2 diabetes, and certain cancers [3]. It has long been established that bone mineral density (BMD) is greater in obesity; however, newer studies suggest that bone quality is altered and show evidence of fractures in this population. The relationship between excess adiposity and bone is likely influenced by the pluripotent stromal cell [4] that differentiates into adipocytes and osteoblasts, as well as chondrocytes. Several endocrine aberrations are seen in obesity, some of which have an important effect on the skeleton. In addition, multiple other factors contribute to BMD and fracture risk in obesity, including mechanical loading of excess body weight on bone [5, 6]. This chapter discusses the unique aspects of bone and fracture risk due to obesity with a focus on the hormonal milieu and its influence on the bone trabecular and cortical compartments of bone and geometry.

Areal and Volumetric Bone Mineral Density: Implications in Obesity

Dual-energy X-ray absorptiometry (DXA) is a valuable two-dimensional bone imaging technique that can assess the relationship between body composition (fat and lean tissue) and bone mineral content (BMC) and areal BMD (aBMD). Although it is the gold standard for BMD measurements, artifacts associated with a two-dimensional measurement of areal bone density (g/cm^2) are considered a limitation at the extremes of BMD (very high or low) or due to excess soft tissue surrounding bone, such as in obesity [7–9]. In addition, the obese have a higher prevalence of vertebral deformities [10] and spinal osteoarthritis [11], which can overestimate BMD and BMC. Careful examination of the lumbar spine measurement for vertebral exclusion is needed in the interpretation of BMD [12] and may require special consideration for the obese.

Information about bone quality can be attained by the inclusion of architectural parameters such as bone size and geometry. This can be assessed with radiography, DXA, peripheral quantitative computed tomography (pQCT), quantitative computed tomography (QCT), or magnetic resonance imaging (MRI). Microarchitectural parameters include cortical and trabecular structural detail which can be evaluated by pQCT or by using high-resolution imaging techniques such as multidetector CT, MRI, and higher-resolution pQCT which will allow for high-precision images and estimation of additional biomechanical properties. In addition, microcomputed tomography techniques are used to examine human bone biopsy samples or excised bone in rodent studies. Bone strength, defined as the force required to cause a material to fail under a given loading condition [13], can be measured directly using biomechanical testing methods in excised bone or can be estimated, in clinical trials, by the amount of mineralized material (BMD) and geometrical properties [14]. These three-dimensional methodologies can assess volumetric BMD (vBMD; mg/cm^3) and bone structural parameters, distinguish between cortical and trabecular bone, and determine the relationship with soft tissue (e.g., muscle and fat cross-sectional area). Measurements of true vBMD that use the density of fat tissue as zero have been found to reduce errors as compared to an areal measurement, such as using DXA technology. Quantitative computed tomography measurements of bone can measure axial sites by QCT and peripheral sites using pQCT. In obesity, potential BMD artifacts may be attenuated or removed by measuring a peripheral (rather than axial) site because less soft tissue surrounds the bone of the arm or leg. In addition, most clinical studies examining vBMD and bone architectural parameters use pQCT due to ease of use and because, compared to QCT, the method produces very low radiation exposure to the patient at only peripheral sites, and therefore is appropriate for both adult and pediatric populations. For example, the total radiation dose is <7 uSv when measuring the tibia and radius using the Stratec-Orthometrix pQCT, and this dose is similar to a DXA measurement at both the hip and spine. In comparison, this dose is less than 1 day of background radiation (~8 uSv/day) or a cross-country flight (~40 uSv).

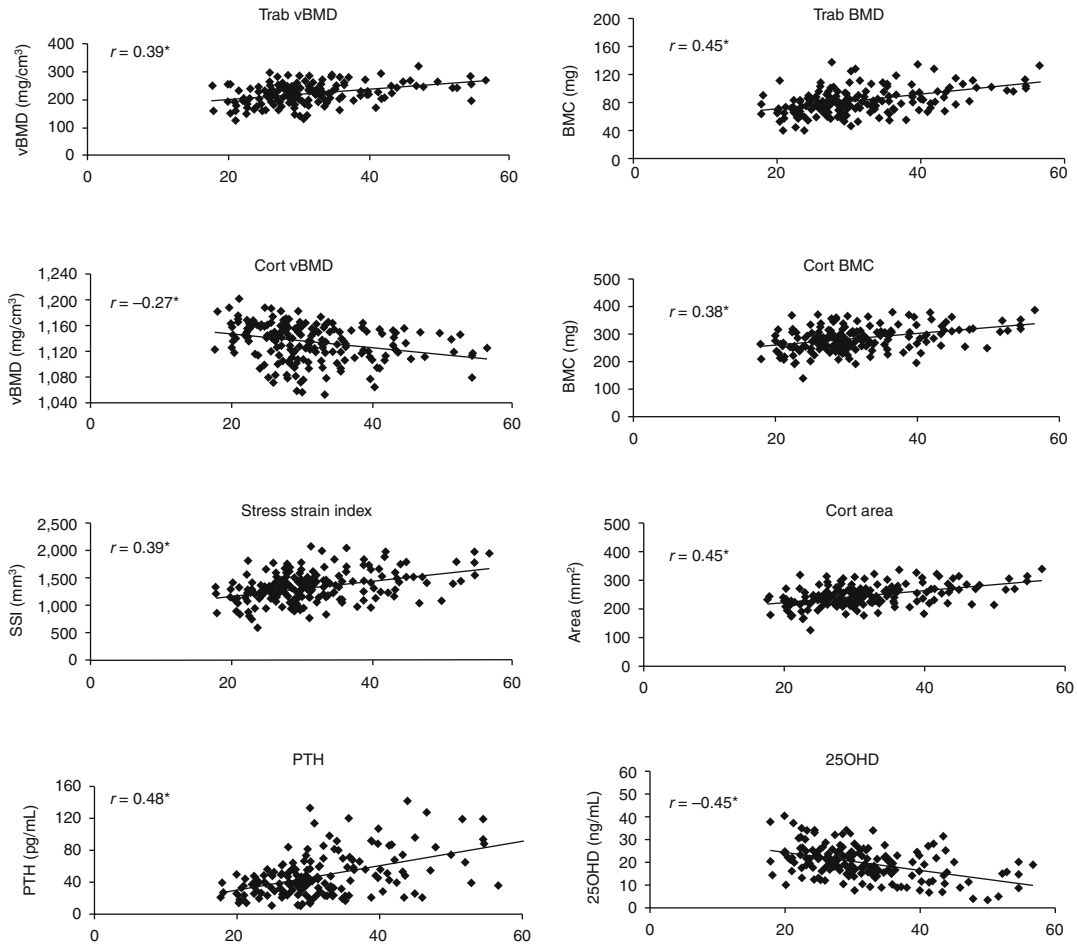

Fig. 4.1 Relationship between body mass index, cortical, and trabecular bone parameters (volumetric bone mineral density (vBMD) and content (BMC), cortical area, and stress-strain index) and serum parathyroid hormone (PTH) and 25-hydroxyvitamin D (25OHD) in 211 women. *$p<0.001$ (Reprinted from Sukumar et al. [19]. With permission from Springer Science + Business Media)

There is an association of peripheral QCT (pQCT) outcomes with fracture, although these studies are limited compared to measurements with DXA.

Volumetric BMD and Bone Quality in Obesity

An altered bone quality may partially explain the greater than expected fracture risk in the overweight and obese for a given BMD. Trabecular and cortical vBMD and geometry differ in the obese compared to normal weight individuals. In children, a higher body weight is associated with a higher trabecular bone, but not cortical vBMD, and may decrease bone strength [15–17]. Lower forearm bone strength found in overweight children has been attributed to the greater fat to muscle ratio in the overweight than normal weight children [18]. In adults, obesity is also associated with higher trabecular and some cortical bone parameters and lower cortical vBMD. In a study with 211 women, we found that the higher trabecular parameters and lower cortical vBMD remain significantly different in the obese even when controlling for confounders (i.e., lean mass and physical activity) (Fig. 4.1) [19]. Also, a higher

Table 4.1 Bone variables obtained by peripheral quantitative computed tomography at the radius and tibia comparing obese to normal weight groups[a,b]

References	Population	Groups	Bone site	Trabecular bone vBMD	Cortical bone vBMD	SSI
				Obese[b] compared to normal weight (%)		
Ducher et al. [18]	Boys and girls	Normal wt. ($n=334$)	Radius	+7.9*	+0.5	+16.2*
	7–10 years	Overweight ($n=93$)	Tibia	+6.9*	0	+21.0*
Pollock et al. [15]	Females	Normal fat ($n=93$)	Radius	−2.9	+0.3	−0.7
	18 years	High fat ($n=22$)	Tibia	−1.5	−0.1	−5.6
Pollock et al. [150]	Black females	Normal fat ($n=33$)	Radius	+5.1	+0.4 %	+5.0
	19 years	High fat ($n=15$)	Tibia	−0.04	−0.5 %	−3.2
Wetzsteon et al. [16]	Boys and girls	Health weight ($n=302$)	Tibia	NA	0	+15.4*
	9–11 years	Overweight ($n=143$)				
Sukumar [19]	Female	Normal ($n=42$)				
	24–75 years	Overweight ($n=119$)	Tibia[c]	+15.5*	−0.3	+6.8*
		Obese ($n=50$)	Tibia[d]	+19.3*	−1.2*	+3.18*
Uusi Rasi et al. [21][e]	Male and female	BMI measured at 12 years of age	Radius	F +5.1	F −0.2	F +14.7
				M −0.8	M −0.9	M +8.6
	36 years	Normal ($n=767$) or overweight ($n=65$)	Tibia	F +7.2	F −0.6	F +17.9
				M −0.9	M −1.1	M +12.9

Abbreviations: *vBMD* volumetric bone mineral density, *SSI* stress-strain index
[a]Studies reported only for those that also included a normal weight control group
[b]"Obese" refers to excess body weight described as either obese, overweight, or high-fat groups based on the terminology used in the study
[c]Overweight compared to normal weight group
[d]Obese compared to normal weight group
[e]Statistical data unavailable for comparison with normal weight
*Significantly different from normal weight

body mass index (BMI) does not confer a positive effect on other cortical parameters such as BMC and area, thickness, and strength indices [19]. Taes et al. [20] showed that greater fat mass is associated with smaller bone size in men at 25–45 years of age. A recent study [21], however, shows that a history of being overweight in childhood is associated with greater total cross-sectional area of long bone sites in men and women (36 years of age) and a 5 % higher trabecular density at the distal radius and tibia in the adult women, but not in men. Hence, the effect of obesity on bone may vary due to gender and a history of obesity. Studies examining the influence of excess body weight on the cortical and trabecular compartments of bone compared to normal weight populations are summarized in Table 4.1.

Fracture Risk in Obesity

In an epidemiological perspective of osteoporosis and fracture risk in overweight and obese individuals, researchers demonstrate that osteoporotic fractures are more problematic in this population than previously believed and that obese men may be particularly susceptible [22, 23]. For example, hip fracture incidence is highest in the underweight, but there is a higher prevalence of fracture in overweight and obese individuals in the USA because they represent the largest portion of the population [24]. Others suggest that a BMI greater than 35 kg/m^2 increases the risk of fracture, when adjusted for BMD [25]. In women presenting with low-trauma fracture, 59 % of obese and 73 % of morbidly obese women had normal BMD, and only 12 and 5 %, respectively,

had evidence of osteoporosis [23]. The normal BMD and higher risk of fracture in obesity are either the result of compromised bone quality or greater forces on the bone during a fall despite the extra body fat padding. It is also possible that excess adiposity overestimates BMD in obese subjects due to measurement artifacts.

The risk of fracture in the obese differs by anatomic site and has been shown in a few epidemiological studies. In a longitudinal study with nearly 11,000 women, high BMI significantly increased the risk of proximal humerus and ankle fractures but was associated with a lower risk at the forearm, spine, and hip [26]. In addition, other researchers have also found a higher humerus fracture risk in obese women [27]. Compston and colleagues report that obese compared to nonobese women have more ankle and upper leg fractures [28]. In 22,444 men, the increased risk of fracture risk with a high BMI only shows a trend for higher fracture risk at the ankle and is lower at other sites, including the proximal humerus [26]. Further analysis is needed to establish a fat-fracture relationship in older men [23, 29] and to distinguish whether it differs from women or if there are racial/ethnic differences. A specific effect of obesity on vertebral fracture compared to normal weight individuals is not clear; however, adiposity is associated with vertebral deformity in obese women and is attributed to excess loading on the thoracic spine [10]. Therefore, obesity is associated with lower hip fracture, but higher risk of proximal humerus fracture and possibly ankle and upper leg fractures in women [23, 26–28]. These findings are consistent with higher forearm fracture risk in children [30]. Also, fractures in both obese pediatric and adult patients increase recovery time and involves more complications [31, 32], so preventing fractures in this population is especially important.

Overall, the strong evidence that bone quality is compromised in obesity may explain fracture risk in this population. In addition, because fractures occur more at certain anatomical sites, the alterations in microarchitecture that is either rich in trabecular or cortical bone may influence the susceptible to fracture. It is also possible that the force upon falling and an altered balance are factors contributing to site-specific fractures in the obese. The different ratios of lean to fat tissue mass or fat depots in obesity may help in understanding the etiology and implications for BMD and fracture risk and is discussed below.

Relationship of a BMD with Soft Tissue

Body composition and its relationship to bone have been examined in numerous studies, and most agree that lean and fat mass are both independent determinants of bone mass. Lean mass and fat mass are strongly influenced by age, gender, dietary intake, and the level of physical activity among other factors which in turn can independently affect bone.

Lean Tissue Mass

When measuring lean tissue mass using DXA, it consists of both skeletal muscle and BMC. For studies that have differentiated these compartments, the term "fat-free soft tissue" is used to indicate skeletal muscle tissue without the inclusion of BMC. The positive effect of a higher fat-free soft tissue on BMD can be attributed to lifestyle factors, steroid hormone sufficiency, genetic influences, or a combination of these factors. Importantly, muscle mass has an independent effect on better balance to prevent frailty and falls associated with osteoporotic fracture risk. The excess weight in obesity consists primarily of excess adipose tissue, yet in general, there is also higher fat-free soft tissue. It has been suggested that the positive effect of a higher body weight on bone and fracture risk reduction occurs only when it is primarily composed of fat-free soft tissue [33, 34]. It is possible that in older individuals, the obese compared to normal weight have a higher incidence of combined sarcopenia and osteopenia due to reduced mobility in this population [35]. In a large study of elderly white and black women and men where hip fracture was validated over a 7-year period, it was found that a decrease of one standard deviation in thigh muscle Hounsfield Unit (an indicator of intramuscular fat) conferred a nearly 40 % increase in fracture risk. Hence, measurement of total fat or

lean mass by DXA may not be able to adequately capture changes in muscle composition in older individuals, suggesting that thigh muscle fat may provide a better estimate of muscle strength and hip fracture risk [29]. Although no defined recommendations are available to consider muscle-related parameters in clinical bone assessments, there is now a greater effort in the field to address these relationships with new trials using 3D bone techniques that are ongoing.

Fat Mass

Because adipose tissue acts as an endocrine organ [36], the hormones and adipokines produced will have a major influence on the bone and this is discussed below. Fat mass, unlike muscle mass, does not always show a direct correlation with bone. It appears to be age and gender specific so while there is a correlation between fat and bone in postmenopausal women [37, 38], this has not been found in children and young adults [39, 40]. Only some of these studies have corrected for muscle mass to determine the independent effect of fat on bone; this may explain some of the different findings in these studies. Also, the influence of soft tissue on bone mass is complicated by variability in the bone site being evaluated [41, 42]. Varying amounts of trabecular or cortical content in different bones, as well as weight bearing of the specific site, may confound the observations. For example, a study in older women showed that total weight influenced BMD at weight-bearing sites, yet only adiposity influenced non-weight-bearing sites, including the radius [43].

Fat Depot

Bone may be influenced by the location and type of white adipose tissue accumulation, including visceral adipose tissue (VAT) compared to subcutaneous tissue. Excess VAT has a greater association with symptoms of metabolic syndrome than the increased total body adipose tissue per se. The metabolic syndrome symptoms (such as dyslipidemia, insulin resistance, and higher inflammatory cytokines) each have independent effects on bone and may explain the inconsistent findings for the influence of excess VAT on bone. For example, the positive influence of VAT on bone reported in postmenopausal women has not been shown in children or men [44–47]. It is also possible that inconsistent findings for an inverse relationship between visceral fat and bone are due to different methodologies and protocols used in each study. Because most of the studies either use waist to hip ratio or measure trunk fat using DXA to estimate VAT, which include both subcutaneous and visceral depots, this limits the interpretation. In addition, studies examining the VAT and bone relationship use different anatomical bone sites. Studies using more precise techniques to measure adipose tissue, such as QCT or MRI, will be important to better understand how the type of fat differentially influences BMD or BMC.

Besides white adipose tissue (subcutaneous and visceral fat), other types of fat (brown fat and bone marrow fat, also referred to as “yellow” fat) may influence BMD. Brown adipose tissue has been reported to maintain bone based on a study in women with anorexia nervosa compared to healthy controls [48], whereas increased bone marrow fat tissue is associated with lower BMD [49]. In addition, a recent study in obese women showed that vertebral bone marrow fat is positively associated with visceral fat and inversely associated with insulin-like growth factor (IGF-1) [50] and BMD. Further studies examining the endocrine function of bone marrow fat in regulating bone and differentiation of mesenchymal stem cells are needed to advance the field.

In summary, the amount and type of soft tissue mass results in differential mechanical support and endocrine regulation of bone that would be expected to influence growth and maintenance. Both fat-free soft tissue and the type and location of adipose tissue are important influences on BMD and may change with age or in different populations. These differences may explain the large body of conflicting data that link body adiposity, bone mass, and fracture risk. Hormonal alterations are influenced by the type and location of fat depots, and the amount of fat-free soft tissue may explain the etiology for the altered bone quality and fracture risk in obesity and is discussed in the next section.

Hormonal Milieu in Obesity That Influence BMD at Cortical and Trabecular Sites and Bone Geometry

Adipose tissue is a metabolically active tissue containing a vast variety of cell types, the more abundant being adipocytes, preadipocytes, immune cells, and endothelial cells [36]. The adipose tissue secretes adipocyte-derived factors that have effects on many organs in the body, including the bone. The altered hormonal milieu and adipokines in obesity have specific actions on BMD, its geometry, and microarchitectural properties that are discussed below.

Sex Steroids

The obese individual has higher levels of serum estrogen and lower sex hormone-binding globulin (SHBG). Serum estrogens in postmenopausal women are largely derived from the metabolism of circulating androstenedione by peripheral tissues, and concentrations are higher in obesity. The higher concentrations of serum estrone in obesity are largely derived from the metabolism of circulating androstenedione by adipose tissue and may also be responsible for higher BMD due to excess body weight [51]. In addition, the adipose-derived enzymes, such as aromatase and hydroxyl steroid dehydrogenase, are elevated in obesity and have known anabolic actions on the osteoblast [52, 53]. Obese men, on the other hand, have low total and free testosterone and low SHBG [54, 55]. The sex steroids, including bioavailable estradiol and testosterone, have been shown to be the major positive hormonal determinants of trabecular microstructure in elderly men and women [56], and the age-related loss of cortical bone is associated with sex steroid deficiency [57]. The GOOD Study [58] in young men shows that free estradiol is an independent negative predictor of cortical parameters such as cross-sectional area, periosteal circumference, and endosteal circumference, whereas it is a positive independent predictor of cortical vBMD at both the tibia and radius. Conversely, free testosterone is an independent positive predictor of cortical cross-sectional area, periosteal circumference, and endosteal circumference, but is not associated with vBMD [58]. SHBG is an independent positive predictor of cortical cross-sectional area and periosteal and endosteal circumference [58]. An obesity-induced association between higher circulating estrogen and lower testosterone concentrations in older adults would be expected to increase trabecular and possibly reduce cortical BMD, but the influence of sex steroids on these bone compartments in obesity has not been specifically addressed.

Serum 25-Hydroxyvitamin D and Parathyroid Hormone

Obesity is associated with higher parathyroid hormone (PTH), lower 25-hydroxyvitamin D (25OHD), and possibly lower 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) and all have specific actions on bone. The lower circulating concentrations of 25OHD in obesity are possibly due to greater deposition in the excess adipose tissue or lower sun exposure in obese individuals [59–61]. In addition, there is a rise in serum 25OHD with weight loss and it has been shown to be proportional to loss of body weight [62]. In the InCHIANTI study conducted in Italy, serum 25OHD was positively associated with total cross-sectional area and cortical vBMD, while PTH was negatively associated with cortical vBMD in women, but not in men [63]. Another rodent study showed that vitamin D deficiency in young growing male rats results in a significant reduction in femoral trabecular bone volume, while cortical bone is maintained [64]. On the other hand, in adult patients with primary hyperparathyroidism (PHPT), in those with low serum 25OHD (<20 ng/mL), there is evidence of higher serum PTH concentrations and a greater catabolic effect on cortical bone and anabolic effect on trabecular bone compared to PHPT patients without low 25OHD [65]. Another study also assessed the association of 25OHD with cortical and trabecular bone parameters in men of Caucasian and African ancestry [66]. Among Caucasians, serum 25OHD was positively associated with cortical vBMD, total BMC, cortical thickness, and strength param-

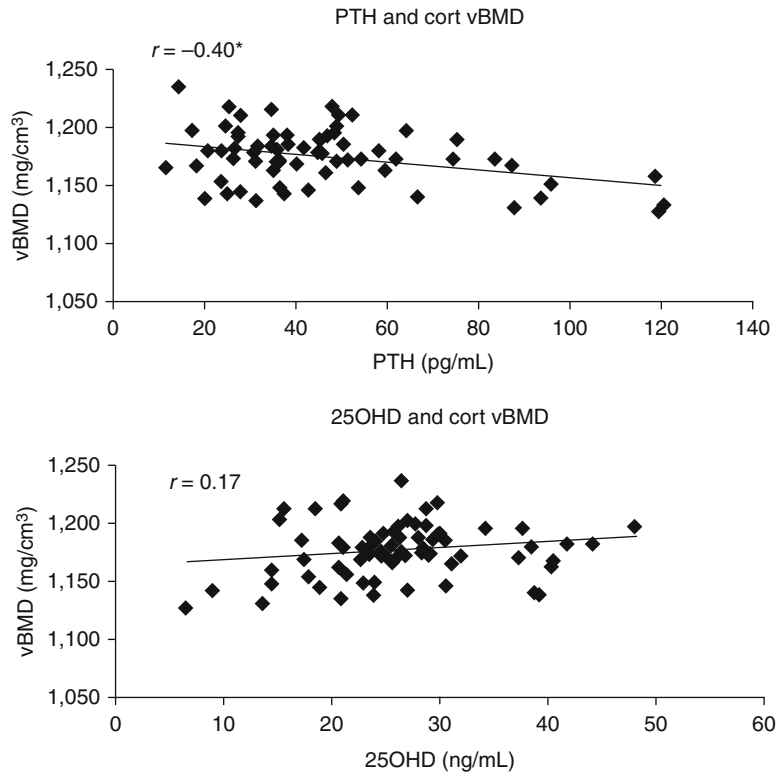

Fig. 4.2 Relationship between cortical volumetric bone mineral density (vBMD) and serum parathyroid hormone (PTH) is positively correlated, but there is no relationship with 25-hydroxyvitamin D (25OHD). ($n = 73$ premenopausal women); *$p < 0.001$ (Modified from Sukumar et al. [19]. With permission from Springer Science + Business Media)

eters at the distal radius. Results also showed that there was an inverse association between serum 25OHD and the cortical cross-sectional area and stress-strain index in men of African ancestry. Whether or not the effects of vitamin D deficiency on bone compartments differ by ethnic/racial difference or are due to a direct effect on bone or due to its parallel increases in PTH is unclear. Currently, there is no data to support a significant association between the lower levels of 25OHD levels in obesity and cortical/trabecular bone [19].

Parathyroid hormone is positively correlated with excess body fat [67, 68]. While short-term increases in PTH are associated with increased calcium absorption and an increase in BMD, chronically elevated PTH will alter calcium metabolism and increase proinflammatory cytokines [69, 70], which would have a detrimental effect on bone. Chronically elevated PTH reduces cortical BMD and inhibits bone collagen synthesis. In contrast, elevated serum PTH preserves or increases trabecular, possibly by increasing osteoblast recruitment [71]. For example, patients with either primary or secondary hyperparathyroidism have increased spine BMD, which is rich in trabecular bone, but decreased cortical bone mass [72, 73]. Patients with osteoporosis who are treated with PTH show higher spine BMD but lower cortical BMD, especially at the distal radius as compared to bisphosphonate treatment [74]. In support of the bone site-specific action of PTH, obese postmenopausal women with high PTH who had a history of gastric bypass surgery compared to obese controls with normal PTH have higher lumbar spine BMD (rich in trabecular bone) and BMC and lower BMC at the femoral neck [75].

The effect of higher PTH levels on bone in 211 women with a wide range of body weights has been examined in a cross-sectional study in our laboratory [19]. The obese women showed a lower cortical vBMD, and in the total population of women with a wide range of body weights, there was a negative association between PTH and cortical vBMD (Fig. 4.2) [19]. It is thus possible that the lower cortical bone in obesity is due to their higher PTH levels. Others have found lower

cortical vBMD in obese children [15] and young adults [20], but circulating hormones were not measured in these studies. Thus, there are currently only limited studies that support the hypothesis that the elevated PTH in obesity is responsible for the lower cortical BMD [19, 75] and none that can establish a cause and effect relationship.

Adipose-Derived Hormones and Peptides, Pancreatic Hormones, and Cytokines

The adipose-derived hormones, adiponectin, leptin, and resistin are altered by obesity and also influence bone. Obesity reduces circulating adiponectin [36], and in vitro observations show it increases osteoblastic activity [76]. Most clinical studies [77–80], but not all [81], show that adiponectin is negatively associated with BMD in adults and children. Adiponectin is also inversely correlated with trabecular and cortical BMD [82]. Consistent with these findings, fracture studies suggest that higher adiponectin is associated with greater fracture risk but may be gender specific [83, 84]. The Health Aging and Body Composition (Health ABC) Study in 3,075 men and women showed that men in the highest tertile of adiponectin had a 94 % higher risk of fracture [hazard ratio (HR) = 1.94; 95 % confidence interval (CI) 1.20–3.16] compared with the lowest tertile, but it was not significant in women [83]. The Osteoporotic Fractures in Men (MrOS) Study also shows that the risk of fracture increases with increasing serum adiponectin with a hazard ratio HR/SD of 1.46 (95 % CI, 1.23–1.72) [85].

Leptin suppresses appetite and increases energy expenditure and there is resistance to leptin associated with the high serum concentrations in obesity. Leptin also has both direct and centrally mediated effects on bone remodeling. The centrally mediated effect on bone occurs through sympathetic tone. It has been shown to inhibit bone formation and enhance bone resorption [86]. In contrast, in vitro studies show a direct effect of leptin on osteoblast differentiation [87, 88]. These different central and peripheral effects of leptin may explain why clinical trials have reported both positive and negative effects of leptin on bone [81, 89–91]. One report suggests that leptin is negatively associated with cortical bone size in adolescents and young men. In obese mice, serum leptin levels negatively correlates with trabecular, but not cortical bone [92]. The two genetic models of obesity, the ob/ob (leptin-deficient) and db/db (leptin null) mouse, have short limbs with thin cortical bone, low trabecular bone volume and BMD, and high marrow adiposity, whereas vertebrae are larger, with elevated BMD and trabecular bone volume, and lower marrow adiposity [93]. Furthermore, there are higher levels of pancreatic hormones such as insulin, amylin, and preptin in the obese, which have anabolic actions on bone [94–96]. In young mice, lower amylin leads to lower trabecular bone volume and thickness [97]; however, its effect on bone compartments in obesity is unclear.

There are also higher circulating concentrations of inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor (TNF-α), monocyte chemoattractant protein-1, and C-reactive protein (CRP) in obesity. Higher inflammatory cytokines have been associated with higher bone turnover [98–101] and have differential effects on cortical and trabecular bone. In mice, IL-6 transgenic mice show severe alterations in cortical and trabecular bone microarchitecture [102]. Serum levels of CRP do not seem to be associated with trabecular [103] or cortical bone [104] in adults. In one study of older women and men (BMI of 27.5 kg/m^2), IL-1 was negatively associated with cortical vBMD, and surprisingly TNF-α was positively associated with total and cortical cross-sectional area [63]. The effect of cytokines on trabecular and cortical bone has not specifically been examined in obese individuals, but may be dependent on the presence of higher serum PTH concentrations [69]. It is possible that the low level of chronic inflammation in obesity is counterbalanced by adipose-derived estrogen, lower adiponectin, and greater weight bearing that act to prevent bone loss in the obese compared to leaner populations.

Conditions of excess adiposity are associated with reduced growth hormone [105, 106] and IGF-1 and insulin-like growth factor binding protein (IGFBP)-1 [107]. However, the implications of low serum IGF-1 concentrations [105] are not

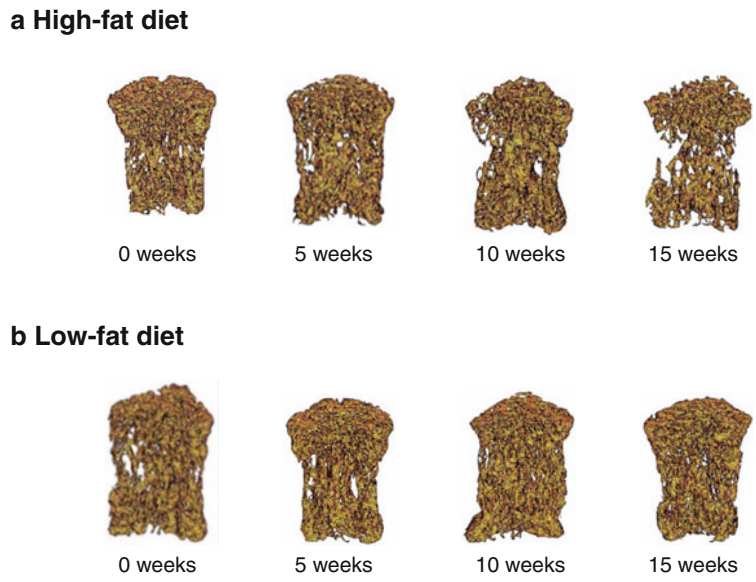

Fig. 4.3 Image shows the typical 3D trabecular microarchitectural changes in the L4 vertebral bodies with micro-CT-based finite element model. In this study, young mice (6 weeks of age) were fed a high-fat diet or a normal low-fat diet for 15 weeks. The HFD (**a**) increases trabecular space, number, and loss of metaphyseal trabeculae compared to control (**b**) (Modified from Woo et al. [114]. With permission from Elsevier)

entirely clear, since it has been reported that *free or bioactive* IGF-1 concentrations are either similar or higher in obese compared to normal weight subjects [106, 107]. In young men, higher serum IGF-I and IGFBP-3 concentrations are associated with conversion of thick trabecular into more numerous and thinner trabeculae from aging to mid-life [56], but this study found that in the older population, sex steroids are the major determinants of trabecular microstructure. In a study of older women, serum IGF-1 was found to be significantly related to cortical, but not to trabecular density [108]. Consistent with these findings, mice with low serum levels of IGF-1 exhibit reduced cortical but normal trabecular bone [109] suggesting a more pronounced role of systemic IGF-1 on cortical than on trabecular bone. It is possible that the lower cortical vBMD in obesity is related to a lower IGF. However, these findings should be confirmed in larger prospective studies.

Obesity also alters the gut peptides, including ghrelin, incretins, CCK, pancreatic polypeptide (PPY), and peptide YY (PYY). These peptides not only regulate satiety but also have reported effects on bone. A meta-analysis [84] shows no convincing data to support an association between visfatin and ghrelin and BMD. In the case of ghrelin, this appetite stimulant is high in obesity, and it increases osteoclastic bone resorption during fasting [110], but also increases bone formation in other studies [111–113]. However, the meta-analysis by Biver et al. [84] did not find an association between ghrelin and BMD. Overall, there are a limited number of studies examining the effect of these peptides on cortical and trabecular bone compartments and the data remain unclear.

Bone and Diet-Induced Obesity Models

Besides hormonal factors, the skeletal consequences of obesity will vary depending on the age at onset, duration, and composition of the diet. Animal models offer an opportunity to determine these effects. Most diet-induced obesity in rodents during growth has shown that it lowers BMD and impairs bone quality [114–116] (Fig. 4.3). Some studies suggest that age influences the BMD response to a high-fat diet (HFD) because the effect may be exaggerated during rapid growth as compared to a more mature skeleton. One study examined the effect of a 16-week HFD in very young (3 weeks of age) and 3-month-old mice [117]. The HFD resulted in greater lean and fat

tissue mass and lower cortical bone biomechanical properties, as compared to the low-fat diet (LFD) [117]. The HFD also increased serum IGF-1 and leptin levels compared to controls, but the rise in IGF-1 was markedly higher in the young compared to adult mice [117]. This may explain the greater bone size in the younger mice vs. smaller bone size in the adult mice compared to their lean counterparts [117]. In mice (9 weeks of age), excessive fat and sucrose intake for 10 weeks impaired bone geometry and mechanical properties of cortical bone in mice [118]. The bone changes are attributed to the upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) mRNA suggesting higher osteoclast activity with obesity. In addition, it was found that the detrimental effects of a high-fat high-sucrose diet (HF/HS) on bone are exacerbated in the femoral neck and lumbar vertebrae after long-term feeding (2 years), showing that duration of dietary exposure is also important [119]. Other studies where the diet was initiated in adolescent or adult rodents have not found a detrimental effect of a HFD on bone. In a study in our lab, 2-month-old female rats were fed either a HFD or control LFD. At 8 months of age, the obese vs. lean rats showed no difference in femoral aBMD and femoral neck vBMD, or trabecular thickness and number [120]. In addition, in 11-month-old male rats who had been fed a HF/HS diet for 16 weeks, most bone parameters were greater than the low-fat controls, except for a lower cortical porosity [121]. Others have studied the effect of excessive caloric intake on bones in rodents by examining different types of dietary sugars. For example, excessive intake of fructose or glucose has been shown to produce a detrimental effect on BMD, BMC, and/or mechanical strength in rats [122, 123]. Protein source during excessive energy intake may also influence the bone response. Researchers studied the bones of 4-month-old rats that were fed 8 weeks of powdered skim milk, casein, or whey added to a HF/HS diet [124]. The rats given the skim milk showed an attenuated weight gain and increased trabecular bone architecture as compared to casein or whey alone [124]. Whether diet composition is influencing the bone parameters measured by pQCT in clinical obesity studies is not known. Overall, it is likely that diet duration and composition, the level of adiposity, and skeletal age are important factors influencing the detrimental effects reported on bone mass, size, and biomechanical properties.

Effect of Weight Loss on Cortical/ Trabecular Bone

Weight loss is associated with 1–2 % bone loss at the hip and possibly more at highly trabecular sites, such as the trochanter and radius [125–133]. Epidemiological studies show that only 5% weight loss is associated with increased fracture risk in both men and women [126, 134, 135]. A variety of anatomical sites are reported to have higher fracture risk in individuals with a history of weight loss. These fracture sites include hip [126, 136], non-vertebral fractures [137], and distal forearm fractures [138]. Bone loss and increased fracture risk due to moderate weight reduction occur in both older women and men [131], but neither has been demonstrated in younger individuals [139–142] unless there is severe weight reduction.

Few studies have evaluated the effect of weight loss on trabecular and cortical bone parameters. In a 1-year study in older women, 7 % weight reduction decreased aBMD at the radius (distal and 33 % sites) and hip [128]. Weight loss also reduced vBMD and area of the tibia, but there were no significant changes in trabecular vBMD and geometry and only a trend to decrease and increase cortical area and vBMD, respectively [128]. In a 3-month study in premenopausal women, a very low-energy diet resulted in a 10 % loss of body weight and a slight increase in cortical vBMD at the radius [142]. However, because there was also a rise in bone turnover markers, it is possible that bone loss may have occurred at other anatomical sites or would occur in a longer-term study.

In rodent studies, energy restriction is associated with a marked decrease in femoral cortical bone mass, but no change in trabecular bone volume fraction [143]. Both age and initial body weight appear to be important factors influencing the effect of energy restriction on bone. For example, older (14 months) compared to younger (6 months)

mature energy-restricted rats result in a greater reduction in biomechanical properties of bone [144]. Others have studied the effect of energy restriction in very young male mice (3 weeks of age) [145]. After energy restriction, there was greater inhibition of cortical and trabecular bone mass accrual in the limbs than in the spine [145]. In addition, energy restriction decreased appendicular cortical and trabecular bone mass while preserving trabecular bone in the spine [145]. In skeletally mature 8-month-old obese and lean female rats [120], energy restriction in obese rats does not decrease BMD compared to ad-libitum fed controls. However, the lean energy-restricted rats had a lower BMD at the femoral neck and distal femur compared to their lean ad libitum-fed controls [120]. Hence, the age and initial body weight before caloric restriction appear to not only affect whether there will be any bone loss but may also differentially influence the anatomical sites, compartments, and geometry of bone.

Several bone-regulating hormones are altered during caloric restriction and may explain at least some of the bone changes associated with weight loss. For example, a reduction in estrogen levels, rise in cortisol [120, 146], and reduction in IGF-1 and leptin [143] occur during energy restriction and have direct detrimental effects on BMD [133]. The importance and role of exogenous hormones in regulating bone during caloric restriction and preventing BMD loss has also been studied [146–149]. Medications to treat osteoporosis, such as estrogen and raloxifene, during weight reduction will prevent bone loss in postmenopausal women [147]. In rodent studies, treatment with IGF-1 [149] or with low-dose PTH [148] has been shown to maintain normal bone formation during rapid weight loss in a rodent study. Importantly, dietary and exercise interventions will influence the hormonal response to caloric restriction and can also attenuate bone loss due to weight reduction [133].

Conclusions

There is strong evidence that bone quality and fracture risk is altered by obesity in both clinical trials and in rodent studies. In addition, the amount, type, and location of the excess adipose tissue; the ratio with muscle mass; and the altered hormonal milieu are important determinants of bone quality and fracture risk in obesity. The higher circulating estrogens and/or lower testosterone due to excess adiposity may have gender-specific effects on trabecular and cortical bone. Higher serum PTH in obesity appears to play a role in reducing cortical BMD, but the lower serum 25OHD associated with obesity may not be low enough to negatively affect bone. The higher leptin and resistin and lower adiponectin may also contribute to the lower cortical vBMD in obesity. There is currently inadequate information on whether the higher pancreatic hormones in obesity alter trabecular or cortical bone compartments. Cytokines have a catabolic effect on both bone compartments; however, higher circulating concentrations do not explain the higher trabecular and lower cortical vBMD in obesity. Because the altered hormonal milieu in obesity does not completely explain bone architectural changes that occur due to excess adiposity, the influence of other factors such as genetics, altered mechanical loading, diet, physical activity, and/or other environmental factors may have independent effects on bone quality and site-specific fracture risk in obesity.

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