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Obesity alters cortical and trabecular bone density and geometry in women

D. Sukumar,

Department of Nutritional Sciences, Rutgers University, 96 Lipman Drive, New Brunswick, NJ 08901-8525, USA

Y. Schlussek,

Department of Nutritional Sciences, Rutgers University, 96 Lipman Drive, New Brunswick, NJ 08901-8525, USA

C. S. Riedt,

Department of Nutritional Sciences, Rutgers University, 96 Lipman Drive, New Brunswick, NJ 08901-8525, USA

C. Gordon,

McMaster University, Hamilton, ON, Canada

T. Stahl, and

Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

S. A. Shapses

Department of Nutritional Sciences, Rutgers University, 96 Lipman Drive, New Brunswick, NJ 08901-8525, USA

S. A. Shapses: shapses@aesop.rutgers.edu

Abstract

Summary—The goal in this study was to determine the relationship between body mass index and trabecular and cortical bone using quantitative computed tomography. A higher body mass index (BMI) was positively associated with trabecular and cortical bone parameters, and serum parathyroid hormone, and negatively associated with cortical volumetric bone mineral density (vBMD) and serum 25-hydroxy-vitamin D. When BMI is greater than 35 kg/m², adiposity affects vBMD and may explain the higher fracture risk in this population without low BMD.

Introduction—The influence of adult obesity on the trabecular and cortical bone, geometry, and strength has not been fully addressed. The goal in this study was to determine the relationship between body mass index and trabecular and cortical bone mass and geometry, over a wide range of body weights.

Methods—We examined 211 women (25–71 years; BMI 18–57 kg/m²) who were classified into three categories of BMI (kg/m²) including normal-weight (BMI<25), overweight and obese-class I (BMI 25–35) and obese-class II–III (BMI>35), and also by menopausal status. Volumetric bone mineral density (mg/cm³), trabecular, and cortical components as well as geometric characteristics at the 4%, 38%, and 66% from the distal tibia were measured by peripheral quantitative computed

tomography, and serum was analyzed for parathyroid hormone (PTH) and 25-hydroxy-vitamin D (25OHD).

Results—Higher BMI was associated with greater values of trabecular bone and cortical BMC and area and PTH ($r>0.39$, $p<0.001$), but lower cortical vBMD and 25OHD ($r>-0.27$, $p<0.001$). When controlling for lower leg muscle area, fat area was inversely associated with cortical vBMD ($r=-0.16$, $p<0.05$). Premenopausal obese women with both higher BMI and PTH had lower cortical vBMD ($r<-0.40$, $p<0.001$). While age is a predictor for most bone variables, fat mass explains more variance for vBMD, and lean mass and 25OHD explain greater variance in geometric and strength indices ($p<0.05$).

Conclusions—Severe obesity (BMI>35) increases trabecular vBMD and in the presence of a higher PTH is associated with a lower cortical vBMD without compromising bone geometry and strength. Whether or not a lower cortical vBMD in obesity influences fracture risk over time needs to be further explored.

Keywords

25-hydroxy vitamin D; Cortical bone; Female; Obesity; Parathyroid hormone; Trabecular bone

Introduction

Obesity is associated with a higher bone mass [1] but more recently it has been suggested that bone mineral density (BMD) is proportionally lower than would be expected in obesity based on body size, and that fracture risk may be increased despite normal BMD [2–5]. The influence of obesity on trabecular (Tb) and cortical (Ct) bone has not been examined and could explain whether it is influenced with excess adiposity.

Although BMD is the most common clinical measurement to diagnose osteoporosis, there is a growing awareness that a reduction in BMD is not the sole pathology underlying fracture risk, nor does a high BMD completely protect an individual from fractures. Risk factors for fracture are also influenced by bone quality that has been defined as a composite of bone structure, composition, microarchitecture, and microdamage that contribute to bone strength independently of BMD [6–8]. Indeed, the FRAX model addresses clinical risk factors along with BMD to better predict fracture risk [9]. In addition, BMI has been used as a surrogate for BMD in instances where BMD cannot be measured, although it has a limited ability to predict fractures at high body weights [3,10].

Peripheral quantitative computed tomography (pQCT) allows for separate yet simultaneous assessment of the Tb and Ct compartments of the bone. It includes measurement of volumetric BMD (vBMD), bone geometry, bone mineral content (BMC), and bone strength indices, and is considered a useful method to assess bone quality and strength [11]. It has also been reported that bone variables measured by pQCT such as Tb and Ct vBMD may be good predictors of fracture risk and in certain cases (e.g., dialysis) may be better than dual-energy X-ray absorptiometry (DXA) [12]. The sex and age effects on Tb and Ct bone have been well established using pQCT [13–15]; however, their relationship with BMI and/or adiposity has not been addressed in an adult population.

The positive influence of body weight on bone is primarily attributed to a greater lean mass but not always in older populations [16–18]. In addition, there is an altered hormonal milieu associated with obesity, including higher serum concentrations of parathyroid hormone (PTH) and lower circulating 25-hydroxy-vitamin D (25OHD) [19,20]. Serum PTH has a negative effect on Ct bone, while 25OHD is positively associated with Tb bone, but this has not been studied in obese women [21–23]. In addition, the influence of both fat and muscle

mass on the Tb and Ct relationship in obesity has been examined in young men and children [24,25], but to our knowledge no report to date has examined this in adults. By simultaneously examining hormones and muscle and fat mass separately in pre- and postmenopausal women, this study clarifies factors that may be influencing Tb and Ct bone due to excess body weight, especially in the higher range of body weight where geometry may be altered and may increase fracture risk [2–5].

Subjects and methods

Subjects

Two hundred and eleven women aged 25–71 years were recruited by advertising in local newspapers and email list-serves. Some of these women later took part in other intervention trials in the lab. Women were excluded if they were osteoporotic, (defined as a T-score < -2.5 at the hip and spine), taking medications known to influence bone or mineral metabolism in the past year, or had evidence of metabolic bone disease, thyroid disorders, diabetes, immune disease, heart attack, or stroke in the past 6 months, kidney stones, diabetes, active cancers, or cancer therapy within the past 12 months or were pregnant or lactating within the past year or used hormone replacement therapy. Premenopausal women who were menstruating monthly were included, and postmenopausal women were required to be at least 2 years since their last menstruation. This study was approved by the Rutgers University Institutional Review Board and all participants signed an informed consent form.

Methods

Weight and height were measured with a balance beam scale and stadiometer, respectively; (Detecto, Webb City, MO, USA). Dual-energy X-ray absorptiometry (Lunar Prodigy Advanced; GE-Lunar, Madison, WI, USA; coefficient of variation (CV) <1% for all sites) scans were performed by using enCORE 2004 software (version 8.10.027; GE Lunar) was used to assess, total hip, lumbar spine, femoral neck, and total body BMD and BMC, as well as total fat and lean mass. Calcium and vitamin D intake was estimated using 3-day food records and analyzed using the Food Works Software, version 10.1 (Long Valley, NJ, USA). Physical activity level was estimated using general practice physical activity questionnaire. Women were advised to consume a multi-vitamin/mineral tablet beginning, approximately 4–6 weeks prior to baseline measurements to equal a total intake of 1,000–1,200 mg Ca/day (diet and supplement). This uniform intake of calcium avoids variability in serum PTH levels that occurs with a wide range of dietary calcium intake.

pQCT—Volumetric BMD, BMC, and geometric and bone strength properties were measured using pQCT (Stratec XCT 3000, Orthometrix). Sectional images were standardized at specific sites (4%, 38%, and 66%) using distal tibia as the anatomical marker and analyzed for density, content, geometry, and strength indices and we report vBMD, BMC, geometry, biomechanical property, muscle, and fat area. The scans were acquired at 0.5 mm voxel and a slice thickness of 2.4 mm. A scout view was used to determine the positioning of the cross-sectional measurements from the tibia and was set by the integrated software (STRATEC XCT-3000, version 5.4) for Tb, Ct, and muscle-fat measurements, respectively. Processing of the images and calculation of the various bone indices were performed using integrated software. At the 4% site, total and Tb vBMD (mg/mm³), BMC (mg), and total bone cross-sectional area (mm²) were calculated with the use of contour mode 2 and peel mode 2 at a threshold of 280 mg/cm³ (21). Cortical vBMD area, BMC, thickness, periosteal circumference (mm), and endosteal circumference (mm) were assessed in the 38% site with the use of cortical mode 1 and the threshold of 710 mg/cm³. The polar strength-strain index (mm³) and moment of inertia (mm⁴) were also calculated at the 38% site with “cort mode 1” and a threshold of 280 mg/cm³. At the 66% site fat area, muscle area

and the ratio of fat/muscle area were calculated using cort mode 1 and peel mode 1. In addition, to ensure accuracy, we performed an in vivo precision analysis using 18 subjects. The coefficient of variation between the two measurements was less than 1.7% for Tb and Ct vBMD, BMC, area, and geometry.

Serum analysis—Blood samples were collected after an overnight fast and serum was extracted using centrifugation and stored at -80°C until further analysis. Concentrations of PTH and 25OHD were analyzed by radioimmunoassay in batch analysis, using both internal and external standards. The CV was $<6.8\%$ for PTH (Scantibodies laboratory, CA, USA) and $<12.5\%$ for 25OHD (Diasorin MN; DSL corp).

Statistical analysis—Women were separated into two menopausal categories and three BMI categories. Two-way ANOVA was used to analyze the differences in Tb and Ct bone variables across BMI categories and menopausal status. Differences among the various study group means were tested by Tukey's post-hoc analysis when the model F ratio was significant ($p<0.05$). Analysis was controlled for physical activity level, nutrient intake, and lean mass in linear models. Partial Pearson correlation coefficients were used to assess the relationships between Tb and Ct variables controlling for lower leg muscle area, to assess the independent influence of adiposity. Multiple regression analysis was used to assess the relative influence of independent variables (age, fat and lean mass, PTH, and 25OHD) on Tb and Ct variables. Analyses were conducted using the SAS statistical package (SAS Institute, Cary, NC, USA; version 9.1.3). p values <0.05 are considered significant. Data are presented as means $\pm$ SD.

Results

The baseline characteristics of the 211 women are presented in Table 1. Study participants (Table 1) were primarily Caucasian (183 out of 211) with 90% and 86% in the pre- and postmenopausal population, respectively. There were 7% and 11% African-Americans in the pre- and postmenopausal groups, respectively, with 3% Asian and Hispanic in the remaining population. Participants were between 25 and 71 years of age, with no age differences between the various weight categories within the same menopausal status. The percent body fat was higher ($p<0.0001$) in the more obese women, and was higher ($p<0.001$) in the post-compared to premenopausal women with BMI between 25 and 35 kg/m^2 (Table 1). Calcium (Ca) intake was not significantly different in the pre- ($1,379\pm521\text{ mg}$) compared to postmenopausal women ($1,148\pm579\text{ mg}$). However, postmenopausal women with BMI >35 had a lower Ca intake ($p<0.02$) compared to normal weight women. There were small differences in total vitamin D intake between postmenopausal ($7.6\pm4.8\text{ }\mu\text{g/day}$) compared to premenopausal ($9.2\pm4.1\text{ }\mu\text{g/day}$) women ($p=0.019$) and was lowest in the heavier postmenopausal women (Table 1). Serum PTH levels were higher in women with BMI >35 compared to leaner women and were highest in this group of premenopausal ($p<0.0001$). Serum levels of 25OHD were lower ($p<0.0001$) in the heaviest (BMI >35) compared to normal-weight women. Areal BMD (g/m^2) at most sites was significantly lower in the post- compared to the premenopausal women ($p<0.01$). The heavier women had significantly higher BMD ($p<0.05$) at the hip, but not other sites compared to normal weight women. Also, among postmenopausal women, femoral neck BMD was also higher in the heavier (BMI >25) compared to normal weight (BMI <25) women ($p<0.01$).

Trabecular and cortical bone

Body mass index—The relationship between BMI and bone parameters was examined in the entire group of women (Fig. 1). A higher BMI was positively associated ($r>0.35$, $p<0.001$) with Tb BMD and BMC, Ct BMC, area, thickness, periosteal, and endosteal

circumference and stress–strain index (SSI). However, a significant inverse association ($r = -0.27, p < 0.001$) was found between BMI and Ct vBMD in all women. In addition, BMI was positively associated with serum PTH ($r = 0.48$) and negatively associated with 25OHD ($r = -0.45$; Fig. 1). When the effect of BMI on these bone parameters was analyzed by menopausal status (data not shown) a positive relationship ($r > 0.30, p < 0.001$) for most variables was observed for pre- and postmenopausal women except with Ct vBMD. Interestingly, the negative association between BMI and Ct vBMD was significant only in the pre- ($r = 0.54, p < 0.0001$) and not in the postmenopausal ($r = 0.14, p = 0.1$) women (Fig. 2). Also, the negative association between Ct vBMD and PTH ($r = -0.4, p < 0.001$) was only observed in the premenopausal women (Fig. 2), who had a higher BMI ($p < 0.05$) and correspondingly higher PTH ($p < 0.05$) as compared to the postmenopausal women.

Adjustment for potential confounders—We also analyzed this relationship separately in pre- and postmenopausal women with BMI and menopausal status as independent variables and controlling for lean mass, physical activity level, and nutrient intake such as carbohydrates, protein, fat, calcium, vitamin D and sodium (Table 2). A significant BMI*menopause interaction was observed for total BMC, Tb BMC, and periosteal circumference ($p < 0.05$). Similar to correlation analysis, there was a significant effect of BMI on total and Tb vBMD, BMC and Ct area, and cort vBMD. Similarly there was a significant effect of menopause on most Tb and Ct variables except circumference. When analyzing the pre- and postmenopausal women separately, the post-hoc analysis showed that the heavier pre- and postmenopausal women mostly had higher Tb vBMD and BMC compared to leaner women. On the other hand Ct vBMD, BMC, geometry, and strength indices were not significantly higher in the pre- and postmenopausal heavier women. In addition Ct vBMD was lower in the heavier premenopausal women compared to normal weight women ($p < 0.05$).

Muscle and fat area, and bone—Partial correlation analysis shows a positive relationship ($r > 0.2, p < 0.05$) between lower leg muscle area and Tb and Ct bone variables, except Ct vBMD. Similarly, a positive association was observed for most Tb and Ct variables and fat area. However, when controlling for muscle area, the positive association of all variables with fat area was no longer observed ($r < 0.1, p = \text{NS}$), but the negative association with Ct vBMD still remained ($r = -0.2, p < 0.05$; Table 3).

Predictors of trabecular and cortical bone—In order to identify how BMI influences Tb and Ct bone parameters, we examined whether whole body fat or lean tissue was more important in predicting the relationship using multiple regression analyses (Table 4). Age, body composition (total fat or lean mass), serum PTH, and 25OHD served as explanatory variables for each of the dependent variables. As expected, age was a primary predictor of Ct vBMD (Table 4). Fat mass explained 9% of the negative and positive influence on Ct and Tb vBMD, respectively, whereas lean mass only explained about half as much (~5%). In contrast, lean mass explained 17% of the geometric and 33% of the strength indices, whereas fat mass only explained about a third of the variance at 6% and 13%, respectively (Table 4). Not surprisingly, when BMI was in the model, it also was a significant predictor ($p < 0.001$) of Tb and Ct vBMD and Ct thickness and SSI (8–16%). When pre- and postmenopausal women were analyzed separately without age in the model, fat and lean tissue mass explained greater variance for all bone variables in the premenopausal women ($\leq 62\%$) than in postmenopausal women ($< 35\%$). We also examined calcium and vitamin D intake as a covariate in the model and found that it was not a significant predictor, explaining less than 0.05% of the bone variables.

Discussion

While the influence of age, PTH, and/or menopausal status on Tb and Ct bone and geometric properties in normal weight and overweight population has been reported [13,21,22,26–28], the aim of this study was to determine how obesity influences these parameters in women with a wide range of body weights (BMI 18–57 kg/m²). Our results indicate that obesity is associated with higher Tb and Ct bone parameters, except Ct vBMD. While age is a predictor for most bone variables, fat mass explains more variance for vBMD, and lean mass and 25OHD explain greater variance in geometric and strength indices. These findings may be important in explaining the apparent discrepancy in studies examining the effect of fat mass on total body BMD, where some show a positive association [1,16,17,22] and other reports show an inverse or less important role [29,30].

Interestingly, there were differences in Tb and Ct bone that were detected using pQCT that were not observed with areal BMD analysis. For example, DXA analysis showed no effect of menopause on BMD and BMC in the obese population, whereas Tb and Ct vBMD and BMC differed between the obese pre- and postmenopausal women. Although a higher BMI is associated with a greater BMD, it is interesting to note that the early protective effect of a higher BMI on maintenance of Tb and Ct BMC may be lost with aging in heavier women.

Trabecular bone is influenced by several factors including BMI, age, estradiol, and physical activity [13,26,31]. Consistent with previous reports [13,26], lower estradiol and/or aging is associated with lower Tb bone, as observed in the post- compared to premenopausal women in this study. Our results also show that Tb bone is positively influenced by body weight and is not associated with serum PTH and 25OHD.

Cortical bone is similarly influenced by BMI, age, estradiol, and also by PTH and 25OHD [23,27,28,31]. A decrease in Ct BMD begins in mid-life and is accelerated after menopause [27,28,31]. The lower Ct vBMD seen in our post- compared to the premenopausal women supports this finding. Our findings also suggest that Ct vBMD is negatively influenced by BMI, but the major contribution of this effect comes from adipose rather than lean tissue, as shown with multiple regression. The more marked negative relationship in the pre- compared to postmenopausal women is probably due to higher PTH and body weight in the premenopausal group. A previous study showed that Ct vBMD was lower in normal (BMI<25) compared to overweight postmenopausal women [32] at the radius, but similar at the tibia. We also found no difference for Ct BMD between these two lower weight categories (BMI<25 compared to BMI 25–35). It appears that BMI may have a differential effect on different bone sites, as has been found in children [33], and the lower Ct density with higher BMI is only present in the extremely obese women with BMI>35. In addition, because the effect of high BMI on Ct BMD was more pronounced in the premenopausal women, it is possible that Ct bone does not decline as dramatically as in leaner women with aging. However, a low Ct bone density over a longer duration may compromise bone quality and explain recent findings of increased fracture risk at peripheral sites [2–5], possibly due to less soft tissue padding as compared to axial sites. Our results also suggest that BMI does not have an additional positive influence on strength indices which may further help explain increased fracture risk at certain sites in this population.

Adiposity is associated with increased PTH levels [19], possibly due to lower circulating concentrations of 25OHD attributed to increased sequestration in the adipose tissue [20]. Our data also show a higher PTH and a lower 25OHD in the heavier compared to leaner women. Patients with primary hyperparathyroidism have a compromised Ct BMD and a normal Tb BMD [21]. The catabolic effect of excess PTH on Ct bone is typically seen in hyperparathyroid patients, and our results show that these extend to obese populations as

well. On the other hand, the absence of a relationship between PTH and Ct BMD in the postmenopausal women may be due to the more dramatic effects of estrogen depletion in early postmenopausal years, which independently has a marked negative effect on Ct bone [34]. Alternatively, it is possible that even a slightly higher estradiol or other hormones associated with excess adiposity contribute to maintenance of Ct bone. A lower Ct vBMD due to high BMI, as found in the obese in this study may be due to factors other than PTH. For example, obesity is associated with higher inflammatory cytokines and sleep [27], which may negatively influence Ct bone.

Consistent with reports that fat mass has a negative influence on BMD [35,36], one short-term weight reduction study [37] found a moderate increase in Ct vBMD with fat loss in obese premenopausal women. Although a higher body weight is associated with higher Tb bone, it provides no additional benefit to the Ct BMD in overweight children [25,33,38]. In late adolescence, a higher body fat has been shown to be negatively correlated with Ct BMD in the tibia and radius [25], and is consistent with our new findings in adults. Although a lower Ct BMD is typically associated with fracture risk, this higher risk is possibly compensated by increased Ct area and BMC in the obese individual, similar to that observed due to aging, to increase bone size and strength [38,39]. In addition, obesity is also associated with higher Tb bone which may further offset fracture risk. Nevertheless, as in aging, one would expect that this compensation to be limited and result in a higher risk of fracture in the obese [3,4]. In addition, our study shows that greater adiposity per se in the obese does not have a positive influence on bone. Specifically the partial correlation analysis, corrected for muscle area, shows that there is indeed a negative relationship of fat mass with Ct bone and no association with strength indices. Taken together, these data help to explain why a BMD in the normal range in obesity is associated with an increased peripheral fracture risk in women [2–5], but it is interesting that this is not observed in men [4].

There are some limitations of this study including the cross-sectional design which does not address a cause/effect relationship. Also the results are not generalizable since we report on a single bone site, the weight-bearing tibia. However, the influence of excess weight in children at different sites (tibia and radius) have been found to be similar [25], yet one study showed the negative effect of higher weight may be more exaggerated at the radius [38]. BMD measurement artifacts are an ongoing concern in the obese population due to excess fat tissue [40–42]. However, previous studies with this concern have examined axial sites with a greater fat thickness compared to the peripheral site used in the current study. Also, true volumetric BMD (mg/cm^3) that uses fat tissue at a density of zero should also eliminate the concern about artifacts due to excess fat tissue, as occurs with areal BMD.

These findings suggest that adiposity has a positive and negative effect on Tb and Ct vBMD, respectively, and serum PTH and 25OHD at least partially explain these findings. The mechanisms that mediate the long-term effects of a higher PTH and lower 25OHD associated with obesity on Tb and Ct bone need to be further explored in longitudinal studies. The role of other hormones and adipokines that are altered in obesity and their specific effect on Tb and Ct bone also need to be addressed. In summary, this study provides novel insight into the trabecular–cortical bone relationships altered by BMI and menopause, and should aid in our understanding of how excess adiposity influences fracture in obesity.

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References

1. Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res* 1993;8:567–573. [PubMed: 8511983]
2. Gnudi S, Sitta E, Lisi L. Relationship of body mass index with main limb fragility fractures in postmenopausal women. *J Bone Miner Metab* 2009;27:479–484. [PubMed: 19277453]
3. Premaor MO, Pilbrow L, Tonkin C, Parker R, Compston J. Obesity and fractures in postmenopausal women. *J Bone Miner Res* 2009;25:292–297. [PubMed: 19821769]
4. Holmberg AH, Johnell O, Nilsson PM, Nilsson J, Berglund G, Akesson K. Risk factors for fragility fracture in middle age. A prospective population-based study of 33, 000 men and women. *Osteoporos Int* 2006;17:1065–1077. [PubMed: 16758143]
5. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. *J Bone Miner Res* 2009;24:1369–1379. [PubMed: 19292617]
6. Compston J. Bone quality: what is it and how is it measured? *Arq Bras Endocrinol Metabol* 2006;50:579–585. [PubMed: 17117283]
7. Felsenberg D, Boonen S. The bone quality framework: determinants of bone strength and their interrelationships, and implications for osteoporosis management. *Clin Ther* 2005;27:1–11. [PubMed: 15763602]
8. Seeman E. Bone quality. *Osteoporos Int* 2003;14:S3–S7. [PubMed: 14504698]
9. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19:385–397. [PubMed: 18292978]
10. De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, Eisman JA, Kroger H, Fujiwara S, Garnero P, McCloskey EV, Mellstrom D, Melton LJ 3rd, Meunier PJ, Pols HA, Reeve J, Silman A, Tenenhouse A. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int* 2005;16:1330–1338. [PubMed: 15928804]
11. Formica CA, Nieves JW, Cosman F, Garrett P, Lindsay R. Comparative assessment of bone mineral measurements using dual X-ray absorptiometry and peripheral quantitative computed tomography. *Osteoporos Int* 1998;8:460–467. [PubMed: 9850355]
12. Jamal SA, Gilbert J, Gordon C, Bauer DC. Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res* 2006;21:543–548. [PubMed: 16598374]
13. Uusi-Rasi K, Sievänen H, Pasanen M, Kannus P. Age-related decline in trabecular and cortical density: a 5-year peripheral quantitative computed tomography follow-up study of pre- and postmenopausal women. *Calcif Tissue Int* 2007;81:249–253. [PubMed: 17768589]
14. Riggs BL 3rd, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, Rouleau PA, McCollough CH, Bouxsein ML, Khosla S. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J Bone Miner Res* 2004;19:1945–1954. [PubMed: 15537436]
15. Havill LM, Mahaney MC, Binkley TL, Specker BL. Effects of genes, sex, age, and activity on BMC, bone size, and areal and volumetric BMD. *J Bone Miner Res* 2007;22:737–746. [PubMed: 17444815]
16. Lindsay R, Cosman F, Herrington BS, Himmelstein S. Bone mass and body composition in normal women. *J Bone Miner Res* 1992;7:55–63. [PubMed: 1549959]
17. Sowers MF, Kshirsagar A, Crutchfield MM, Updike S. Joint influence of fat and lean body composition compartments on femoral bone mineral density in premenopausal women. *Am J Epidemiol* 1992;136:257–265. [PubMed: 1415147]
18. Reid IR. Relationships among body mass, its components, and bone. *Bone* 2002;31:547–555. [PubMed: 12477567]
19. Bolland MJ, Grey AB, Ames RW, Horne AM, Gamble GD, Reid IR. Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women. *Bone* 2006;38:317–321. [PubMed: 16199216]

20. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72:690–693. [PubMed: 10966885]
21. Charopoulos I, Tournis S, Trovas G, Raptou P, Kaldrymides P, Skarandavos G, Katsalira K, Lyrilis GP. Effect of primary hyperparathyroidism on volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in postmenopausal women. *J Clin Endocrinol Metab* 2006;91:1748–1753. [PubMed: 16492695]
22. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto Chihara K. Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. *J Clin Endocrinol Metab* 2003;88:4655–4658. [PubMed: 14557436]
23. Lauretani F, Bandinelli S, Russo CR, Maggio M, Di Iorio A, Cherubini A, Maggio D, Ceda GP, Valenti G, Guralnik JM, Ferrucci L. Correlates of bone quality in older persons. *Bone* 2006;39:915–921. [PubMed: 16709469]
24. Taes YE, Lapauw B, Vanbillemont G, Bogaert V, De Bacquer D, Zmierzak H, Goemaere S, Kaufman JM. Fat mass is negatively associated with cortical bone size in young healthy male siblings. *J Clin Endocrinol Metab* 2009;94:2325–2331. [PubMed: 19401374]
25. Pollock NK, Laing EM, Baile CA, Hamrick MW, Hall DB, Lewis RD. Is adiposity advantageous for bone strength? A peripheral quantitative computed tomography study in late adolescent females. *Am J Clin Nutr* 2007;86:1530–1538. [PubMed: 17991669]
26. Khosla S, Melton LJ 3rd, Achenbach SJ, Oberg AL, Riggs BL. Hormonal and biochemical determinants of trabecular microstructure at the ultradistal radius in women and men. *J Clin Endocrinol Metab* 2006;91:885–891. [PubMed: 16368747]
27. Specker BL, Binkley T, Vukovich M, Beare T. Volumetric bone mineral density and bone size in sleep-deprived individuals. *Osteoporos Int* 2007;18:93–99. [PubMed: 16909195]
28. Hasegawa Y, Schneider P, Reiners C, Kushida K, Yamazaki K, Hasegawa K, Nagano A. Estimation of the architectural properties of cortical bone using peripheral quantitative computed tomography. *Osteoporos Int* 2000;11:36–42. [PubMed: 10663357]
29. Wang MC, Bachrach LK, Van Loan M, Hudes M, Flegal KM, Crawford PB. The relative contributions of lean tissue mass and fat mass to bone density in young women. *Bone* 2005;37:474–481. [PubMed: 16040285]
30. Zhao LJ, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. *J Clin Endocrinol Metab* 2007;92:1640–1646. [PubMed: 17299077]
31. Boonen S, Cheng XG, Nijs J, Nicholson PH, Verbeke G, Lesaffre E, Aerssens J, Dequeker J. Factors associated with cortical and trabecular bone loss as quantified by peripheral computed tomography (pQCT) at the ultradistal radius in aging women. *Calcif Tissue Int* 1997;60:164–170. [PubMed: 9056165]
32. Hernández ER, Seco C, Cortés-Prieto J, Villa LF, Revilla M, Rico H. Gynecological factors and body mass index as determinants of bone mass in normal postmenopausal women. A study with peripheral quantitative computed tomography (pQCT). *Eur J Obstet Gynecol Reprod Biol* 2000;92:193–198. [PubMed: 10996680]
33. Ducher G, Bass SL, Naughton GA, Eser P, Telford RD, Daly RM. Overweight children have a greater proportion of fat mass relative to muscle mass in the upper limbs than in the lower limbs: implications for bone strength at the distal forearm. *Am J Clin Nutr* 2009;90:1104–1111. [PubMed: 19710192]
34. Jarvinen TL, Kannus P, Sievanen H. Estrogen and bone—a reproductive and locomotive perspective. *J Bone Miner Res* 2003;18:1921–1931. [PubMed: 14606503]
35. Blum M, Harris SS, Must A, Phillips SM, Rand WM, Dawson-Hughes B. Leptin, body composition and bone mineral density in premenopausal women. *Calcif Tissue Int* 2003;73:27–32. [PubMed: 14506951]
36. Zhao LJ, Jiang H, Papasian CJ, Maulik D, Drees B, Hamilton J, Deng HW. Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis. *J Bone Miner Res* 2008;23:17–29. [PubMed: 17784844]

37. Uusi-Rasi K, Sievanen H, Kannus P, Pasanen M, Kukkonen-Harjula K, Fogelholm M. Influence of weight reduction on muscle performance and bone mass, structure and metabolism in obese premenopausal women. *J Musculoskelet Neuronal Interact* 2009;9:72–80. [PubMed: 19516082]
38. Wetzsteon RJ, Petit MA, Macdonald HM, Hughes JM, Beck TJ, McKay HA. Bone structure and volumetric BMD in overweight children: a longitudinal study. *J Bone Miner Res* 2008;23:1946–1953. [PubMed: 18684083]
39. Orwoll ES. Towards an expanded understanding of the role of the periosteum in skeletal health. *J Bone Miner Res* 2003;18:949–954. [PubMed: 12817746]
40. Frost, H. Mechanical usage, bone mass, bone fragility: a brief overview. In: Kleerekoper, M.; Krane, S., editors. *Clinical disorders of bone and mineral metabolism*. New York: Liebert; 1989. p. 15-40.
41. Hangartner TN, Johnston CC. Influence of fat on bone measurements with dual-energy absorptiometry. *Bone Miner* 1990;9:71–81. [PubMed: 2337690]
42. Bolotin HH. A new perspective on the casual influence of soft tissue composition on DXA-measured in vivo bone mineral density. *J Bone Miner Res* 1998;13:1739–1746. [PubMed: 9797483]

Fig. 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-dihydroxy-vitamin D (*25OHD*) in 211 women. * $p < 0.001$

Fig. 2.

Relationship between cortical volumetric bone mineral density (*vBMD*) and body mass index (*BMI*), serum parathyroid hormone (*PTH*), and 25-dihydroxy-vitamin D (*25OHD*) in premenopausal women ($n=73$). $*p<0.001$

Table 1

Characteristics of 211 women by menopausal status and BMI category

BMI category	Premenopausal women (N=73)			Postmenopausal women (N=138)			Menop	BMI ^a menop
	BMI<25	BMI 25–35	BMI>35	BMI<25	BMI 25–35	BMI>35		
Age (years)	44±7 ^a	40±8 ^a	40±9 ^a	58±5 ^b	58±6 ^b	59±6 ^b	<0.001	0.059
Weight (kg)	59.1±6.4 ^a	75.4±5.7 ^b	129.5±25.7 ^c	57.1±6.5 ^a	79.5±9.4 ^b	109.4±16.6 ^d	0.002	<0.001
BMI (kg/m ²)	22.1±1.7 ^a	28.5±2.1 ^b	45.6±6.6 ^c	22.5±2.3 ^a	30.1±2.6 ^d	40.9±4.9 ^e	0.078	<0.001
DXA								
Lean mass (kg) [†]	37.8±4.7 ^a	41.8±3.4 ^b	49.8±4.9 ^c	36.2±4.6 ^a	41.1±4.6 ^a	50.9±7.8 ^c	0.552	0.581
Fat mass (kg) [†]	18.6±5.2 ^a	29.1±4.8 ^b	50.9±17.7 ^c	18.3±5.0 ^a	35.2±6.8 ^d	44.9±18.2 ^c	0.942	0.008
Fat (%)	32.8±7.4 ^a	40.9±4.7 ^b	52.9±2.7 ^c	33.3±7.7 ^a	45.9±4.6 ^d	49.8±3.7 ^c	0.870	<0.001
BMD (g/m ²)								
Femoral neck	0.942±0.131 ^a	0.984±0.126 ^{ab}	1.057±0.184 ^a	0.795±0.105 ^c	0.915±0.112 ^b	0.977±0.143 ^{ab}	<0.001	0.244
Total hip	0.896±0.127 ^a	1.039±0.123 ^b	1.157±0.185 ^c	0.809±0.119 ^a	0.973±0.119 ^b	1.058±0.152 ^c	<0.001	0.815
Lumbar spine	1.127±0.058	1.243±0.156	1.306±0.184	1.113±0.289	1.179±0.162	1.264±0.225	0.097	0.960
Total body	1.169±0.120	1.204±0.063	1.256±0.095	1.047±0.114	1.164±0.089	1.245±0.113	0.006	0.269
Hormones								
PTH (pg/ml)	32.9±11.2 ^a	40.2±16.3 ^a	74.9±31.3 ^b	33.7±11.8 ^a	43.2±22.4 ^a	60.5±30.9 ^c	0.330	0.107
25OHD (ng/ml)	28.3±8.8 ^a	28.8±7.9 ^a	19.5±6.4 ^c	27.9±7.9 ^a	23.6±6.1 ^b	17.6±8.1 ^c	0.064	0.300
Nutrient intake [*]								
Calcium (mg/day)	1415±543 ^a	1435±512 ^a	1192±499 ^{ab}	1501±548 ^a	1132±586 ^{ab}	995±513 ^b	0.129	0.178
Vit D (ug/day)	9.9±1.8 ^a	8.5±4.5 ^{ab}	9.8±5.3 ^a	8.6±4.9 ^{ab}	7.7±4.7 ^b	6.6±5.2 ^b	0.019	0.378

Values are mean±SD. Values with different superscripts within a row are significantly different (Tukey's post-hoc test p<0.05). The number of women in the BMI<25, BMI 25–35, and BMI>35 groups were n=23, n=34, and n=16 for the premenopausal group, and n=19, n=85, and n=34 for the postmenopausal group, respectively

BMI body mass index, PTH parathyroid hormone, 25OHD 25 hydroxy vitamin D, vit vitamin

* Includes intake of calcium and D from multivitamins and calcium pills

† Total body fat and lean mass was not available in 10 women

Table 2
Volumetric bone mineral density, content, geometry, and strength indices in 211 women

BMI category	Premenopausal women (N=73)			Postmenopausal women (N=138)			BMI	Menop	BMI* menop
	BMI<25	BMI 25-35	BMI>35	BMI<25	BMI 25-35	BMI>35			
Total vBMD (mg/m ³)	286±31.7 ^a	310±39.6 ^b	328±38.2 ^b	252±38.7 ^c	293±37.5 ^{ab}	307±36.9 ^{ab}	0.0002	0.0022	0.5751
Total BMC (mg)	290±35.7 ^a	304±36.7 ^{ab}	334±55.1 ^b	251±40.2 ^c	288±37.2 ^a	270±37.9 ^{ac}	0.0048	<0.0001	0.0180
Total area (mm ²)	1021±122 ^a	993±140 ^a	1010±191 ^a	995±134 ^a	991±108 ^a	885±127 ^b	0.3022	0.0226	0.0669
Trabecular site (4%)									
BMC (mg)	94.8±16.2 ^a	102.4±17.5 ^a	120.6±26.1 ^c	82.1±15.8 ^b	98.4±18.6 ^a	90.5±17.4 ^{ab}	0.0042	<0.0001	0.0086
vBMD(mg/m ³)	203±28 ^{ab}	226±37 ^b	260±32 ^c	183±35 ^a	220±32 ^b	226±28.3 ^b	<0.0001	0.0028	0.1735
Cortical site (38%)									
BMC (mg)	321±44 ^{ac}	338±44 ^a	350±41 ^a	290±45 ^b	315±38 ^c	293±43.6 ^b	0.0209	<0.0001	0.1172
vBMD (mg/m ³)	1185±18 ^a	1175±21 ^a	1159±17 ^b	1140±30 ^b	1144±35 ^b	1137±30 ^b	0.0383	<0.0001	0.3227
Area (mm ²)	272±39 ^{ac}	287±36 ^{ab}	302±37 ^{ab}	256±39 ^c	275±30 ^{ac}	257±38 ^c	0.0186	<0.0001	0.0563
Thickness (mm)	5.1±0.5 ^a	5.2±0.6 ^a	5.5±0.9 ^a	4.6±0.7 ^b	5.1±0.5 ^a	4.9±0.6 ^{ab}	0.0706	<0.0001	0.1045
Peri circ (mm)	69.3±4.9 ^{ac}	71.2±4.1 ^b	71.8±4.9 ^{ab}	70.3±5.3 ^{abc}	70.7±4 ^{ab}	68.2±4.5 ^c	0.0806	0.1033	0.0487
Endo circ (mm)	37.1±3.6 ^a	39.1±4.1 ^{ab}	37.4±4.1 ^{ab}	41.4±6.4 ^b	39.2±5.0 ^{ab}	37.8±4.9 ^{ab}	0.4908	0.0907	0.0752
Ip (mm ⁴)	22,530±6,067 ^{ac}	24,941±5,214 ^{bc}	27,093±7,554 ^{bc}	22,504±5,165 ^{ac}	23,280±4,613 ^c	20,198±6,078 ^a	0.2363	0.0019	0.0134
SSI (mm ³)	1,505±274 ^{ac}	1,640±266 ^b	1,679±294 ^{bc}	1,446±267 ^{ac}	1,511±240 ^c	1,366±296 ^a	0.0780	0.0003	0.0930

Values are mean±SD. Values with different superscripts within a row are significantly different (Tukey's post-hoc test p<0.05). Controlled for lean mass, physical activity level, and nutrient. The number of women in the BMI<25, BMI 25-35, and BMI>35 groups were n=23, n=34, and n=16 for the premenopausal group, and n=19, n=85, and n=34 for the postmenopausal group, respectively

vBMD volumetric bone mineral density, Circ circumference, Endo endosteal, Peri periosteal, Ip polar moment of inertia, SSI stress strain index

Table 3

Partial correlation analysis examining relationship between bone variables and tibia fat and muscle area

	Tibia fat area	Tibia muscle area	Fat area ^a (<i>r</i>)
Tb BMC	0.10	0.27**	0.009
Tb BMD	0.15	0.21*	0.09
Ct BMC	0.18*	0.38**	0.04
Ct BMD	-0.18*	-0.08	-0.16*
Ct Ar	0.21*	0.41**	0.07
Ct thk	0.14	0.31**	0.05
Peri C	0.19*	0.39**	0.05
Endo C	0.07	0.13	0.14
SSI	0.19*	0.38**	0.04
Ip	0.18*	0.37**	0.06

*
 $p < 0.05$;**
 $p < 0.01$ ^a Controlled for muscle area

Ct cortical, *Tb* trabecular, *vBMD* volumetric bone mineral density, *Circ* circumference, *Endo* endosteal, *Peri* periosteal, *Ip* polar moment of inertia, *SSI* stress strain index

Table 4
Multiple regression analysis of relative contribution of age, body composition (fat and lean mass), and hormones

	Total fat mass				Total lean mass			
	Beta coefficient	p value	R ² %	Model r ²	Beta coefficient	p value	R ² %	Model r ²
Tb vBMD								
Fat or lean	0.41	<0.001	9.1	10.2	0.23	0.0025	5.4	6.6
Age	-0.15	0.028	1.1		-0.10	0.163	1.1	
PTH	-0.09	0.259	0.03		0.009	0.909	0.03	
25OHD	0.09	0.229	0.08		0.007	0.928	0.08	
Ct vBMD								
Age	-0.43	<0.001	23.6	37.8	-0.46	<0.001	23.6	33.0
Fat or lean	-0.20	0.007	9.1		-0.17	<0.001	4.4	
25OHD	0.10	0.139	5.0		0.13	0.048	5.0	
PTH	0.06	0.358	0.06		0.03	0.641	0.06	
Ct Thk								
Fat or lean	0.34	<0.001	5.8	16.5	0.41	<0.001	16.6	27.3
Age	-0.33	<0.001	8.3		-0.28	<0.001	8.3	
25OHD	0.15	0.044	0.08		0.11	0.094	0.08	
PTH	0.06	0.395	2.4		0.10	0.128	2.4	
SSI								
Fat or lean	0.44	<0.001	12.9	20.4	0.57	<0.001	33.4	41.0
Age	-0.24	<0.001	3.1		-0.17	0.002	3.2	
25OHD	0.16	0.028	0.04		0.12	0.052	0.04	
PTH	0.07	0.337	4.4		0.11	0.067	4.4	

vBMD volumetric bone mineral density, PTH parathyroid hormone, 25OHD 25 hydroxy vitamin D, Tb trabecular, Ct cortical, Thk thickness, SSI stress strain index