Published in final edited form as:

Curr Osteoporos Rep. 2011 June ; 9(2): 67–75. doi:10.1007/s11914-011-0051-6.

The Role of Bone Marrow and Visceral Fat on Bone Metabolism

Yahtyng Sheu and

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 North Bellefield Avenue, Room 467, Pittsburgh, PA 15213, USA

Jane A. Cauley

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A524, Pittsburgh, PA 15216, USA

Yahtyng Sheu: sheuy@edc.pitt.edu; Jane A. Cauley: jcauley@edc.pitt.edu

Abstract

The protective effect of total fat mass on bone mineral density (BMD) has been challenged with studies showing no or negative association after adjusting for weight. Subsequently, more studies have evaluated the relationship of regional adiposity with BMD, and findings were inconsistent for central obesity. Advancements in imaging techniques enable us to directly and noninvasively study the role of adiposity on skeletal health. Visceral adiposity measured by computed tomography (CT) has consistently been shown to have negative effects on bone. Availability of magnetic resonance spectroscopy (MRS) also allows us to noninvasively quantify bone marrow fat (BMF), which has been known to be associated with osteoporosis from histomorphometric studies. Using MRS along with dual energy x-ray absorptiometry, studies have reported a detrimental role of BMF on BMD. With the increase in aging and obesity of the population, it is important to continue this effort in identifying the contribution of adipose tissues to bone quality and fracture.

Keywords

Bone marrow fat; Visceral adipose tissue; Bone; BMD; Fracture; Central obesity; Metabolic syndrome

Introduction

The effect of fat on bone metabolism is in part explained through the function of adipocytes. Along with the mechanical loading from body weight, hormones secreted by adipocytes such as leptin, adiponectin, and sex hormones have also been shown to influence bone mineral density (BMD). The relationship between adiposity and bone has traditionally been approached from two different perspectives: the relationships of bone phenotypes (eg, BMD and turnover markers) with (1) total body weight and fat mass, and (2) regional adiposities,

with the latter receiving less attention. This review summarizes the less discussed relationship between bone and visceral adiposity as well as the emerging research identifying the role of marrow fat on bone.

From Total Fat Mass to Regional Fat

Greater body weight or body fat mass has been known to have a positive effect on BMD [1•]. This positive association is thought to be explained not only by stresses from mechanical loading, but also by metabolic response from bone-related hormones that are secreted or regulated by adipocytes. However, some studies also suggest that the positive association between body fat mass and bone reversed once body weight was accounted for [1•, 2••, 3]. Moreover, recent studies have also suggested a lack of or negative association between body fat mass and bone [1•, 4, 5]. In addition, the positive effect of body weight and fat mass does not always translate into lower fracture risk. In fact, individuals with excessive weight, who often have type 2 diabetes, are at increased fracture risk, in part, due to related pharmacologic treatment [6, 7]. Whether or not the conflicting findings between body fat mass and BMD in the population level are the result of differences in regional fat distribution is unknown. Studies have suggested that the pattern of regional fat deposition into subcutaneous and visceral compartments is associated with cardiovascular diseases (CVDs) and diabetes stronger than total body fat mass [8–10]. Central obesity or visceral adipose tissue (VAT) has been linked to adverse health outcomes such as atherosclerosis, diabetes, and mortality [8–11]; however, the relationship between VAT and skeletal health is much less understood. In studying the effect of adiposity on bone metabolism, it is important to distinguish VAT from total body fat mass or body weight because VAT can continue to increase despite an overall decrease in body mass index (BMI) or body weight with aging [12].

Visceral Fat

Adipose tissue has been defined in recent studies as a dynamic organ that stores excess fat and a secretory organ that produces adipokines and cytokines, which play critical roles in human biology. It is also suggested that the function of adipose tissues may depend on the location of fat deposition, visceral or subcutaneous. This is supported by the increased risk of CVD, diabetes, and mortality with elevated VAT as opposed to subcutaneous adipose tissue (SAT) [8–11]. Although abundant studies have focused on the negative effect of VAT on CVD or metabolic syndrome (MetS), which are known to be strongly associated with abdominal obesity, the role of VAT on bone has not been elucidated. Previous studies have shown no relationship, inverse or positive association between fat mass and BMD [4, 5, 13, 14]. These investigations were limited by the use of dual-energy x-ray absorptiometry (DXA), which is unable to distinguish VAT from SAT.

Central Adiposity and Bone

More recently, several studies have attempted to evaluate the relationship of VAT with bone using either direct or surrogate measures of VAT, including waist, waist-hip-ratio (WHR), abdominal fat (truncal fat) measured by DXA (including both visceral and subcutaneous fat), and MetS (Table 1). Central adiposity or obesity measures have conveniently been used

as surrogates for VAT and have been linked to several adverse health outcomes [15, 16]. However, evidence regarding the association between central obesity and BMD is mixed. Waist circumference, WHR, and abdominal fat were reported to be positively associated with BMD in both men and women in some studies [17•, 18], whereas other studies showed a negative association between waist circumference or WHR and BMD, bone mineral content (BMC) or osteoporosis, independent of weight or BMI [19•, 20, 21•]. A study by Nguyen et al. [22] showed that the contribution of abdominal fat measured by DXA to hip fracture risk is likely to be modest. They found that low abdominal fat was associated with an increased risk of hip fracture in elderly women in Australia, but the association was not independent of weight or femoral neck BMD [22]. A similar pattern was found when hip girth was used to predict hip fracture in elderly women in the United States [23]. Because the measure of central obesity includes both subcutaneous and visceral depots, it is possible that the inconsistent associations were related to the differential effects of subcutaneous and visceral fat on bone health [24•, 25•].

Metabolic Syndrome and Bone

Central obesity is one of the key features of MetS; therefore, studies evaluating the relationship between MetS and skeletal health may also provide information regarding the effect of central obesity on bone. Yamaguchi et al. [2••] compared BMD at different skeletal sites between diabetic participants with and without MetS. They found that BMD at the femoral neck, but not total, spine or wrist, was higher among individuals with MetS. This difference was not adjusted for or stratified by gender. Given the gender difference in fat distribution, prevalence of MetS, and BMD, it is possible that the effect of VAT on bone varies by gender. In addition, femoral neck BMD was also found to be higher among subjects with MetS (including both men and women) after multivariable adjustment using NHANES III (National Health and Nutrition Examination Survey III) data [26•]. However, when gender-specific association was evaluated, the results were inconsistent. Szulc et al. [27•] reported a significant lower BMD at multiple skeletal regions among men with MetS including total hip, subregions of hip and forearm, after controlling for age, BMI, height, and other potential confounders. In contrast, findings from von Muhlen et al. [17••] indicated that the relationship between MetS and BMD was only significant in men but not in women, and the significant association found in men was for femoral neck BMD but not total hip or lumbar spine.

Several authors have also evaluated the relationship between MetS and fracture. In a cross-sectional analysis, von Muhlen et al. [17••] found no association between MetS and prevalence of osteoporotic fractures. However, after an average of 2 years of follow-up, women with MetS were at higher risk (odds ratio [OR]=3.76, $P=0.02$) of developing nonvertebral fracture than those without. In men, the magnitude of this association was less and insignificant (OR=2.48, $P=0.27$) [17••]. Interestingly, two other studies showed that MetS and features of MetS were associated with reduction in fracture risk for both men and women [27•, 28].

Optimally Measured Visceral Fat and Bone

It is unclear whether the inconclusive relationship between central obesity and BMD is, in part, due to the inability of these surrogate measures to distinguish VAT from other tissues. Few studies have used advanced technology to isolate and quantify visceral fat and evaluated its relationship with skeletal parameters. In contrast to the inconsistent results using central obesity, findings were reported to be in agreement for studies applying direct VAT measurement with CT or MRI. In these studies, VAT was negatively associated with bone density, content, structure, and strength [2•, 19•, 24•, 25•, 29]. Yamaguchi et al. [2•] found that VAT area measured by CT was positively associated with BMD in 312 Japanese men and women 21 to 83 years of age with diabetes; however, the association became negative but insignificant once body weight was adjusted for. In the same study, VAT area was significantly lower in diabetic men with vertebral fracture compared to those without fracture independent of weight, spine BMD, duration of diabetes, and diabetic therapies. The authors suggested that VAT may have a preventive effect on fracture through underlying mechanisms that enhance other measures of bone quality than increased BMD. Two other studies using CT measures of VAT reported significant and negative associations with BMD and BMC in overweight/obese individuals. For example, one study by Russell et al. [24•] found that VAT measured by MRI was a negative predictor of BMD at various skeletal sites in 30 adolescent girls with and without controlling for SAT. Another study with 150 prepubertal overweight children also supported the negative effect of VAT on BMC after controlling for gender, race, height, fat mass, lean mass, and SAT [29]. In addition to obese or diabetic individuals, the detrimental role of VAT on BMD was also observed in healthy adults. VAT measured by CT showed independent and negative association with BMD at the lumbar spine, femoral neck, and total hip among 461 healthy Korean men and women [19•], whereas another study revealed the same association (but insignificant) with cortical bone structure and strength indices including femoral cross-sectional area, cortical bone area, principal moment maximum, principal moment minimum, and polar moment [25•]. Overall, studies using direct measures of VAT appear to provide more consistent finding on the association between VAT and BMD than those using surrogate measures.

Differential Effects of Visceral and Subcutaneous Fat on Bone?

Although an inverse relationship was observed between VAT and BMD using CT or MRI measurement, no association or a negative association was observed for SAT. Among healthy adults, SAT was positively correlated with BMD at various skeletal sites, but the correlation became negative and insignificant once body weight was taken into account [19•]. However, Gilsanz et al. [25•] found SAT had a beneficial effect on cortical bone structure and strength independent of leg length and thigh musculature, but no results with adjustment for body weight were reported. In prediabetic overweight children, SAT was negatively correlated with BMC after controlling for demographic and anthropometric characteristics [29]. In this study, SAT and VAT, but not total body fat mass, were found to be independent predictors of bone mass. Similarly, a negative correlation of SAT was observed with whole-body and femoral neck BMD among diabetic adults [2•].

Very few studies have compared the effects of SAT and VAT on bone using direct measurements. In addition, participants recruited for these studies were diverse in terms of race, age, and metabolic features. Therefore, it remains unclear whether the effects of SAT and VAT on bone are similar, opposite, and/or at a different degree. Various hormones and inflammatory factors have regulatory roles of biological functions related to bone metabolism and have depot-specific differences in gene expression [30•]. For example, VAT is known to play an important role in CVD and mortality, in part due to its association with increased level of proinflammatory cytokines that increase bone resorption and consequently promote osteoporosis. In contrast, adiponectin and leptin, exclusively secreted by adipose tissue, are shown to be protective against osteoporosis, partially due to their effects to stimulate the proliferation and differentiation of osteoblasts. These two hormones are found to be less abundant in the VAT [25••]. In addition, estrogen production and expression of aromatase (which converts androgen to estrogen) is also associated with reduced osteoclast activity. These hormones were also reported to be lower in VAT than SAT [25••]. Importantly, despite the inconclusive results on the differential effects of SAT and VAT on bone, all three studies support the inverse association between VAT and bone.

New Approach: Bone Marrow Fat

In the past decade, a new approach has emerged to evaluate the bone-fat relationship targeting bone marrow fat (BMF). There is evidence suggesting that total body and regional fat have different metabolic responses than BMF, and their effects on bone may also vary. Another connection between fat and bone comes from stem cell differentiation. Adipocytes and osteoclasts share common precursors, and the differentiation of this precursor is thought to be affected by normal aging processes favoring adipogenesis. This process occurs in the bone marrow, and histomorphometric studies have shown a positive connection between BMF and osteoporosis [31, 32]. Not until the recent advances in medical imaging technology have we been able to further investigate the relationship between BMF and bone health with noninvasive methods. Compared with VAT, findings on the associations between BMF and bone are more consistent; however, the role of BMF in skeletal health and factors associated with this connection remained largely unidentified.

Fat in Bone Marrow

Bone marrow is a highly vascular and cellular substance within bone that is responsible for the production and delivery of blood cells. It occupies approximately 85% of the bone cavity, and the rest is filled with trabecular bone. There are two main components of bone marrow: hematopoietic (red) marrow and fatty (yellow) marrow [33]. The composition of bone marrow is location-, age-, and gender-specific [33, 34]. For example, at birth, all bone marrow is red and contains cells for blood formation. With age, red marrow is progressively replaced by yellow marrow with a higher conversion in the appendicular skeleton. By age 10 to 20 years, the shafts of long bones are predominantly filled with yellow marrow. In adults, half of the medullary cavity is occupied by yellow marrow, with its chemical composition of 80% fat, 15% water, and 5% protein. By the age of 25 years, red marrow, consisting of only 40% fat, can be found primarily in the axial skeleton, rib, sternums, and metaphysis of femora and humeri with a progressive increase of fat cell proportion [34].

Connection Between BMF and Osteoblastogenesis

Bone is a dynamic organ, constantly being remodeled under the actions of osteoclastic bone resorption and osteoblastic bone formation. When the bone formation rate cannot keep up with the bone resorption rate, spaces created by osteoclasts will not be refilled with new bone cells, which consequently results in the loss of bone mass. This coupling process is believed to be mediated by osteoblasts and cells in the osteogenic lineage [35]. Mesenchymal stem cells (MSCs), where osteoblasts originate, are precursors for adipocytes. Differentiation of MSCs into either adipocytes or pre-osteoblasts is regulated by a complex process involving many growth and transcription factors [36]. MSC differentiation is thought to be affected by the normal aging process favoring adipogenesis due to, in part, physiologic declines in growth factor secretion as well as oxygen tension and blood supply within the bone marrow [37, 38]. As a result, more adipose tissue is stored in the bone cavity with advancing age. This mechanism is also supported by histomorphometric studies on iliac crest biopsies where a positive correlation was observed between BMF and age [31, 32]. However, it remains unclear whether marrow adipocytes induce the reduction in bone formation and increase in bone resorption that leads to age-related bone loss in older individuals or whether BMF merely occupies the empty spaces created by the reduced osteoblastogenesis process. More importantly, to what extent BMF actually affects bone metabolism requires further investigation.

BMF and Osteoporosis in Histomorphometric Studies

Previously, the measurement of BMF relied on biopsies from cadavers before advanced medical imaging technology became available. Histomorphometric studies performed on iliac crest biopsies not only demonstrated a positive correlation between BMF and age, but also found elevated BMF in male and female subjects with osteoporosis or low trabecular bone volume [31, 32]. Moreover, MRI, a noninvasive approach to quantify BMF, has provided additional support for the earlier findings on iliac crest biopsies. MRI is the choice for diagnosis of bone marrow disorders because of its high sensitivity and ability to distinguish red and yellow marrow [39].

BMF and Osteoporosis in Clinical Studies

Most clinical studies of the bone-BMF relationship have used proton magnetic resonance spectroscopy (MRS) to analyze separate water and fat signals of BMF at the vertebrae (Table 2) [40–45, 46•]. In MRS studies, BMF is expressed based on fat and water ratio. For example, Schellinger et al. [45] reported a linear rise in BMF with age, ranging from 20.5% for the 2nd and 3rd decades of life to 49.9% for the 8th and 9th decades, in males and females 15 to 87 years of age. Other studies also demonstrated a similar positive correlation between age and vertebral BMF [42, 43]. In contrast, a most recent study has shown no association between BMF and age among 47 healthy premenopausal women 19 to 45 years of age [47••]. Although limited studies have used MRS to evaluate the relationship between BMF and skeletal health, the results have been consistent across different measures of skeletal strength. Similar to histomorphometric studies, higher BMF content measured by MRS has been shown in osteoporotic Chinese men and women 55 years of age and older, when compared to those with low or normal bone density [40–42, 46•]. In addition, the

percent BMF in the osteoporotic group was 8%, or approximately one standard deviation, higher than the normal BMD group [40, 41]. Schellinger et al. [45] examined percent BMF in subjects with and without bone weakness, defined with MRI of Schmorl's nodes, endplate depression, wedging of vertebrae, and vertebral body compression fracture. Compared with the control group, BMF content was 45% higher in the bone weakness group, and this observation was significant and consistent across age groups. Another study by the same authors using the same method found that percent BMF may predict bone weakening as well as BMD; however, the finding did not reach statistical significance, likely due to small sample size [44]. Although studies have shown significantly and consistently elevated BMF in osteoporotic subjects, the linear relationship between BMF and BMD measured by DXA is less defined. Several studies found a significantly negative correlation of percent BMF with BMD and T-scores in Chinese men and women [40–42, 46]. This negative correlation was also supported by another study in which pelvic bone mineral adipose tissue was shown to be inversely correlated with whole-body and pelvic BMD [48•]. In addition, a recent study demonstrated an inverse correlation between BMF and trabecular BMD measured by CT [47••]. However, another study found a weak and inconclusive correlation between BMF and BMD once age was accounted for [43].

Studies investigating the association between BMF and skeletal health predominately include Chinese and Caucasian subjects. It is unknown whether the same association also applies to other ethnicities. In addition, it is very likely that the effect of BMF on bone will be different depending on the bone parameter of interest. For example, bone marrow is highly concentrated in trabecular bone, and the correlation between BMF and trabecular bone might be stronger than that with BMD. More data are needed on the association between BMF and skeletal health. In particular, no prospective study has related BMF to fracture, the most important clinical consequence of osteoporosis.

BMF and Other Fat Tissue

Previous studies in humans have shown a lack of association between marrow adiposity and anthropometric or body fat measures [32, 48•, 49]. It has been suggested that the role of BMF is distinct from that of visceral and subcutaneous adiposity. This hypothesis is supported by studies in anorexia nervosa (AN) patients, in which extreme low body fat mass (including VAT and SAT) is present [50]. Not only do AN patients have a high prevalence of osteoporosis, but there is also a high vertebral BMF content. A study by Bredella et al. [51••] evaluated the relationship of BMF at the lumbar vertebra and femur with regional fat and BMD among young women with and without AN. Compared to women without AN, those with AN had a higher percentage of BMF at both the vertebra and femur. They also found a significant inverse correlation between BMF and BMD at the spine and hip. Interestingly, BMF was inversely correlated with SAT, VAT, BMI, and total abdominal adipose tissue in this study, but the correlation with VAT did not reach statistical significance. Given the observation that both VAT and BMF seem to have detrimental effects on bone health, it is paradoxical that osteoporosis is present in AN patients while VAT was noticeably reduced. It is unknown whether the impaired bone formation observed in AN patients causes a shift in bone marrow mesenchymal differentiation into the fat lineage. In addition, Bredella et al. [47••] hypothesized that individuals with high VAT also

have increased BMF. They found that women with high VAT also have significantly high BMF, and the correlation between VAT and BMF was significant and positive among 47 healthy premenopausal women. In addition, the association between VAT and BMF remained significant after adjusting for BMD. These results suggest that the associations between BMF and fat may depend on the adiposity of interest and possibly individuals' health status or adipose distribution.

Conclusions

Osteoporosis and osteoporotic fracture are major public health concerns for the elderly. With an increase in life expectancy and increase in the number of elders, the burdens of osteoporosis and osteoporotic fracture are on the rise. In addition, these issues are being aggravated by the growing trend of obesity and type 2 diabetes. Although obesity was traditionally thought to be protective against osteoporosis, more studies have found a higher risk of fracture among diabetic individuals. Recent studies have suggested that central obesity may be more relevant to bone health than total body fat [29]. However, studies on the effect of central obesity on bone have yielded inconsistent results. Crude measures of central obesity that are unable to separate VAT from other soft tissues have been primarily used; therefore, the contribution of VAT on bone is difficult to define. Instead, studies using direct measures of VAT, such as CT and MRI, have consistently reported its detrimental role on BMD, suggesting that further investigation on the roles of different adipose tissues on bone using advanced imaging technique is indispensable for future research regarding the relationship between body composition and skeletal health. This phenomenon is also supported by the rising research interest in marrow fat. Similar to VAT, studies also reported a negative impact of BMF on bone in which elevated BMF was found to be associated with osteoporosis or low BMD. Furthermore, it is also important to extend the focus from two-dimensional bone density to other bone indices such as volumetric BMD and bone geometry/strength. It is possible that mechanisms underlying the bone-fat relationship may be reflected through different bone phenotypes.

The limited publications on BMF suggest that BMF may have different metabolic functions because BMF is not correlated with other body composition measures in most studies. However, in general, both BMF and VAT appear to have unfavorable effects on bone, but the connection between bone and fat is complex. It is unclear whether the effects of VAT and BMF on bone are independent. It is also unknown whether obesity or diabetes, which is usually accompanied with increased VAT, is associated with high or low BMF.

The high cost of advance imaging techniques to quantify various adipose tissues often results in mostly cross-sectional studies with less optimal sample sizes. The lack of longitudinal studies makes it difficult to confirm causality between bone and fat, especially for BMF and incident fracture outcome. Nevertheless, understanding the relationship between fat and bone is necessary to ultimately provide primary and secondary prevention for the most devastating outcome: osteoporotic fracture. With the rising public health concern on osteoporosis and osteoporotic fracture in conjunction with increasing prevalence of obesity and diabetes, more studies are needed to further investigate the role of adipose

tissues on various bone phenotypes and fracture, and factors underlying this critical relationship.

Acknowledgments

Y. Sheu is supported as a post-doctoral fellow on National Institute on Aging grant T32-AG000181-16. J.A. Cauley receives institutional support from a National Institutes of Health grant.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

- 1•. Zhao LJ, Liu YJ, Liu PY, et al. Relationship of obesity with osteoporosis. *J Clin Endocrinol Metab.* 2007; 92(5):1640–6. This study demonstrates a negative correlation between fat mass and bone mass, both environmentally and genetically, after controlling for body weight. [PubMed: 17299077]
- 2••. Yamaguchi T, Kanazawa I, Yamamoto M, et al. Associations between components of the metabolic syndrome versus bone mineral density and vertebral fractures in patients with type 2 diabetes. *Bone.* 2009; 45(2):174–9. This study uses direct measure of VAT and demonstrated its protective role on vertebral fracture. [PubMed: 19446053]
3. Hsu YH, Venners SA, Terwedow HA, et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. *Am J Clin Nutr.* 2006; 83(1):146–54. [PubMed: 16400063]
4. Janicka A, Wren TA, Sanchez MM, et al. Fat mass is not beneficial to bone in adolescents and young adults. *J Clin Endocrinol Metab.* 2007; 92(1):143–7. [PubMed: 17047019]
5. Travison TG, Araujo AB, Esche GR, et al. Lean mass and not fat mass is associated with male proximal femur strength. *J Bone Miner Res.* 2008; 23(2):189–98. [PubMed: 17922610]
6. Langlois JA, Visser M, Davidovic LS, et al. Hip fracture risk in older white men is associated with change in body weight from age 50 years to old age. *Arch Intern Med.* 1998; 158(9):990–6. [PubMed: 9588432]
7. Ensrud KE, Fullman RL, Barrett-Connor E, et al. Voluntary weight reduction in older men increases hip bone loss: the osteoporotic fractures in men study. *J Clin Endocrinol Metab.* 2005; 90(4):1998–2004. [PubMed: 15671096]
8. Goodpaster BH, Krishnaswami S, Resnick H, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care.* 2003; 26(2):372–9. [PubMed: 12547865]
9. Miyawaki T, Abe M, Yahata K, et al. Contribution of visceral fat accumulation to the risk factors for atherosclerosis in non-obese Japanese. *Intern Med.* 2004; 43(12):1138–44. [PubMed: 15645647]
10. Mori Y, Hoshino K, Yokota K, et al. Differences in the pathology of the metabolic syndrome with or without visceral fat accumulation: a study in pre-diabetic Japanese middle-aged men. *Endocrine.* 2006; 29(1):149–53. [PubMed: 16622304]
11. Kuk JL, Katzmarzyk PT, Nichaman MZ, et al. Visceral fat is an independent predictor of all-cause mortality in men. *Obesity (Silver Spring).* 2006; 14(2):336–41. [PubMed: 16571861]
12. Kuk JL, Saunders TJ, Davidson LE, et al. Age-related changes in total and regional fat distribution. *Ageing Res Rev.* 2009; 8 (4):339–48. [PubMed: 19576300]
13. Edelstein SL, Barrett-Connor E. Relation between body size and bone mineral density in elderly men and women. *Am J Epidemiol.* 1993; 138(3):160–9. [PubMed: 8356959]
14. Weiler HA, Janzen L, Green K, et al. Percent body fat and bone mass in healthy Canadian females 10 to 19 years of age. *Bone.* 2000; 27(2):203–7. [PubMed: 10913912]

15. Hu G, Tuomilehto J, Silventoinen K, et al. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med.* 2007; 167(13):1420–7. [PubMed: 17620537]
16. Katzmarzyk PT, Janssen I, Ross R, et al. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. *Diabetes Care.* 2006; 29(2):404–9. [PubMed: 16443895]
- 17•. von Muhlen D, Safii S, Jassal SK, et al. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. *Osteoporos Int.* 2007; 18(10): 1337–44. This study investigates the longitudinal relationship between MetS and nonvertebral fracture. A positive association is found. [PubMed: 17492393]
18. Warming L, Ravn P, Christiansen C. Visceral fat is more important than peripheral fat for endometrial thickness and bone mass in healthy postmenopausal women. *Am J Obstet Gynecol.* 2003; 188(2):349–53. [PubMed: 12592238]
- 19•. Choi HS, Kim KJ, Kim KM, et al. Relationship between visceral adiposity and bone mineral density in Korean adults. *Calcif Tissue Int.* 2010; 87(3):218–25. This study investigates the relationship of BMD with various measures of body composition and metabolic factors. [PubMed: 20631995]
20. Jankowska EA, Rogucka E, Medras M. Are general obesity and visceral adiposity in men linked to reduced bone mineral content resulting from normal ageing? A population-based study. *Andrologia.* 2001; 33(6):384–9. [PubMed: 11736801]
- 21•. Kim CJ, Oh KW, Rhee EJ, et al. Relationship between body composition and bone mineral density (BMD) in perimenopausal Korean women. *Clin Endocrinol (Oxf).* 2009; 71(1):18–26. This study shows that WHR is negatively associated with spine BMD after adjusting for all confounders, whereas fat mass shows an inconsistent correlation with BMD. [PubMed: 19178508]
22. Nguyen ND, Pongchaiyakul C, Center JR, et al. Abdominal fat and hip fracture risk in the elderly: the Dubbo Osteoporosis Epidemiology Study. *BMC Musculoskelet Disord.* 2005; 6:11. [PubMed: 15727686]
23. Ensrud KE, Lipschutz RC, Cauley JA, et al. Body size and hip fracture risk in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Am J Med.* 1997; 103 (4): 274–80. [PubMed: 9382119]
- 24•. Russell M, Mendes N, Miller KK, et al. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. *J Clin Endocrinol Metab.* 95(3):1247–55. This study uses MRI to measure SAT and VAT, and demonstrates a different effect of these two adipose tissues on BMD. [PubMed: 20080853]
- 25•. Gilsanz V, Chalfant J, Mo AO, et al. Reciprocal relations of subcutaneous and visceral fat to bone structure and strength. *J Clin Endocrinol Metab.* 2009; 94(9):3387–93. This article summarizes underlying mechanisms contributing to the differential effect of SAT and VAT on BMD. [PubMed: 19531595]
- 26•. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S. sample. *J Clin Endocrinol Metab.* 2007; 92(11):4161–4. This study uses data from the NHANES III to evaluate the relationship between metabolic function and BMD. [PubMed: 17785365]
- 27•. Szulc P, Varennes A, Delmas PD, et al. Men with metabolic syndrome have lower bone mineral density but lower fracture risk—the MINOS study. *J Bone Miner Res.* 2010; 25(6):1446–54. This study reports lower BMD but lower fracture risk among men with MetS than those without. They also identify factors that contribute to this paradoxical observation. [PubMed: 20200928]
28. Ahmed LA, Schirmer H, Berntsen GK, et al. Features of the metabolic syndrome and the risk of non-vertebral fractures: the Tromso study. *Osteoporos Int.* 2006; 17(3):426–32. [PubMed: 16437192]
29. Pollock NK, Bernard PJ, Wenger K, et al. Lower bone mass in prepubertal overweight children with pre-diabetes. *J Bone Miner Res.*
- 30•. MacKenzie SM, Huda SS, Sattar N, et al. Depot-specific steroidogenic gene transcription in human adipose tissue. *Clin Endocrinol (Oxf).* 2008; 69(6):848–54. This study uses paired

adipose tissues and demonstrates that steroidogenic gene expressed in both adipose tissues, but the transcript level is different. [PubMed: 18410552]

31. Verma S, Rajaratnam JH, Denton J, et al. Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis. *J Clin Pathol.* 2002; 55(9):693–8. [PubMed: 12195001]
32. Justesen J, Stenderup K, Ebbesen EN, et al. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. *Biogerontology.* 2001; 2(3):165–71. [PubMed: 11708718]
33. Machann J, Stefan N, Schick F. (1)H MR spectroscopy of skeletal muscle, liver and bone marrow. *Eur J Radiol.* 2008; 67(2):275–84. [PubMed: 18406092]
34. Vande Berg BC, Malghem J, Lecouvet FE, et al. Magnetic resonance imaging of the normal bone marrow. *Eur Radiol.* 8(8):1327–1334. [PubMed: 9853209]
35. Baron, R. General principle of bone biology. In: Favus, MJ., editor. *Primer on the metabolic bone diseases and disorders of mineral metabolism.* 5. Washington, DC: American Society for Bone and Mineral Research; 2003. p. 1-8.
36. Rosen CJ, Bouxsein ML. Mechanisms of disease: is osteoporosis the obesity of bone? *Nat Clin Pract Rheumatol.* 2006; 2(1):35–43. [PubMed: 16932650]
37. Wang Y, Wan C, Gilbert SR, et al. Oxygen sensing and osteogenesis. *Ann N Y Acad Sci.* 2007; 1117:1–11. [PubMed: 18056033]
38. Zhou S, Greenberger JS, Epperly MW, et al. Age-related intrinsic changes in human bone-marrow-derived mesenchymal stem cells and their differentiation to osteoblasts. *Aging Cell.* 2008; 7 (3): 335–43. [PubMed: 18248663]
39. Vogler JB 3rd, Murphy WA. Bone marrow imaging. *Radiology.* 1988; 168(3):679–93. [PubMed: 3043546]
40. Griffith JF, Yeung DK, Antonio GE, et al. Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy. *Radiology.* 2005; 236(3):945–51. [PubMed: 16055699]
41. Griffith JF, Yeung DK, Antonio GE, et al. Vertebral marrow fat content and diffusion and perfusion indexes in women with varying bone density: MR evaluation. *Radiology.* 2006; 241 (3): 831–8. [PubMed: 17053202]
42. Yeung DK, Griffith JF, Antonio GE, et al. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study. *J Magn Reson Imaging.* 2005; 22(2):279–85. [PubMed: 16028245]
43. Shih TT, Chang CJ, Hsu CY, et al. Correlation of bone marrow lipid water content with bone mineral density on the lumbar spine. *Spine.* 2004; 29(24):2844–50. [PubMed: 15599288]
44. Schellinger D, Lin CS, Lim J, et al. Bone marrow fat and bone mineral density on proton MR spectroscopy and dual-energy X-ray absorptiometry: their ratio as a new indicator of bone weakening. *AJR Am J Roentgenol.* 2004; 183(6):1761–5. [PubMed: 15547224]
45. Schellinger D, Lin CS, Hatipoglu HG, et al. Potential value of vertebral proton MR spectroscopy in determining bone weakness. *AJNR Am J Neuroradiol.* 2001; 22(8):1620–7. [PubMed: 11559519]
46. Tang GY, Lv ZW, Tang RB, et al. Evaluation of MR spectroscopy and diffusion-weighted MRI in detecting bone marrow changes in postmenopausal women with osteoporosis. *Clin Radiol.* 2010; 65(5):377–381. This is a recent article evaluating the relationship of BMF with osteoporosis and BMD (in T-score). [PubMed: 20380936]
47. Bredella MA, Torriani M, Ghomi RH, et al. Vertebral bone marrow fat is positively associated with visceral fat and inversely associated with IGF-1 in obese women. *Obesity.* 2010; 19(1):49–53. Although BMF is known to have different metabolic function than other fat depots, both BMF and VAT have been reported to have detrimental effects on bone. This study investigates the association among BMF, VAT, and BMD, as well as important hormones for bone homeostasis. [PubMed: 20467419]
48. Shen W, Chen J, Punyanitya M, et al. MRI-measured bone marrow adipose tissue is inversely related to DXA-measured bone mineral in Caucasian women. *Osteoporos Int.* 2007; 18(5):641–7. This is a unique study using MRI to measure total-body BMF. It evaluates the relationship of BMF with BMD and body composition. [PubMed: 17139464]

- 49•. Di Iorgi N, Rosol M, Mittelman SD, et al. Reciprocal relation between marrow adiposity and the amount of bone in the axial and appendicular skeleton of young adults. *J Clin Endocrinol Metab.* 2008; 93(6):2281–6. This study includes a relatively large number of adolescents and young adults to evaluate the relationship of BMF with cortical and trabecular bone. [PubMed: 18381577]
50. Ecklund K, Vajapeyam S, Feldman HA, et al. Bone marrow changes in adolescent girls with anorexia nervosa. *J Bone Miner Res.* 2010; 25(2):298–304. [PubMed: 19653811]
- 51••. Bredella MA, Fazeli PK, Miller KK, et al. Increased bone marrow fat in anorexia nervosa. *J Clin Endocrinol Metab.* 2009; 94 (6):2129–36. This study shows negative correlations between BMF and BMD at both lumbar spine and femur, as well as between BMF and adipose tissues at femur only in patients with AN. [PubMed: 19318450]

Table 1

Studies evaluating relationship of central obesity, MetS, VAT, and SAT on bone indices

Study	Population	Adiposity measure	Bone phenotype	Overall study result
Central obesity and MetS				
Warming et al. [18]	531 women (48–65 y)	Abdominal fat by DXA	Bone mass	Positive correlation between abdominal fat mass and total body bone mass
Nguyen et al. [22]	78 men and 189 women (60+ y)	Abdominal fat by DXA	BMD Fracture	Positive correlation with FN BMD ↓ Abdominal fat was associated with ↑ risk of hip fracture, but result was not significant after adjusting for FN BMD
Choi et al. [19•]	295 men and 166 women (21–83 y)	Waist	BMD	Weak and nonsignificant correlation for men; negative correlation for women at the LS, FN, and TH
von Muhlen et al. [17••]	417 men and 671 women (38–97 yrs)	Waist	BMD	Positive associations at the LS, FN, and TH for both genders
Choi [19•]	295 men and 166 women (21–83 y)	WHR	BMD	Negative correlation with LS, FN, and TH BMD for both men and women
Jankowska et al. [20]	272 men (20–60 y)	WHR	BMC by pQCT	WHR was negatively associated with trabecular, cortical, and total BMC
Kim et al. [21•]	1694 women (mean age: 51 y)	WHR	BMD	Negative association between WHR and LS BMD
Choi et al. [19•]	295 men and 166 women (21–83 y)	Hip	BMD	No significant correlation with LS, FN, TH BMD for both genders
Ensrud et al. [23]	8011 women (65+ y)	Hip girth	Fracture	↓ Hip girth was associated with ↑ fracture risk, but this association was not independent of BMD
Yamaguchi et al. [2••]	187 men (28–83 y)	MetS	BMD	↑ FN BMD among men with MetS, not women
	125 women (46–82 y)		Fracture	Men with MetS were less likely to have vertebral fracture
Kinjo et al. [26•]	8197 men and women (20+ y)	MetS	BMD	↑ FN BMD in MetS group, but no difference after stratifying by BMI
von Muhlen et al. [17••]	417 men and 671 women (38–97 y)	MetS	BMD Fracture	↓ FN BMD among men with MetS, not women ↑ Fracture risk in women, not men
Ahmed et al. [28]	12,866 men and 14,293 women (25–98 y)	MetS	Fracture	MetS was associated with ↓ fracture risk
Szulc et al. [27•]	762 men (55–85 y)	MetS	BMD Fracture	↓ FN, TH, and trochanter BMD in MetS group MetS was associated with ↓ vertebral fracture risk
Visceral adipose tissue				
Gilsanz et al. [25••]	100 women (15–25 y)	VAT by CT	Bone geometry	Moderate and negative association
Choi et al. [19•]	295 men and 166 women (21–83 y)	VAT by CT	BMD	Negative correlation with LS, FN, TH BMD for both genders, but correlation was stronger in women
Yamaguchi et al. [2••]	187 men (28–83 y)	VAT by CT	BMD	↑ FN BMD among men with VAT area 100 cm ² .
	125 women (46–82 y)		Fracture	Negative association with R BMD and T BMD in women only. ↑ VAT in men without vertebral fracture
Pollock et al. [29]	140 overweight children (7–11 y)	VAT by MRI	BMC	VAT was negatively associated with total body BMC

Study	Population	Adiposity measure	Bone phenotype	Overall study result
Russell et al. [24••]	30 girls (12–18 y)	VAT by MRI	BMD	VAT inversely predicted LS and whole-body BMD
Subcutaneous adipose tissue				
Choi et al. [19•]	295 men and 166 women (21–83 y)	SAT by CT	BMD	Negative and insignificant correlation with LS, FN, and TH BMD
Yamaguchi et al. [25••]	187 men (28–83 y) 125 women (46–82 y)	SAT by CT	BMD Fracture	Negative association with R BMD in women only ↑ SAT in men and women without vertebral fracture with borderline significance
Gilsanz et al. [25••]	100 women (15–25 y)	SAT by CT	Bone geometry	Moderate and positive association
Pollock et al. [29]	140 overweight children (7–11 y)	SAT by MRI	BMC	SAT was negatively associated with total-body BMC
Russell et al. [24••]	30 girls (12–18 y)	VAT by MRI	BMD	SAT positively predict LS and whole-body BMD

BMC bone mineral content; *BMD* bone mineral density; *BMI* body mass index; *DXA* dual-energy x-ray absorptiometry; *CT* computed tomography; *FN* femoral neck; *LS* lumbar spine; *MetS* metabolic syndrome; *pQCT* peripheral quantitative computed tomography; *R* radius; *SAT* subcutaneous adipose tissue; *T* total body; *TH* total hip; *VAT* visceral adipose tissue; *WHR* waist to hip ratio

Table 2

Studies evaluating relationship between BMF and bone indices

Study	Population	Adiposity measure	Bone phenotype	Overall study result
Bone marrow fat				
Griffith et al. [40]	110 women (67–84 y)	BMF by MRS	OP	BMF among OP group
Griffith et al. [41]	90 men (67–101 y)	BMF by MRS	OP	BMF among OP group
Yeung et al. [42]	50 women (60+ y)	BMF by MRS	OP BMD	BMF among OP group. Negative correlation between BMF and LS BMD
Shih et al. [43]	58 women (39–78 y)	BMF by MRS	BMD	Negative correlation between BMD and LS BMD
Tang et al. [46•]	78 women (55–81 y)	BMF by MRS	OP T-score	Higher BMF among OP group. Negative correlation with T-score at the LS
Schellinger et al. [44]	2 men and 13 women (44–65 y)	BMF by MRS	Bone weakening BMD	Higher BMF among bone weakening group. Negative but weak correlation with LS BMD
Schellinger et al. [45]	48 men and 46 women (15–87 y)	BMF by MRS	Bone weakening	BMF among bone weakening group
Shen et al. [48•]	56 women (18–88 y)	BMF by MRI	BMD	Negative association between BMF and total-body and pelvic BMD
Bredella et al. [51••]	20 women (20–42 y) with and without anorexia nervosa	BMF by MRS	BMD T-score	Strong and negative correlation between BMF and LS, TH, and whole-body BMD/T-score

BMD bone mineral density; *BMF* bone marrow fat; *LS* lumbar spine; *MRS* magnetic resonance spectroscopy; *OP* osteoporosis; *TH* total hip