Journal of the Endocrine Society, 2023, **7**, 1–7
https://doi.org/10.1210/jendso/bvad008
Advance access publication 23 January 2023
Clinical Research Article

Visceral Adipose Tissue is Negatively Associated With Bone Mineral Density in NHANES 2011-2018

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Abstract

Context: The relationship of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) with bone mineral density (BMD) is not well established.

Objective: To examine the associations of VAT and SAT with total body BMD in a large, nationally representative population with a wide range of adiposity.

Methods: We analyzed 10 641 subjects aged 20 to 59 years in National Health and Nutrition Examination Survey 2011-2018 who had undergone total body BMD and had VAT and SAT measured by dual-energy X-ray absorptiometry. Linear regression models were fitted while controlling for age, sex, race or ethnicity, smoking status, height, and lean mass index.

Results: In a fully adjusted model, each higher quartile of VAT was associated with an average of 0.22 lower T-score (95% CI, −0.26 to −0.17, $P < 0.001$), whereas SAT had a weak association with BMD but only in men (−0.10; 95% CI, −0.17 to −0.04, $P = 0.002$). However, the association of SAT to BMD in men was no longer significant after controlling for bioavailable sex hormones. In subgroup analysis, we also found differences in the relationship of VAT to BMD in Black and Asian subjects, but these differences were eliminated after accounting for racial and ethnic differences in VAT norms.

Conclusions: VAT has a negative association with BMD. Further research is needed to better understand the mechanism of action and, more generally, to develop strategies for optimizing bone health in obese subjects.

Key Words: visceral adipose tissue, subcutaneous adipose tissue, bone density, osteoporosis

Abbreviations: BMD, bone mineral density; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; LMI, lean mass index; MRI, magnetic resonance imaging; NHANES, National Health and Nutrition Examination Survey; SAT, subcutaneous adipose tissue; TB, total body; VAT, visceral adipose tissue.

Although obesity has generally been thought to be protective against osteoporosis, we recently demonstrated that higher fat mass index was associated with lower bone mineral density (BMD) among more than 10 000 subjects in the National Health and Nutrition Examination Survey (NHANES) [1]. This observation could partly explain the higher risk of fracture at the ankle, humerus [2, 3], and possibly other fracture sites seen in subjects with obesity.

The cause of lower BMD is not clear, and it did not appear that sex hormones or fat distribution fully explained our observations. One possibility is that adipokines and cytokines released from adipose tissue negatively affect BMD. If true, we should expect differing associations between BMD and visceral adipose tissue (VAT) vs subcutaneous adipose tissue (SAT). VAT is adipose tissue located within the abdominal cavity and within mesenteric fat, whereas SAT lies outside the abdominal cavity. VAT is known to be a secretory organ and is associated with metabolic syndrome, diabetes, cardiovascular disease, and cancer [4]. Studies demonstrate that VAT releases high levels of proinflammatory cytokines, such as TNF-α and IL-6, which could increase bone resorption [5]. Simultaneously, it is believed that VAT releases less leptin, a hormone thought to stimulate proliferation and differentiation of osteoblasts [6]. Despite these theoretical effects, the effect of VAT on bone health remains unclear, with previous studies being relatively small and limited to younger age groups, specific diseases, or homogeneous populations [7–11]. Similarly, the effect of SAT is not clear due to conflicting findings in prior studies [7, 12].

Although VAT and SAT have traditionally been measured by computed tomography (CT) or magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA) is able to quantify VAT and SAT and compares well with these modalities [13]. Thus, we sought to evaluate the associations between VAT, SAT, and total body BMD from NHANES 2011-2018.

Materials and Methods

Subjects

Subjects who underwent total body DXA in NHANES 2011-2018 were studied. Methods used in NHANES have

Received: 13 November 2022. **Editorial Decision:** 11 January 2023. **Corrected and Typeset:** 13 February 2023

been reported previously [14], and our analytic methods were also previously described [1]. Briefly, NHANES is a nationally representative US sample that uses a complex survey design. A subset of subjects aged 8 to 59 years underwent total body DXA with Hologic Discovery model A densitometers (Hologic, Inc., Bedford, MA). NHANES staff also used Hologic APEX 4.0 software to evaluate VAT and SAT inside the abdominal cavity, measured at approximately the interspace location of L4 and L5. In our analysis, we report VAT and SAT in grams and restricted the subjects to those with valid data aged older than 20 years (ie, 20-59 years).

Total body (TB) BMD was used based on our previous work showing high correlation to regional DXA of the spine and proximal femur and similar associations with previous fracture as regional sites [15]. We calculated T-scores for total body DXA sites from reference data, as previously described [1]. For our main analysis, we also split VAT and SAT into quartiles for the whole study population of 10 641 and analyzed sex-specific and race-specific VAT and SAT quartiles as specified.

For our sensitivity analyses, we also examined associations of VAT and SAT with regional hip and spine BMD. These regional examinations had been done in years 2013-2014 (n = 1461) using Hologic QDR-4500A fan-beam densitometers (Hologic, Inc). T-scores were calculated for these sites from reference data from NHANES 2005-2008 (n = 236-262). Menopause status was evaluated by questionnaire (available in 92.4% of women) and was considered present if women reported no menstrual periods in the past 12 months. The possible effect of biochemical parameters that were available in NHANES were explored and included vitamin D, high sensitivity C-reactive protein, ferritin, testosterone, and estradiol. Detailed laboratory methods for NHANES are publicly available [16]. Briefly, vitamin D is tested using HPLC-tandem mass spectrometry, and we analyzed the sum of 25-OH vitamin D2 and 25-OH vitamin D3 (henceforth referred to as simply 25-OH vitamin D). The high-sensitivity C-reactive protein reagent was based on highly sensitive near-infrared particle immunoassay rate methodology. It was measured using SYNCHRON systems on Beckman Coulter chemistry analyzers. Ferritin was measured on the Roche Elecsys-170 using a sandwich principle. Testosterone and estradiol were performed in NHANES via isotope dilution liquid chromatography tandem mass spectrometry based on the National Institute for Standards and Technology's reference method. SHBG measurement is based on the reaction of SHBG with immune antibodies and chemoluminescence. In our analysis, we calculated bioavailable testosterone and estradiol based on the methods of Södergard et al and described by De Ronde et al [17, 18]. Only testosterone measurements from NHANES 2013-2016 were used, as SHBG was not available in NHANES 2011-2012 for bioavailable hormone calculations.

Statistical Analysis

We used population-based sampling weights to account for NHANES' complex survey design and conducted statistical analyses with Stata 17 (StataCorp, College Station, TX). Standard errors of the mean for all estimates were obtained using a linearization method (Taylor series). In subpopulation analyses, strata with a single sampling unit were centered at the overall mean to calculate standard errors. Adjusted Wald tests were used to compare demographic variables and bone density by VAT quartile. Linear regression models were created with BMD T-score as the outcome, while examining VAT and SAT and controlling for age, sex, race or ethnicity, height, smoking status, and lean mass index (LMI; lean mass in kilograms divided by height squared). For the main analyses, when examining the associations with VAT quartile, SAT was entered as a continuous variable. When examining the associations with SAT quartile, VAT was entered as a continuous variable. When examining sex- and race-specific quartiles, the quartiles were entered simultaneously into a single model. Age was entered in 5-year age groups to properly model differences in how age affects BMD, particularly in those aged older than 50 years. "Other" race was not analyzed separately because of likely heterogeneity of this group.

Fat mass index (fat mass in kilograms divided by height squared) and body mass index (BMI) were not included in regression models because of strong collinearities with VAT, SAT, and/or LMI (variance inflation factors >10). Strong collinearity was not present between VAT, SAT, LMI, and height (variance inflation factors <2).

Results

Subjects

The subjects' characteristics are presented in Table 1, stratified by VAT quartile. In general, the subjects in the highest VAT quartile were older, more male, more likely to be White, and had higher BMI, LMI, fat mass index, and SAT, but significantly lower BMD than quartiles 2 and 3. The mean and range of SAT by quartile were 692 g (range, 111-1018 g), 1254 g (range, 1018-1491 g), 1773 g (range, 1491-2096g), and 2725 g (range, 2096-5494 g). Women had lower VAT (461 ± 282 g vs 532 ± 270 g, $P < 0.001$) and higher SAT (1915 ± 796 g vs 1314 ± 678 g, $P < 0.001$) than men. We also found important racial/ethnic differences in VAT and SAT as shown in Table 2. In particular, Asian and Black subjects had the lowest VAT, whereas Mexican Americans had the highest VAT. Asian subjects had the lowest SAT, whereas Black and Mexican Americans had the highest SAT.

Associations Between TB BMD, VAT, and SAT

In univariate analyses, TB BMD was negatively associated with SAT, but not VAT, though this was substantially affected with covariate adjustment (Table 3). In a fully adjusted model, we found that each higher quartile of VAT was associated with an average of 0.22 lower T-score (95% CI, −0.26 to −0.17, $P < 0.001$). Effects were most prominent in the highest quartile (Fig. 1; −0.66 T-score in highest quartile of VAT vs quartile 1) though the highest quartile had the widest range of VAT. There was also a weak association of higher SAT with lower BMD (Fig. 1; 0.06 lower T-score per higher quartile of SAT, 95% CI, −0.10 to −0.01; $P = 0.01$). We further examined the what appeared to be a nonlinear relationship of VAT and BMD (Fig. 1) by examining VAT in 100-g increments, rather than by quartiles, and found that the relation was largely linear, even in the higher range (available in an online repository [19]).

Sex, Racial/Ethnic, and Age Differences in the Associations of VAT, SAT, and BMD

There were no significant differences in the association of VAT and BMD by sex (Table 4). However, we found the negative association of SAT with BMD was present only in men

Table 1. Demographics of subjects by VAT quartile

	Lowest quartile of VAT (n = 2661)	Second quartile of VAT (n = 2660)	Third quartile of VAT (n = 2660)	Highest quartile of VAT (n = 2660)
Age, y	***32.3 ± 10.6***	***37.4 ± 11.1***	***41.8 ± 10.9***	***45.8 ± 9.6***
Male	**40.1%**	**51.5%**	**53.7%**	**57.5%**
Race or ethnicity	62.8% White ***15.1% Black*** ***4.9% MA*** 6.5% other His 7.3% Asian 3.4% Other	57.8% White ***12.9% Black*** 9.8% MA 7.8% other His 7.9% Asian 3.9% Other	57.3% White ***10.3% Black*** 13.1% MA 8.5% other His 6.6% Asian 4.3% Other	***67.0% White*** ***6.4% Black*** 13.3% MA 7.3% other His ***3.1% Asian*** 2.9% Other
BMI, kg/m^2, (range)	***23.0 ± 3.8*** ***(13.6-63.4)***	***27.0 ± 4.3*** ***(17.4-55)***	***30.2 ± 5.3*** ***(17.9-65.5)***	***34.3 ± 6.1*** ***(20.6-64.2)***
Lean mass index, kg/m^2	***15.9 ± 2.6***	***17.5 ± 2.8***	***18.8 ± 2.9***	***20.6 ± 3.0***
Fat mass index, kg/m^2	***6.5 ± 2.5***	***8.8 ± 3.1***	***10.7 ± 3.8***	***13.0 ± 4.2***
VAT, g	***198 ± 55***	***361 ± 49***	***543 ± 58***	***871 ± 197***
SAT, g	***965 ± 534***	***1465 ± 639***	***1828 ± 724***	***2174 ± 707***
Total body BMD T-score	0.45 ± 1.25	0.51 ± 1.23	0.50 ± 1.28	0.34 ± 1.22

Mean ± SD. Values in bold and italics are significantly different than all other VAT quartiles.
Abbreviations: BMD, bone mineral density; BMI, body mass index; His, Hispanic; MA, Mexican American; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 2. VAT and SAT by race or ethnicity

	White	Black	Mexican American	Other Hispanic	Asian
VAT	509 ± 221 g	***414 ± 317 g***	566 ± 302 g	499 ± 310 g	***412 ± 307 g***
SAT	1603 ± 507 g	1712 ± 1378 g	1738 ± 872 g	1610 ± 892 g	***1269 ± 818 g***

Bold and italicized groups are significantly lower than all other racial and ethnic groups not in bold/italics. Underlined groups are significantly higher than all other racial groups not underlined.
Abbreviations: SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 3. Regression coefficients of VAT and SAT quartile on total body BMD T-score with various model adjustments

	Unadjusted	Age- and sex-adjusted	LMI-adjusted	Adjusted for all except VAT/SAT and LMI	Adjusted for all except VAT/SAT	Fully adjusted
VAT	−0.03 (−0.07-0.00, $P = 0.06$)	−0.06 (−0.10 to −0.03, $P < 0.001$)	−0.34 (−0.38 to −0.30, $P < 0.001$)	−0.04 (−0.07 to −0.005, $P = 0.03$)	−0.29 (−0.33 to −0.25, $P < 0.001$)	−0.22 (−0.26 to −0.17, $P < 0.001$)
SAT	−0.06 (−0.10 to −0.03, $P = 0.001$)	0.08 (0.05-0.11, $P < 0.001$)	−0.25 (−0.29 to −0.22, $P < 0.001$)	0.06 (0.02-0.09, $P = 0.001$)	−0.20 (−0.25 to −0.16, $P < 0.001$)	−0.06 (−0.11 to −0.01, $P = 0.004$)

95% CI in parentheses. Statistically significant values have 95% CI that do not cross 0. Fully adjusted is adjusted for age (5-y groups), sex, race, height, smoking status, LMI, VAT, or SAT (continuous adjustment of VAT or SAT).
Abbreviations: LMI, lean mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

and not women, but the use of sex-specific quartiles substantially attenuated the association of SAT with BMD in men. Furthermore, adjusting for bioavailable estrogen, testosterone, or both (in 2491 or 2526 with available data) eliminated the association of SAT and BMD in men.

When examining by race or ethnicity, we found that the association between VAT and BMD was stronger in Black and Asian than in White subjects (Table 5), but the interaction was eliminated when using race-ethnic specific VAT quartiles. Conversely, the relationship of SAT was not significantly associated with BMD in Asians (P for interaction <0.001) even when using race-specific quartiles.

Associations between SAT or VAT with BMD did not significantly differ by age group except there was a less negative relationship between VAT and BMD in those aged older than 50 years (32% of total study population) than those aged younger than 50 years (−0.10 vs −0.27 T-score per quartile, P for interaction <0.001). In women, there was no interaction between VAT or SAT with menopause status.

Adjusting for Vitamin D or Inflammatory Markers

We also examined whether the relationship between VAT and BMD changed when adjusting for 25-OH vitamin D, C-reactive protein, or ferritin levels but found no substantial change (Table 6).

Sensitivity Analysis Using Regional BMD

Given previously noted differences in results between TB and regional BMD, we examined 1461 subjects aged 40 to 59

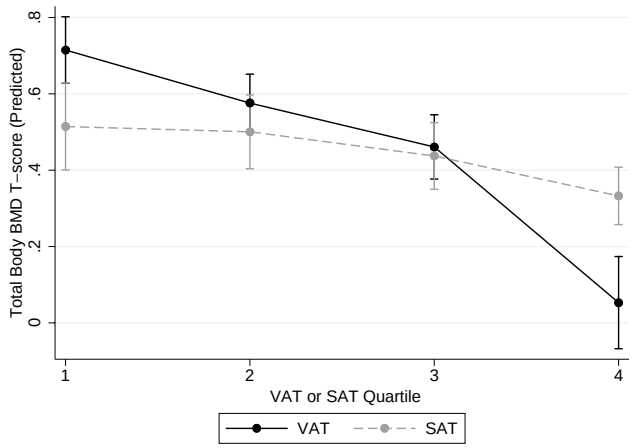

Figure 1. Total body BMD T-scores by VAT or SAT quartile, as predicted by a model that adjusts for age, sex, race/ethnicity, smoking status, height, LMI, and SAT or VAT, respectively. There is a decrease in BMD T-score with increasing VAT that appears most prominent in quartile 4 (highest VAT).

years in NHANES 2013-2014 who had also undergone spine, total hip, and femoral neck BMD. The characteristics of these 1461 are available in an online repository and significantly differed from the rest of the study population in age, fat mass index, and VAT [19]. Among these subjects, VAT and SAT, measured by total body DXA, did not have significantly different associations with TB BMD than the rest of the subjects. However, when adjusting for age, sex, race or ethnicity, height, smoking status, and lean mass, the association of VAT with spine and femoral neck T-score was less striking when compared with TB BMD and was generally limited to the highest quartile of VAT (−0.45 and −0.46 T-score vs Q1, $P = 0.02$ and $P = 0.008$). Total hip T-score was not associated with VAT. There were also no significant associations between regional BMD and SAT among these subjects.

We also examined arm BMD because this site may have less soft-tissue interference than other regions. Similar to total body BMD, we found that VAT had a strong negative relationship with arm BMD, whereas SAT had a slightly negative relationship with BMD (−0.23 T-score per quartile; 95% CI,

Table 4. Regression coefficients of VAT and SAT on total body BMD T-score by sex

		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Women	*VAT*	*Reference*	*−0.09 (−0.19 to 0.008)*	***−0.24 (−0.35 to −0.12)***	***−0.60 (−0.75 to −0.45)***
	SAT	Reference	4.1×10^{-4} (−0.16 to 0.15)	0.05 (−0.09 to 0.19)	−0.004 (−0.18 to 0.17)
	SAT (sex specific)	Reference	0.09 (−0.02 to 0.20)	0.06 (−0.07 to 0.18)	−0.07 (−0.22 to 0.08)
Men	*VAT*	*Reference*	***−0.20 (−0.33 to −0.08)***	***−0.30 (−0.44 to −0.15)***	***−0.74 (−0.95 to −0.54)***
	SAT	*Reference*	*−0.002 (−0.10 to 0.10)*	*−0.14 (−0.31 to 0.03)*	***−0.35 (−0.55 to −0.16)***
	SAT (sex specific)	Reference	−0.02 (−0.15 to 0.10)	−0.03 (−0.16 to 0.11)	**−0.22 (−0.41 to −0.04)**

95% CI in parentheses. Statistically significant values have 95% CI that do not cross 0. Italics denote a statistically significant trend. Bold denotes statistical significance compared with the reference group. There was a statistically significant interaction between sex and SAT quartile ($P = 0.002$) but this was eliminated with the use of sex-specific quartiles. All values adjusted for age (5-y groups), sex, race, height, smoking status, LMI, and VAT/SAT (continuous).
Abbreviations: BMD, bone mineral density; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 5. Regression coefficients of VAT on total body BMD T-score by race or ethnic group

		Quartile 1	Quartile 2	Quartile 3	Quartile 4
White	VAT	Reference	**−0.12 (−0.23 to −0.007)**	**−0.21 (−0.34 to −0.07)**	**−0.62 (−0.82 to −0.43)**
	VAT (ethnic specific)	Reference	**−0.13 (−0.25 to −0.02)**	**−0.25 (−0.40 to −0.10)**	**−0.67 (−0.86 to −0.48)**
Black	VAT	Reference	**−0.24 (−0.38 to −0.11)**	**−0.39 (−0.54 to −0.24)**	**−0.76 (−0.98 to −0.55)**
	VAT (ethnic specific)	Reference	−0.07 (−0.22 to 0.08)	**−0.25 (−0.41 to −0.09)**	**−0.55 (−0.76 to −0.34)**
Asian	VAT	Reference	**−0.26 (−0.44 to −0.09)**	**−0.54 (−0.78 to −0.30)**	**−0.91 (−1.18 to −0.63)**
	VAT (ethnic specific)	Reference	−0.16 (−0.33 to 0.02)	**−0.39 (−0.64 to −0.13)**	**−0.75 (−1.06 to −0.44)**

95% CI in parentheses. All trends were statistically significant. Bold denotes statistical significance compared with the reference. There was a statistically significant interaction between VAT and Black and Asian race-ethnicity ($P = 0.02$, and $P = 0.01$, respectively) as compared with White but this interaction was eliminated when using race-ethnic-specific VAT quartiles. All values adjusted for age (5-y groups), sex, race, height, smoking status, LMI, and SAT.
Abbreviations: BMD, bone mineral density; LMI, lean mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 6. Regression coefficients of VAT quartile on total body BMD T-score before and after adjustment for 25-OH vitamin D or inflammatory markers

Marker	Number of subjects	Before adjusting for marker	After adjusting for marker
25-OH vitamin D	10 235	−0.21 (−0.26 to −0.17)	−0.21 (−0.25 to −0.16)
C-reactive protein	4638	−0.24 (−0.30 to −0.17)	−0.23 (−0.30 to −0.17)
Ferritin	3039	−0.23 (−0.30 to −0.15)	−0.23 (−0.31 to −0.16)

95% CI in parentheses. All values adjusted for age (5-y groups), sex, race, height, smoking status, LMI, and SAT.
Abbreviations: BMD, bone mineral density; LMI, lean mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

−0.27 to −0.18, $P < 0.001$ for VAT and −0.05 T-score per quartile; 95% CI, −0.10 to −0.001, $P = 0.02$ for SAT). Finally, given an increase in ankle fractures in those with obesity [20], we examined leg BMD and found relatively similar associations as with total body BMD (−0.18 T-score per quartile; 95% CI, −0.22 to −0.13, $P < 0.001$ for VAT and −0.07 T-score per quartile; 95% CI, −0.12 to −0.01, $P = 0.01$ for SAT).

Discussion

In a large, diverse US sample, we found that VAT had a negative association with BMD, whereas SAT had slightly negative or no association with BMD. These observations were found across sex and racial or ethnic lines and at all age ranges. Although simple definitions of obesity, such as those using BMI, generally show higher BMD [2, 21], including in our study, our study adds to the evidence that adiposity, in particular visceral adiposity, and lean mass have divergent effects on bone health. This study is among the largest examinations of the relationship of VAT and SAT to BMD and included large numbers of men, US racial or ethnic subgroups, and subjects with higher weights than previous studies. Our study results expand the understanding of how adiposity affects bone mass and suggests further research to aid in the development of screening strategies for osteoporosis in obese individuals.

Previous studies have demonstrated a negative relationship between VAT and bone density, though this is not a uniform finding [22]. A study of 509 predominantly White subjects (57% men) by Ng et al demonstrated a negative association between VAT and cortical thickness at the ultradistal radius and volumetric BMD at the ultradistal radius, lumbar spine, and femoral neck but only in young men and not in other groups after adjustment [10]. Gilsanz et al demonstrated that visceral abdominal fat had a negative impact on CT-derived femoral cross-section area, cortical bone area, and moments of inertia in 100 healthy young women, though lean mass was not examined [7]. Finally, while controlling for body mass but not lean mass or SAT, Zhu et al demonstrated a negative relationship between DXA-derived VAT and total body and axial bone density in 4865 older, predominantly White Australian subjects [11]. Although these are important contributions, omitting lean mass and the lack of racial diversity are important limitations. On the other hand, George et al studied Black and Asian Indian subjects and found relationships between visceral adiposity and subtotal BMD but the effects of visceral adiposity were 25- to 30-fold weaker than that of lean mass [23]. In contrast, our study showed VAT's negative association to be approximately 60% that of the positive association of lean mass. Therefore, our study substantially adds to the evidence base for VAT as a negative correlate of BMD by demonstrating a clinically relevant effect size, while studying a unique population in size and in racial and ethnic diversity. Indeed, the population in NHANES is representative of the United States and includes substantial numbers of racial and ethnic minorities, and subjects with chronic medical conditions and higher weights than in previous studies.

The impact of SAT has differed across studies, and this may be related to the various adjustments made in each study. SAT, VAT, LMI, BMI, and body weight are all correlated to one another, and care must be taken to avoid including variables with excess collinearity [24]. LMI, as previously shown in multiple studies, has a strong, positive relationship with BMD [25, 26]. However, if studying SAT and VAT and not considering LMI, SAT may appear to have a positive relationship with BMD because of omitted variable bias [27]. As seen in Table 3, adding LMI to the model dramatically altered the relationship between SAT and BMD. Although we did see a slight negative relationship between SAT and BMD in men, this was a tenuous relationship and was no longer present when further adjusting for bioavailable sex hormones.

Although we found a strong negative association of VAT with total body BMD, the relationship was less striking for dedicated BMD sites such as the spine, total hip, and femoral neck. This mirrors the weaker relationship we and others have found for the association of fat mass with regional BMD vs total body BMD [1, 28, 29]. It is possible that these differences represent truly different actions of adipokines or cytokines throughout the skeleton, as has been seen with estrogen [30]. Another possibility is that the number of subjects in the regional BMD sample is substantially smaller, which could make it more difficult to demonstrate the effect. Although the dedicated sites are used in formal definitions of osteoporosis, studies, including our own, have demonstrated that total body BMD also is highly associated with fracture [15, 31, 32]. The differences between skeletal sites could also relate to artifacts of tissue thickness at the regional sites, which have been shown to affect the accuracy of BMD at axial sites [33]. We also examined arm BMD, a site likely with lower tissue interference compared with axial sites and found a similar relationship as with a total body BMD. Given the differences by BMD site, a larger study that measures VAT and examines fracture as the outcome would be important to verify the generalizability of our findings.

Adipokines and cytokines could be the link between bone density and visceral fat, although we were not able to demonstrate this in our study. Inflammatory cytokines, such as IL-6 and TNF-α, are secreted by adipocytes and have been associated with bone loss in obesity and autoimmune diseases [34]. Adiponectin, which is secreted by adipocytes and is present in measurable levels in the serum, has been found to regulate bone turnover and is negatively associated with BMD [35, 36]. Leptin, best known for its role in appetite regulation, also has effects in osteoblast development and has been shown to be positively associated with BMD in a meta-analysis [35, 37]. Because cytokine and adipokine information was not available in NHANES, we examined the available markers of inflammation, C-reactive protein and ferritin. We did not find significant associations of these with BMD, and neither affected the relationship of BMD to VAT, suggesting that these markers may not be sensitive enough to detect inflammation related to obesity that could affect bone. Further studies examining VAT and specific adipokines and cytokines, as well as hormonal influences, may be needed to clarify the relationship with BMD.

We did not find sex differences in the relationship of VAT and BMD. In our previous work, we had found that fat mass index had a stronger negative association with BMD in men than women [1]. Our findings suggest then that visceral adiposity does not explain the sex differences noted for fat mass index, and that there could potentially be other mechanisms leading to worse bone density loss in men with high levels of adiposity. For example, there could be sex differences in comorbid illnesses, physical activity, or other factors that affect the relationship between overall fat mass and BMD.

We noted the importance of racial or ethnic norms of VAT or SAT. These differences have been explored in previous studies and have largely shown lower VAT in Black subjects compared with White subjects [38–40], though work in Asians has demonstrated higher VAT in some studies. Given the sampling methods used in NHANES, this population may represent a more US representative sample, though the breakdown of Asian ethnicity would be important. When examining by quartile without regard to race, there was a stronger association between VAT and BMD in Black and Asian subjects. However, when using race-specific quartiles, these differences were no longer present. The differences in racial and ethnic norms in VAT likely need to be considered by investigators when studying other outcomes, such as cardiovascular events or cancer. The differences noted with VAT by race or ethnicity are quite similar to BMI, where, for example, the risk of diabetes at a given BMI differs by race or ethnicity [41].

Our study has significant strengths. We used a large, diverse population drawn from a US representative sample that included a large number of men and subjects in racial or ethnic subgroups. This allowed us to examine differences by sex or race-ethnicity. NHANES uses a sophisticated method of sampling to find a US representative sample; thus, this population is not prone to the referral bias that may result from recruiting from provider clinics. Even the size of the study population is a notable strength because VAT measurement is not a routine clinical measurement and requires either total body DXA or CT or MRI. Because of this, few studies are of the size as our study. Finally, NHANES used a densitometer with a 450-lb weight limit, which is higher than many previous models, allowing for a wide range of VAT and BMI in the study.

There are limitations of this work. Although we attempted to control for important variables related to BMD, we cannot rule out residual confounding. Second, we used DXA for VAT and SAT measurements and, even though this has been well validated against MRI in multiple studies [13, 42–44], it is still a relatively new modality for VAT assessment. One study, using the same densitometer used in NHANES, showed higher accuracy of VAT assessment in overweight and obese individuals than normal weight or underweight individuals with CT used as the gold standard [13, 45]. The BMI range in the study was 15.6- to 47.5 kg/m^2, a large range that encompasses more than 98% of the subjects included in our analysis. Another limitation is that we used total body BMD, rather than the axial sites, which are not used in clinical practice for fracture risk assessment. However, we have shown in a subset of these subjects that total body BMD correlated well with axial sites and was similarly related to previous fracture and, thus, could be used to investigate the effects of adiposity on bone health [15]. Finally, we did not have measurements of specific adipokines or cytokines, which could have helped us better understand how VAT may affect BMD.

In conclusion, we found that VAT was negatively associated with BMD, regardless of sex or race, whereas SAT had a weak relationship with BMD in men. Our findings add to the body of evidence that adiposity may have negative repercussions on bone. More work is needed to both understand mechanisms of action and develop strategies to optimize bone health in obese patients.

Funding

None declared.

Disclosure

R.K.J. receives grant support from the Amgen Foundation and is an investigator for Ascendis and Radius Health. T.V. is an investigator for Radius Health, consultant for Takeda, and investigator for Ascendis.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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