

Regional body fat depots differently affect bone microarchitecture in postmenopausal Korean women

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Abstract

Summary In a prospective community-based cohort study, we investigated the relationship between trabecular bone score (TBS) and regional fat depots in 1474 Korean postmenopausal women. TBS was positively related with subcutaneous fat and negatively related with visceral fat.

Introduction The effect of fat distribution (visceral/subcutaneous) on bone quality or microarchitecture has rarely been investigated due to measurement difficulty. We aimed to investigate the relationship between TBS reflecting bone microarchitecture and regional fat depots in Korean women.

Methods Cross-sectional data evaluation was made from subjects participating in an ongoing prospective community-based cohort study since 2001. A total of 1474 postmenopausal women in the Ansung cohort were analyzed. Regional body fat mass, bone mineral density (BMD) at the lumbar spine,

and total hip and lumbar spine TBS were measured by dual energy X-ray absorptiometry (DXA).

Results In an age-adjusted partial correlation analysis, TBS was not associated with total fat mass, but negatively associated with trunk fat mass. However, TBS was positively related with leg ($r=0.102$, $P<0.05$) and gynoid fat mass ($r=0.086$, $P<0.05$) and negatively related with android fat mass ($r=-0.106$; $P<0.05$). In linear regression models controlling age, BMI, and physical activity, android fat was inversely associated with TBS ($\beta=-0.595$, $P<0.001$), whereas gynoid fat was positively associated with TBS ($\beta=0.216$, $P<0.001$). Lumbar spine and total hip BMDs revealed positive associations with total and all regional fat depots regardless of fat distribution.

Conclusion Our findings suggest that relatively large visceral fat and small subcutaneous fat may have a detrimental effect on TBS, a bone microarchitecture index.

Keywords Android fat · Body fat · Gynoid fat · Trabecular bone score

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Introduction

The link between obesity and osteoporosis has been widely explored as a global health burden in an aging society. Nonetheless, whether fat mass is beneficial or detrimental to bone is still uncertain. Some researchers have reported that fat protects bone through a mechanical loading effect or by stimulating bone formation by producing estrogen or increasing insulin and leptin levels [1–3]. On the contrary, others have asserted that fat may exert an adverse effect on bone due to increased inflammatory cytokines and insulin resistance [4–7].

The underlying heterogeneous relationships between fat and bone may be attributed to different regional fat depots,

which consist of visceral and subcutaneous fat. With aging, the relative intra-abdominal visceral fat volume increases and that of the legs decreases, which is accelerated by menopause in women [8]. Previously, researchers have reported the different roles of visceral and subcutaneous fat in determining bone mass [4, 5, 9–12]. Visceral fat has been described as a pathogenic fat depot harmful to bone amount or strength while subcutaneous fat is believed to positively affect bone [5, 9, 11, 12]. Android (or central) fat is considered to be visceral fat, whereas gynoid (or peripheral) fat is similar to subcutaneous fat [13].

Bone quality, despite being another important component of bone strength, has been studied to a lesser degree compared with bone quantity regarding its link with fat. There are few studies regarding the relationship between bone quality or bone strength and fat [9, 14]. Using computed tomography, Gilsanz et al. have provided compelling evidence that bone structure and strength have an opposite relationship with visceral and subcutaneous fat in young women [9]. Ng et al. have also reported that trabecular microarchitecture is positively related with visceral and subcutaneous fat using high-resolution peripheral quantitative computed tomography, but after further adjustment for age and weight, the relationship was eliminated [14]. Recently, trabecular bone score (TBS) has been introduced with a bone texture parameter derived from dual energy X-ray absorptiometry (DXA) images [15]. TBS was invented to overcome the pitfalls of DXA, which does not account for bone quality [16, 17]. Although TBS is not a direct parameter for bone quality, previous studies have presented TBS as a good index reflecting bone microarchitecture. In addition, TBS declined more rapidly with aging and is weakly related with BMI in contrast to BMD [18]. As a new technology, TBS has not been assessed in terms of its relationship with fat distribution. In the present study, we investigated the relationship in Korean postmenopausal women between TBS and regional fat depots compared to BMD.

Methods

Study population

The present study is a cross-sectional evaluation of the Ansung prospective cohort study. It is community-based prospective cohort study that is part of the Korean Health and Genome Study since 2001 designed to investigate the prevalence of chronic diseases in Korea. The details of the Ansung cohort study have been previously published [19]. In brief, Ansung is a representative rural farming community that had a population of 132,906 in 2000. The eligibility criteria included an age of 40–69 years at baseline, residence within the borders of the survey area for at least 6 months before

testing, and sufficient mental and physical ability to participate. A total of 5018 (women, $n=2778$) of the 7192 eligible individuals in Ansung was surveyed (70 % response rate) using a cluster sampling method stratified by age, sex, and residential district. DXA commenced from 2006, but the maximal number of participants ($n=1993$) underwent DXA from 2009 to 2010 (5th wave). There were 165 premenopausal women, and DXA exams were inadequate in 81 women. We also excluded those subjects who were receiving bisphosphonates, selective estrogen receptor modulators, or estrogen therapy ($n=213$). Ultimately, we included 1474 healthy ambulating postmenopausal women in the Ansung cohort who participated in the 5th wave (Fig. 1). The data including the lumbar spine TBS, BMD, and clinical parameters were also collected from 2009 to 2010. Study procedures were in accordance with institutional guidelines and approved by an institutional review board. Informed consent was obtained from the study participants.

Bone mineral density and trabecular bone score

The BMD (g/cm^2) was measured in the lumbar spine, femoral neck, and total hip using DXA (Lunar Prodigy, Systems, Chalfont St. Giles, UK) and analyzed using Encore Software 11.0 (Encore Software Inc., Minneapolis, MN, USA) in accordance with the manufacturer's instruction. The precision error (%CV) was 1.7 % for the lumbar spine (L) BMD, 1.8 % for the femoral neck BMD, and 1.7 % for the total hip BMD. For the lumbar spine BMD, the L1–4 value was chosen for the analyses. We used all evaluable L1–4 vertebrae and only exclude vertebrae that are affected by local structural change or artifact. We used three vertebrae if four cannot be

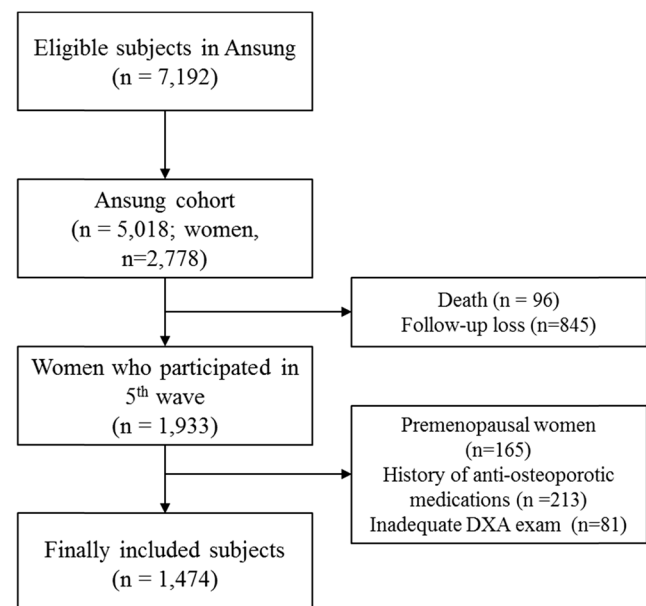


Fig. 1 Flow diagram of the study subjects

used and two if three cannot be used. We also excluded anatomically abnormal vertebrae from analysis if they are clearly abnormal and non-assessable within the resolution of the system; or there is more than a 1.0 T-score difference between the vertebra in question and adjacent vertebrae [20]. All TBS measurements were retrospectively performed through TBS iNsight Software, version 2.1 (Med-Imaps, Pessac, France) using spine DXA files from the database to ensure blinding of the investigators to all clinical parameters and outcomes. The software uses the anteroposterior spine raw DXA image for the same region of interest as the BMD measurement. Instruments were calibrated using anthropomorphic phantoms. The precision error (%CV) was 1.5 % for the lumbar spine TBS.

Total and regional (trunk, android, gynoid, and leg) fat masses were also measured by DXA and analyzed by Encore Software 11. Trunk fat was designated from the pelvis cut (lower boundary) to the neck cut (upper boundary) [13]. Android fat was defined from the pelvis cut to above the pelvis cut by 20 % of the distance between the pelvis and neck cuts. Gynoid fat was also described from the lower boundary of the umbilicus to a line equal to twice the height of the android fat distribution (Fig. 2). Trunk-to-fat ratio was calculated from the trunk fat divided by leg fat. Android-to-gynoid fat ratio was calculated by the android fat divided by the gynoid fat.

Anthropometric and body composition parameters

Height and body weight were measured at the time of DXA by standard methods with light clothing. BMI was calculated as the weight divided by height squared (kg/m^2). Waist circumference (WC) was measured at the narrowest point between the lower limit of the ribcage and the iliac crest. Hip circumference (HC) was measured as the maximal circumference above the buttocks.

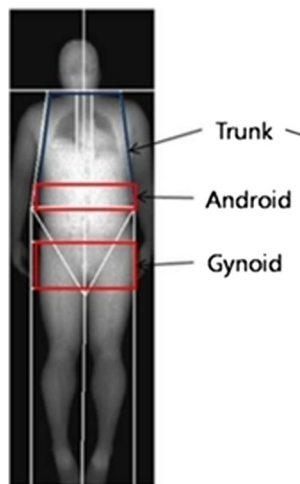


Fig. 2 Regions of interests (ROI) of android and fat mass measured by dual energy X-ray absorptiometry

Statistical analysis

Data are shown as the mean±standard deviation or *n* (%). We analyzed continuous variables with an analysis of variance (ANOVA) and age, BMI-adjusted analysis of covariance (ANCOVA) according to the TBS tertiles (<1.319, 1.319–1.397, ≥ 1.398). Post hoc analysis was performed by Bonferroni correction. Pearson's and age-adjusted partial correlation analyses among TBS, BMD, and adiposity parameters were performed. We used multivariable linear regression models for TBS and BMD using age, BMI, and android, gynoid fat mass. A variance inflation factor <10 was applied to evaluate the collinearity. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using PASW SPSS for Windows (version 21, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the enrolled women ($n=1474$) are shown in Table 1. Their mean age was 63.4 ± 8.6 (range, 47–78) years, and their BMI was $24.7 \pm 3.4 \text{ kg}/\text{m}^2$. Subjects within the lower tertile of TBS tended to be older and had a lower BMI and BMD at all sites. BMI, total fat mass, and HC were highest in subjects within the 3rd tertile of TBS. Leg and gynoid fat mass were lowest within the 1st tertile of TBS. Subjects within the 3rd tertile of TBS were likely to have a lower WC and android fat mass than those within the 1st tertile. The amount of trunk fat mass was not different among the groups. However, waist-to-hip, trunk-to-leg, and android-to-gynoid fat ratios were lowest in women within the 3rd tertile of TBS.

TBS and BMD at all sites were inversely associated with age (TBS, $r=-0.519$; lumbar spine BMD, $r=-0.470$; total hip BMD, $r=-0.577$; all $P < 0.001$; Fig. 1). BMI was positively related to TBS ($r=0.099$; $P < 0.001$), lumbar spine BMD ($r=0.563$, $P < 0.001$), and total hip BMD ($r=0.522$, $P < 0.001$). The link between BMI and TBS was weaker compared to its relationship with BMD. There were positive correlations between TBS and areal BMD at the spine ($r=0.562$, $P < 0.001$) and the hip ($r=0.516$, $P < 0.001$). We present unadjusted and age-adjusted correlation coefficients between skeletal measures and adiposity parameters in Table 2. Total lean and fat masses were not associated with TBS after adjustment but were positively associated with lumbar spine and total hip BMD. Lumbar spine TBS showed a negative relationship with trunk fat mass, android fat mass, waist-to-hip ratio, trunk-to-leg ratio, and android-to-gynoid fat ratio. Those with higher TBS were prone to exhibit larger HC as well as leg and gynoid fat masses, which were considered equivalent to subcutaneous or peripheral fat mass. On the other hand, the lumbar spine and total hip BMD revealed positive associations

Table 1 Bone mineral density and adiposity parameters of study subjects according to the TBS tertiles ($n=1474$)

Variables	1st tertile (<1.319)	2nd tertile (1.319–1.397)	3rd tertile (≥ 1.398)	<i>P</i> for trend	Post hoc analysis
<i>n</i>	490	491	493		
Lumbar spine TBS (unitless)	1.253±0.054	1.360±0.022	1.456±0.048	<0.001	*, **, ***
Lumbar spine BMD (g/cm ²)	0.849±0.152	0.939±0.139	1.076±0.170	<0.001	*, **, ***
Lumbar spine BMD T-score	-2.1±1.3	-1.4±1.2	-0.2±1.4	<0.001	*, **, ***
Lumbar spine BMD Z-score	-0.5±1.1	-0.1±1.1	0.4±1.3	<0.001	*, **, ***
Total hip BMD (g/cm ²)	0.769±0.124	0.846±0.123	0.943±0.137	<0.001	*, **, ***
Total hip BMD T-score	-1.3±1.0	-0.7±1.0	0.1±1.1	<0.001	*, **, ***
Total hip BMD Z-score	0.3±0.8	0.7±0.9	1.0±1.0	<0.001	*, **, ***
Age (years)	68.5±6.5	64.0±7.9	57.7±7.8	<0.001	*, **, ***
Height (cm)	151.1±6.2	152.4±6.0	153.1±6.0	<0.001	*, **
Weight (kg)	56.0±9.9	56.9±8.3	59.2±8.1	<0.001	**, ***
Body mass index (kg/m ²)	24.5±3.7	24.5±3.1	25.2±3.3	<0.001	**, ***
Total lean mass (kg)	34.03±4.53	34.84±4.06	35.99±4.05	<0.001	*, **, ***
Total fat mass (kg)	20.32±6.19	20.36±5.19	21.19±5.19	0.012	**, ***
Waist circumference (cm)	86.5±9.6	85.0±8.6	83.6±9.2	<0.001	*, **, ***
Hip circumference (cm)	91.6±6.6	91.6±5.8	92.7±6.3	0.005	**, ***
Waist-to-hip ratio	0.94±0.06	0.93±0.06	0.90±0.06	<0.001	*, **, ***
Trunk fat mass (kg)	11.63±4.01	11.42±3.39	11.63±3.29	0.549	—
Leg fat mass (kg)	5.49±1.68	5.73±1.50	6.23±1.63	<0.001	*, **, ***
Trunk-to-leg fat ratio	2.13±0.55	2.02±0.48	1.90±0.45	<0.001	**, ***
Android fat mass (kg)	1.80±0.71	1.72±0.59	1.71±0.59	0.037	*, **
Gynoid fat mass (kg)	2.80±0.82	2.92±0.73	3.19±0.74	<0.001	*, **, ***
Android-to-gynoid fat ratio	0.63±0.16	0.59±0.15	0.54±0.14	<0.001	*, **, ***
Physical activity score (METs/week)	14709±9504	13770±8823	13537±9266	0.122	

Variables are expressed as mean±SD

TBS trabecular bone score, BMD bone mineral density

P*<0.05 between 1st and 2nd tertile; *P*<0.05 between 1st and 3rd tertile; ****P*<0.05 between 2nd and 3rd tertile

Table 2 Pearson’s and age-adjusted partial correlation coefficients between skeletal measures and adiposity parameters

	TBS		Lumbar spine BMD		Total hip BMD	
	<i>r</i>	Age-adjusted <i>r</i>	<i>r</i>	Age-adjusted <i>r</i>	<i>r</i>	Age-adjusted <i>r</i>
Total lean mass	0.164*	-0.025	0.463*	0.361*	0.475*	0.357*
Total fat mass	0.060*	-0.004	0.330*	0.313*	0.320*	0.310*
Waist circumference	-0.141*	-0.017	0.151*	0.310*	0.066*	0.267*
Hip circumference	0.060*	0.058*	0.283*	0.309*	0.225*	0.264*
Waist-to-hip ratio	-0.274*	-0.086*	-0.041	0.179*	-0.113*	0.160*
Trunk fat mass	0.015	-0.055*	0.310*	0.320*	0.288*	0.312*
Trunk lean mass	0.144*	-0.026	0.433*	0.339*	0.425*	0.315*
Leg fat mass	0.202*	0.102*	0.289*	0.212*	0.307*	0.222*
Leg lean mass	0.178*	-0.018	0.437*	0.322*	0.471*	0.342*
Trunk-to-leg fat ratio	-0.222*	-0.165*	0.113*	0.216*	0.053	0.181*
Android fat mass	-0.080*	-0.106*	0.296*	0.325*	0.265*	0.313*
Gynoid fat mass	0.211*	0.086*	0.333*	0.241*	0.352*	0.249*
Android-to-gynoid fat ratio	-0.288*	-0.208*	0.116*	0.255*	0.050	0.226*

TBS trabecular bone score, BMD bone mineral density, *r* correlation coefficient

**P*<0.05

with total and all regional fat depots regardless of fat distribution. Even after adjustment for age, all relations remained similar except waist-to-hip ratio. TBS was positively associated with trunk and leg lean mass, but after adjusting for age, the relationship became insignificant. Higher lumbar spine and total hip BMD was related with higher trunk and leg lean mass regardless of age adjustment.

In the linear regression models (Table 3), android fat was inversely associated with TBS, whereas gynoid fat was positively associated with TBS after adjusting for age, BMI, and physical activity. Women had a positive relationship between lumbar spine BMD and android fat mass, but no significant relationship with gynoid fat mass. Total hip BMD was not related with android or gynoid fat mass.

We compared the least square means (LSM) of the waist-to-hip ratio, trunk-to-leg fat ratio, and android-to-gynoid fat ratio after adjusting for age and BMI across the tertiles of TBS (Fig. 2). The LSMs (\pm standard errors) of waist-to-hip ratio were 0.929 ± 0.003 for 1st tertile, 0.928 ± 0.002 for 2nd tertile, and 0.911 ± 0.003 for 3rd tertile of TBS (P for trend <0.001). Regarding trunk-to-leg fat ratio, the LSMs were 2.140 ± 0.023 for 1st tertile, 2.027 ± 0.021 for 2nd tertile, and 1.906 ± 0.022 for 3rd tertile of TBS (P for trend <0.001). The LSMs of android-to-gynoid fat ratio were 0.632 ± 0.007 , 0.592 ± 0.006 , and 0.539 ± 0.006 from the lowest to the highest tertiles of TBS. All parameters indicating a central-to-peripheral fat ratio revealed that subjects with a higher central-to-peripheral ratio had lower TBS values (Fig. 3).

Discussion

In community-dwelling Korean postmenopausal women, we demonstrated that lumbar spine TBS was negatively associated with central or visceral obesity, but positively associated

Table 3 Multivariable linear regression analyses for TBS and BMD using age, BMI, physical activity, android and gynoid fat mass

Variables	Standardized β	t	P
TBS			
Android fat mass	-0.595	-14.5	<0.001
Gynoid fat mass	0.216	6.13	<0.001
Lumbar spine BMD			
Android fat mass	0.139	3.23	0.001
Gynoid fat mass	-0.077	-2.08	0.038
Total hip BMD			
Android fat mass	0.070	1.700	0.077
Gynoid fat mass	-0.039	-1.14	0.254

Adjustment for age, BMI, and physical activity

β standardized coefficient, TBS trabecular bone score, BMD bone mineral density

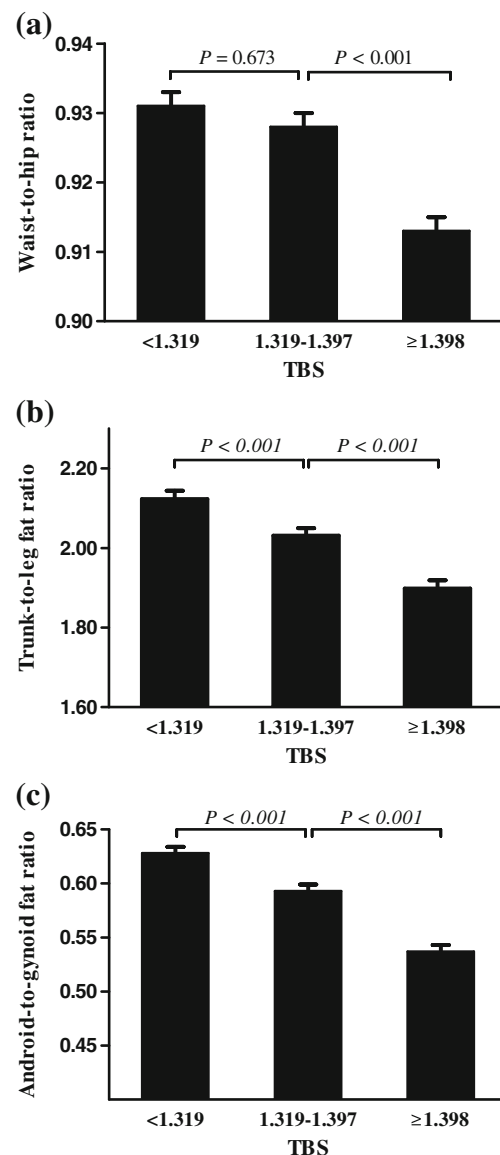


Fig. 3 Least square means of **a** waist-to-hip ratio, **b** trunk-to-leg fat ratio, and **c** android-to-gynoid fat ratio after adjusting for age and BMI according to the tertiles of TBS (all P for trend <0.001)

with peripheral or subcutaneous obesity after adjustment for age. By contrast, higher lumbar spine and total hip BMDs were linked with larger total and regional fat mass regardless of fat distribution.

Previous studies approached the link between adiposity and bone through assessment of bone quantity. There is an intrinsic limitation in DXA-measured BMD, which may be confounded by fat mass and bone size [21]. Moreover, BMD accounts for 60–70 % of the variation in bone strength and is inevitably limited in assessing bone quality [22]. In this view, we applied the newly developed TBS as an easily measurable bone quality index. Another confounder to assessing the interaction between fat and bone is the mechanical loading effect of fat mass. The association between fat and BMD after

adjustment for weight or BMI has provoked criticism since fat mass is already incorporated into both parameters [23]. Several studies have shown that the relationship between fat mass and bone mass is positive before adjustment but converts negative after adjustment body weight [4, 6, 7]. To overcome the collinearity, the mechanical loading effect needed to be avoided in a research study of the link between fat and bone. Although lumbar spine TBS is derived from a DXA image, its relationship with BMI is very weak compared with BMD [24]. Hence, TBS is less affected by mechanical loading, which can compensate for the limitation of a weight effect in exploring the relationship between fat and bone. Even after adjustment for mechanical loading effect such as BMI or lean mass, bone quality was impaired in postmenopausal women with a large visceral fat mass.

The conflicting data regarding the fat-bone relationships may be attributable to differences in fat distributions. Body fat tissue is composed of visceral (or central) and subcutaneous (or peripheral) fat. Depot-specific fat has been known to play a different role in terms of obesity and metabolism. There have been several studies showing that different fat depots may have distinct relationships with bone. For instance, using waist-hip ratio, visceral fat has a negative association among postmenopausal Korean women with lumbar spine BMD after adjustment for weight [5]. Although the discriminative function of DXA is not perfect, android fat reflects visceral fat and gynoid fat represents peripheral fat. Zilliken et al. also revealed an inverse association between bone mass and android fat depots after adjustment for BMI, which suggested central fat is not beneficial and maybe harmful for bone [12]. Likewise, in postmenopausal Chinese women, the DXA-measured android to gynoid fat ratio, a marker of visceral fat, is negatively associated with BMD at multiple sites [25]. In another study involving healthy Korean subjects, the visceral fat area measured by abdominal CT is inversely associated with BMD, whereas the subcutaneous fat area does not show any significant association [11]. However, there were few studies regarding bone microarchitecture or strength and regional fat depots. A Dutch study had found CT-measured visceral fat exerts harmful effects on femoral bone strength and structure, whereas the subcutaneous fat has beneficial effects in healthy young women [9]. We demonstrated that in postmenopausal Korean women, bone microarchitecture, presented as TBS, is negatively correlated with central fat such as WC and android fat mass and is positively correlated with peripheral fat such as hip circumference, leg fat mass, and gynoid fat mass. Thick android fat mass can underestimate TBS, but it can also underestimate lumbar spine BMD. Hence, android fat mass surrounding the lumbar spine was not enough to explain the negative relationship between TBS and android fat. Our study was distinctive in terms of using bone microarchitecture instead of BMD and showing the different relationships with bone microarchitecture according to the different fat depots.

In contrast with the previous studies, lumbar spine BMD was positively associated with visceral fat and negatively with subcutaneous fat. Different covariates such as height, weight, or BMI used in adjusted models and ethnic difference may explain the discrepancy.

The previous study showed that the relative intra-abdominal visceral fat mass increased and that of the legs decreased with age, and the accumulation of visceral fat is much accelerated by menopause in women by about 2.6 times [8]. Ovarian hormone depletion resulted in a higher omental/subcutaneous lipoprotein lipase activity ratio and predominant fat storage in visceral fat depot in postmenopausal women [26]. The relationship between visceral fat and TBS might be prominent in our study subjects, postmenopausal women.

The mechanisms of how visceral and subcutaneous fat have contrasting roles in bone metabolism remain to be elucidated. Hormones, cytokines, and inflammatory markers that affect bone metabolism are secreted by adipose tissue but have depot-specific gene expression [27]. For example, adiponectin, which is potentially protective against the development of osteoporosis, is expressed at a lower level in visceral than in subcutaneous fat tissue [28]. Leptin, which inhibits the appetite, promotes the differentiation of osteoblasts and downregulates bone resorption and is also less abundant in visceral than that in subcutaneous fat tissue [29, 30]. Furthermore, visceral adipocytes express aromatase at a lower level than subcutaneous ones [31]. In postmenopausal women, extragonadal estrogen synthesized in fat tissue is the source of the majority of estrogen [32]. The enzyme aromatase converts androgen to estrogen and increases estrogen levels, which reduces osteoclast-mediated bone resorption and stimulates osteoblast-mediated bone formation [21]. In addition, visceral fat compared with subcutaneous fat secretes higher levels of proinflammatory cytokines such as TNF- α and IL-6, which increase bone resorption and precipitate osteoporosis [33–36].

There are several strengths in the present study. First, our study subjects were recruited from a homogenous relatively large cohort. Second, our study is the first study to highlight the link between the lumbar spine TBS and body fat distribution. Third, we present several indices including anthropometric parameters and DXA-measured fat mass to advocate for our hypothesis. It is noticeable that android and gynoid fat exhibit a differential relationship with the lumbar spine TBS in contrast to the lumbar spine or total hip BMD regardless of BMI.

Several limitations should be mentioned. The present study was based on a cross-sectional design, which does not affirm a causal relationship. In addition, men were not included in our analysis since the lumbar spine TBS in men is not well validated. We did not include the premenopausal women. Hence, the generalizability of our data is limited. Also, the ethnic difference needed to be mentioned. Asian people have a

greater amount of visceral fat mass than their European counterparts for a given amount of body fat [37]. Therefore, the negative relationship between visceral fat and TBS may be applied only in Asians. Although the correlations between TBS and body composition parameters were significant, we conceded that the correlation coefficients were not strong ($r=0.1-0.2$). Fracture data were not included due to the lack of time data. Computed tomography of the abdomen was not applied, which is considered to be the gold standard to discriminate a fat depot. We did not measure estrogen, testosterone, leptin, or adiponectin, so we did not directly prove the mechanism for our hypothesis.

Taken together, the present study provides compelling evidence using lumbar spine TBS that visceral and subcutaneous fat may play different roles in regulating bone metabolism in postmenopausal Korean women; visceral fat has a detrimental effect on bone microarchitecture while subcutaneous fat is beneficial. Further longitudinal studies in diverse aspects are needed to prove the interaction between osteoporosis and obesity.

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Conflicts of interest None.

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