Clinical relevance of the relationship between Trabecular Bone Score and metabolic syndrome

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ABSTRACT

The Trabecular Bone Score (TBS) is an indirect measurement of bone quality, and studies have shown that TBS is an independent predictor of fracture risk. This cross-sectional investigation aimed to explore the relationship between metabolic syndrome (MetS) and TBS using data from the 2005–2006 US National Health and Nutrition Examination Survey. The association between individual MetS components and TBS was examined. There was a significant linear decrease in TBS with an increase in the number of MetS components. The β coefficients of TBS among participants with 3 and ≥4 MetS components were −0.015 and −0.041 (p=0.006 and p<0.001, respectively). Among participants with MetS, high systolic blood pressure, abdominal obesity, and high serum levels of triglycerides and glucose were significantly associated with lower TBS in fully adjusted models (p<0.05). Furthermore, there was a significant linear decrease in TBS with an increase in the number of MetS components in both sexes. TBS significantly decreased with an increasing number of MetS components in a US population. The components of MetS, including systolic blood pressure, waist circumference, and serum levels of triglyceride and glucose, exhibited a negative association with TBS.

Significance of this study

What is already known about this subject?

- The Trabecular Bone Score (TBS) is a measure of bone texture, and studies have emerged that support TBS as an independent predictor of fracture probabilities.
- The relationship between TBS and metabolic syndrome (MetS) remained controversial and not all MetS components were correlated with TBS.
- Traditionally, obesity was viewed as a protective factor against osteoporosis through mechanical loading; however, several studies have reported that body fat might have a negative impact on TBS.

What are the new findings?

- This study disclosed a negative relationship between TBS and an increased number of MetS components.
- We determined that only increased waist circumference, high systolic pressure, high serum triglyceride levels, and high serum glucose levels were significantly correlated with low TBS.
- Among the components of MetS, the association between a high serum glucose level and a low TBS was the most apparent.

How might these results change the focus of research or clinical practice?

- Our findings showed the associations between each component of MetS and TBS.
- In addition, a stronger negative correlation was found between the number of MetS components and TBS.

INTRODUCTION

Fragility fractures affect millions of individuals worldwide and are progressing to be a global problem. Fragility fractures incur costly human and socioeconomic burden. In 2016, it was estimated that 8.9 million fractures worldwide were caused by osteoporosis, with a fragility fracture estimated to occur every 3 s.[1] To identify individuals with poor bone strength, bone mineral density (BMD) measurements have been used as a primary examination method of bone evaluation using dual-energy X-ray absorptiometry (DXA). However, the International Society for Clinical Densitometry reported that only 60%–80% of bone strength could be predicted by BMD.[2–4] In 2006, the Trabecular Bone Score (TBS) was developed as a new metric for fracture prediction and was patented by MED-I Maps (Bordeaux, France).[5] Unlike BMD, which measures bone quantity, the TBS is an indirect measurement used to assess bone quality that reflects the structural condition of the bone microarchitecture of the trabeculae. TBS is a textural parameter that quantifies gray-level variations among the pixels of the anterior-posterior lumbar spine DXA images.

Although it is possible to identify individuals with osteoporosis who are at high risk of fragility fractures, there are more who experience fragility fractures with osteopenia (T-score between −1.0 and −2.5) and do not fulfill the criteria for osteoporosis.[6] As such, several validated risk factors that are independent of BMD have been proposed, including advanced age, previous low-trauma fracture, long-term glucocorticoid therapy, and low body weight.[7–9]

Metabolic syndrome (MetS) was once regarded a risk factor for osteoporosis. However, previous studies have reported inconsistent results, with positive, negative, and non-significant relationships between the two conditions.[10–12] Despite the inconclusive relationship between MetS and osteoporosis, epidemiological studies have focused on the association between MetS and bone fracture risk.[13–16] Other than osteoporosis, previous studies have reported that TBS demonstrated a positive correlation with bone quality, thus supporting TBS as an independent predictor of fracture risk.[17] However, the relationship between MetS and TBS remains unclear. Since TBS is a potentially predictive factor for fracture(s), we aimed to explore the relationship between specific MetS components and TBS. Furthermore, we hypothesized that the presence of a greater number of MetS components would be associated with a more negative effect on TBS.

MATERIALS AND METHODS

Informed consent was obtained from all participants before the study.

Study population

Demographic and health information from the US population was derived from the National Health and Nutrition Examination Survey (NHANES), which is a program of the National Center for Health Statistics (NCHS). As part of the Centers for Disease Control and Prevention (Atlanta, Georgia, USA), the NCHS has conducted the NHANES, a continuous annual survey to produce vital health statistics since 1999. Information regarding the participants, including demographic information, educational level, medical examination results, and questionnaires addressing medical and personal history, was collected by trained examiners during home interviews. Subsequently, all medical examinations were performed at a mobile examination center (MEC), and all data are released every 2 years. In the present study, data sets from the 2005–2006 NHANES were analyzed. The age of the population ranged from 18 to 65 years. Participants with missing data, those who received an intravenous injection of radiographic contrast agent(s) in the past 7 days, and those who underwent nuclear medicine examinations in the past 3 days or weighed >136 kg (weight limit of the DXA table) were excluded from the study. Pregnant female participants were ineligible for DXA.

Calculating TBS

This study acquired TBS data from the 2005–2006 NHANES. The protocol for TBS examinations has been described previously.[18] Lumbar spine (L1–L4) DXA was performed by trained radiology technicians using a fan-beam densitometer (QDR-4500A; Hologic, Bedford, Massachusetts, USA), which is the same device used in the NHANES MEC. Each of the raw DXA images of the lumbar spine was then uploaded to TBS software (Med-Imap SA TBS Calculator version 2.1.0.2), which was first applied in 2013 to estimate TBS for the lumbar spine (L1–L4).[19 20]

Definition of MetS

Based on the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP: ATP III), MetS in the present study was defined as the presence of ≥3 of the following features: abdominal obesity (waist circumference ≥102 cm for male or ≥88 cm for female); serum triglyceride level ≥150 mg/dL or on lipid-lowering medications; serum high-density lipoprotein cholesterol (HDL-C) level <40 mg/dL for male or <50 mg/dL for female; high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, or on antihypertensive drugs); and fasting glucose level ≥110 mg/dL, or on insulin or oral medications for elevated glucose.[21]

Covariates

Using a computer-assisted personal interviewing method, information from each participant was collected. Demographic information, including age, sex, race, smoking status, and medical history, was gathered at the MEC. Medical history, including congestive heart failure, coronary artery disease, or malignancy, was collected from self-reports of physician diagnoses. Smoking status was based on lifetime consumption of >100 cigarettes. Anthropometric data, including weight, waist circumference, height, and blood pressure, were collected by trained NHANES staff using standard protocols. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Specimen collection and processing procedures are provided in detail in the 2005–2006 NHANES Laboratory Procedures Manual.[18]

Statistical analyses

All statistical analyses were performed using SPSS V.18.0. Continuous data were assessed using Student's t-test and categorical data were assessed using Pearson's χ^2 tests. Two-sided p values ≤0.05 were considered statistically significant. The effect of each MetS component on TBS was examined using a linear regression model. In addition, several extended models were established for covariate adjustment. Model 1 was unadjusted; model 2 was adjusted for age, sex, and race; model 3 was further adjusted for BMI and serum C reactive protein (CRP) level; and model 4 was further adjusted for smoking status, congestive heart failure, coronary heart disease, and cancer. In addition, MetS components were treated as continuous variables (1-4) to perform trend tests and to explore the associations between the number of MetS components and TBS.

RESULTS

A total of 3792 participants were enrolled in this study, of whom 1105 (29.1%) exhibited ≥3 criteria for MetS. The clinical characteristics of the MetS and non-MetS groups are summarized in table 1. Participants with MetS were older and had a significantly higher prevalence of congestive heart failure, coronary heart disease, and cancer. BMI, waist circumference, blood pressure, and fasting glucose, CRP, and serum triglyceride levels were significantly higher in participants with MetS. Serum HDL-C levels were significantly lower in the MetS group than in the non-MetS group.

The results of the analysis investigating the association between presence of MetS and TBS are summarized in table 2. As shown, the β coefficients of TBS among participants with MetS were −0.024 in the fully adjusted model

Table 1 Characteristics of the study population

Variables	MetS (n=1105)	Non-MetS (n=2685)	P value
Continuous variables, mean (SD)			
Age (years)	54.83 (16.75)	44.88 (18.52)	<0.001
BMI	32.14 (5.84)	27.14 (5.89)	<0.001
Fasting glucose (mg/dL)	124.84 (43.62)	97.29 (22.50)	<0.001
Serum glucose (mg/dL)	118.93 (47.35)	92.04 (24.17)	<0.001
C reactive protein (mg/dL)	0.56 (0.77)	0.42 (0.85)	<0.001
Systolic blood pressure (mm Hg)	134.74 (21.72)	120.33 (17.41)	<0.001
Diastolic blood pressure (mm Hg)	73.32 (15.45)	67.57 (13.17)	<0.001
Triglycerides (mg/dL)	238.74 (163.39)	120.0 (79.57)	<0.001
Waist circumference (cm)	108.31 (13.31)	94.03 (14.29)	<0.001
HDL-C (mg/dL)	45.61 (13.54)	59.02 (16.32)	<0.001
Categorical variables (%)			
Male	548 (49.6)	1292 (48.1)	0.409
Race/Hispanic origin			
Non-Hispanic white	606 (54.8)	1355 (50.5)	<0.001
Non-Hispanic black	181 (16.4)	617 (23.0)	<0.001
Other	318 (28.8)	712 (26.5)	<0.001
Cigarette smoking	553 (50.0)	1259 (46.9)	0.166
Congestive heart failure	56 (5.1)	54 (2.0)	<0.001
Coronary heart disease	76 (6.9)	71 (2.6)	<0.001
Cancer or malignancy	122 (11.0)	183 (6.8)	<0.001

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

4 ($p<0.05$). Furthermore, there was a linear decrease in TBS with an increase in the number of MetS components. With the adjustment for covariates in model 4, the β coefficients of TBS of participants with 3 and ≥4 MetS components were −0.015 and −0.041, respectively ($p=0.006$ and $p<0.001$, respectively).

Among participants with MetS, high systolic blood pressure, abdominal obesity, and high levels of serum triglycerides and glucose were significantly associated with lower TBS in the fully adjusted models ($p<0.05$) (table 3). Other components of MetS, such as diastolic blood pressure and serum HDL-C level, revealed no significant association with TBS.

The effect of the number of components of MetS on TBS was further examined by separating the study population according to sex (table 4). In model 4, which was fully adjusted by multivariable analysis, there was a significant linear decrease in TBS in both groups with ≥4 MetS components. A significantly negative association was also observed in the male group with three MetS components.

A subanalysis was performed to examine the association between TBS and increased number of MetS components in each of the subpopulations of Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races (men and women) (online supplemental table 1). A significantly negative association between TBS and increased number of MetS components was observed only in the subpopulations of Mexican American women, other Hispanic men, and non-Hispanic black individuals (men and women) in a fully adjusted model.

DISCUSSION

Using the NCEP: ATP III criteria, we found a significant association between MetS and TBS among US adults. Our study revealed a negative relationship between TBS and an increased number of MetS components in a fully adjusted model of both sexes, especially in men with ≥3 and in women with ≥4 MetS components. Notably, only increased waist circumference, high systolic blood pressure, and high serum triglyceride and glucose levels were significantly correlated with low TBS. A study by Romagnoli *et al*[22] reported similar results in a group of men. The authors revealed that waist circumference had a more pronounced effect on TBS than BMI, and that there was an association between higher fasting glucose levels and TBS. However, a recent study by Bagherzadeh *et al*[23] demonstrated that TBS was not significantly associated with MetS in either sex. Despite the inconsistency in the results, both studies reported a negative impact of waist circumference on TBS. Traditionally, obesity has been regarded as a protective factor against osteoporosis and improves BMD through mechanical loading.[24 25] Recently, several studies have focused on the impact of visceral adipose tissue on bone quality, which may be associated with bone microarchitecture.[26] Lv *et al*[25] reported that body fat, especially android and visceral fat, may have a negative impact on TBS. This negative impact was also demonstrated in a study involving premenopausal women with varying degrees of central

Table 2 Association between number of MetS components and Trabecular Bone Score

Variables	Model 1* β (95% CI)	P value	Model 2* β (95% CI)	P value	Model 3* β (95% CI)	P value	Model 4* β (95% CI)	P value
One or more components of MetS	−0.090 (−0.098 to −0.082)	<0.001	−0.069 (−0.077 to −0.062)	<0.001	−0.025 (−0.031 to −0.018)	<0.001	−0.024 (−0.031 to −0.018)	<0.001
Number of MetS components								
1	−0.048 (−0.058 to −0.038)	<0.001	−0.031 (−0.041 to −0.022)	<0.001	0.004 (−0.004 to 0.013)	0.331	0.004 (−0.005 to 0.012)	0.362
2	−0.087 (−0.098 to −0.077)	<0.001	−0.062 (−0.072 to −0.052)	<0.001	−0.004 (−0.014 to 0.005)	0.394	−0.004 (−0.013 to 0.006)	0.446
3	−0.119 (−0.13 to 0.108)	<0.001	−0.089 (−0.100 to −0.079)	<0.001	−0.015 (−0.026 to −0.005)	0.004	−0.015 (−0.025 to −0.004)	0.006
≥4	−0.164 (−0.177 to −0.152)	<0.001	−0.127 (−0.139 to −0.115)	<0.001	−0.041 (−0.053 to −0.029)	<0.001	−0.041 (−0.053 to −0.029)	<0.001

*Adjusted covariates: model 1: unadjusted; model 2: adjustment for age, sex, and race; model 3: adjustment for age, sex, race, body mass index, and C reactive protein; model 4: adjustment for age, sex, race, body mass index, C reactive protein, cigarette smoking, ever told you had congestive heart failure, ever told you had coronary heart disease, and ever told you had cancer or malignancy.
MetS, metabolic syndrome.

Table 3 Association between each component of metabolic syndrome and Trabecular Bone Score

Variables	Model 1* β (95% CI)	P value	Model 2* β (95% CI)	P value	Model 3* β (95% CI)	P value	Model 4* β (95% CI)	P value
High blood pressure	−0.066 (−0.075 to −0.058)	<0.001	−0.023 (−0.031 to −0.014)	<0.001	−0.013 (−0.020 to −0.006)	<0.001	−0.013 (−0.02 to −0.006)	<0.001
Abdominal obesity	−0.102 (−0.108 to −0.095)	<0.001	−0.087 (−0.093 to −0.081)	<0.001	−0.015 (−0.023 to −0.007)	<0.001	−0.014 (−0.022 to −0.007)	<0.001
Low HDL-C	−0.023 (−0.032 to −0.015)	<0.001	−0.032 (−0.040 to −0.025)	<0.001	−0.003 (−0.01 to −0.003)	0.30	−0.004 (−0.010 to 0.003)	0.268
High triglycerides	−0.047 (−0.054 to −0.039)	<0.001	−0.039 (−0.045 to −0.032)	<0.001	−0.014 (−0.020 to −0.008)	<0.001	−0.014 (−0.020 to −0.008)	<0.001
High glucose	−0.069 (−0.076 to −0.061)	<0.001	−0.041 (−0.048 to −0.034)	<0.001	−0.016 (−0.022 to −0.010)	<0.001	−0.016 (−0.022 to −0.010)	<0.001

*Adjusted covariates: model 1: unadjusted; model 2: adjustment for age, sex, and race; model 3: adjustment for age, sex, race, body mass index, and C reactive protein; model 4: adjustment for age, sex, race, body mass index, C reactive protein, cigarette smoking, ever told you had congestive heart failure, ever told you had coronary heart disease, and ever told you had cancer or malignancy.
HDL-C, high-density lipoprotein cholesterol.

obesity according to the biopsy of the transiliac bone.[27] Several mechanisms have been proposed to explain the relationship between bone loss and adipose tissue. Adipocytes secrete high levels of interleukin 6, which promotes osteoclast differentiation and activation. Tumor necrosis factor-α, which is also produced by adipocytes and adipose tissue-infiltrated macrophages, promotes osteoclastogenesis and leads to bone resorption.[28 29]

Additionally, our study revealed a negative correlation between fasting glucose levels and TBS, which is consistent with previous studies.[22 30] The possible mechanisms may be related to the dysregulation of growth hormone (GH) and insulin-like growth factor (IGF)-1 in individuals with impaired glucose tolerance. The GH/IGF-1 axis plays a major role in the determination of bone mass and stimulates osteoblastogenesis.[31] Low IGF-1 levels have a negative impact on bone formation and are significantly associated with greater femoral bone loss.[32] Other potential mechanisms for poor bone quality, such as the accumulation of advanced glycation end products in the organic bone matrix and low bone turnover in patients with diabetes, have also been reported.[33] However, a study by Holloway *et al* reported that the correlation between TBS and blood glucose was only present in individuals with diabetes, and there was no difference in TBS between those with normoglycemia and impaired fasting glucose.[34] Further studies are needed to determine the impact of impaired fasting glucose on TBS.

In this study, serum triglyceride levels were negatively associated with TBS. Three previous studies have examined the relationship between serum triglyceride levels and TBS; however, the results were inconsistent.[20 23 30] Bagherzadeh *et al*[23] indicated that there was no association between serum triglyceride levels and degradation of the TBS (lumbar TBS ≤1.2). In contrast, the other two studies reported that serum triglyceride levels were negatively associated with TBS, although one of the studies did not report statistical significance.[20 30] Furthermore, in the present study, a negative correlation between TBS and the number of MetS components persisted in the fully adjusted model for both sexes. MetS appeared to play a more important role in TBS among men because a negative correlation was shown in men with three MetS components, and statistical significance in women with the same number of MetS components was not reached. Our results were different from those of a previous research by Bagherzadeh *et al*, which revealed no association between an increased number of MetS components and TBS in either sex.[23] Further studies are required to clarify this relationship.

This study had several limitations. First, due to its cross-sectional design, the study revealed an association and did not determine causality. Second, not all confounding factors were considered owing to the retrospective design of the study. Finally, the association between MetS and fracture risk remains controversial. Due to the lack of fracture data, further studies are needed to determine the actual effect of MetS on TBS and fracture.

Our study emphasizes that selected components of MetS, including blood pressure, waist circumference, and serum triglyceride and glucose levels, were negatively associated with TBS in a US adult population. Among the components of MetS, the association between a high serum glucose level

Table 4 Regression coefficients of number of MetS components for Trabecular Bone Score

Variables	Model 1* β† (95% CI)	P value	Model 2* β† (95% CI)	P value	Model 3* β† (95% CI)	P value	Model 4* β† (95% CI)	P value
	Male							
1	−0.048 (−0.061 to −0.034)	<0.001	−0.030 (−0.043 to −0.017)	<0.001	0.005 (−0.006 to 0.017)	0.356	0.005 (−0.007 to 0.016)	0.417
2	−0.069 (−0.083 to −0.055)	<0.001	−0.048 (−0.062 to 0.035)	<0.001	0.008 (−0.005 to 0.020)	0.232	0.008 (−0.004 to 0.020)	0.203
3	−0.123 (−0.139 to −0.108)	<0.001	−0.098 (−0.113 to −0.083)	<0.001	−0.015 (−0.030 to −0.001)	0.034	−0.015 (−0.029 to 0.00)	0.043
≥4	−0.167 (−0.184 to −0.150)	<0.001	−0.137 (−0.154 to −0.121)	<0.001	−0.034 (−0.051 to −0.018)	<0.001	−0.034 (−0.051 to −0.018)	<0.001
	Female							
1	−0.049 (−0.064 to −0.035)	<0.001	−0.034 (−0.047 to −0.021)	<0.001	0.003 (−0.009 to 0.016)	0.589	0.003 (−0.009 to 0.016)	0.614
2	−0.109 (−0.124 to −0.093)	<0.001	−0.076 (−0.090 to −0.062)	<0.001	−0.013 (−0.027 to 0.001)	0.071	−0.013 (−0.027 to 0.001)	0.077
3	−0.115 (−0.131 to −0.099)	<0.001	−0.081 (−0.096 to −0.066)	<0.001	−0.008 (−0.024 to 0.007)	0.273	−0.008 (−0.023 to 0.007)	0.295
≥4	−0.161 (−0.179 to −0.143)	<0.001	−0.114 (−0.131 to −0.096)	<0.001	−0.032 (−0.050 to −0.014)	<0.001	−0.032 (−0.050 to −0.014)	<0.001

*Adjusted covariates: model 1: unadjusted; model 2: adjustment for age and race; model 3: adjustment for age, race, body mass index, and C reactive protein; model 4: adjustment for age, race, body mass index, C reactive protein, cigarette smoking, ever told you had congestive heart failure, ever told you had coronary heart disease, and ever told you had cancer or malignancy.
†β was interpreted as change in Trabecular Bone Score for each increase in MetS.
MetS, metabolic syndrome.

and a low TBS was the most apparent. In addition, TBS significantly decreased with more MetS components, which may suggest that resolution of MetS may have a positive effect on bone structure. Future studies are needed to investigate other, more effective factors of TBS and to determine the net impact of MetS on TBS and fracture risk.

Contributors W-LC accepted full responsibility for the work and the conduct of the study, had access to the data, critically reviewed, and controlled the decision to publish. C-WS contributed to the design of the study, was responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, and drafted the initial manuscript. C-WS, W-HF, and W-LC decided on data collection methods and were also responsible for data analysis decisions. All authors read and approved the final manuscript.

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