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ORIGINAL ARTICLE

Effects of metabolic syndrome on bone health in older adults: the Bushehr Elderly Health (BEH) program

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Abstract

Summary Based on the clinical, BMD, and TBS data of 2380 participants aged ≥ 60 which was gathered during the BEH program, stage II, we showed that MetS was positively associated with BMD, while a negative or no association was observed between MetS and TBS depending on the sex and the adjustment model.

Introduction The results of previous reports in regard to the effect of metabolic syndrome (MetS) on bone health are not conclusive. This study aimed to evaluate the association between MetS with bone mineral density (BMD) and trabecular bone score (TBS) as an indicator of bone quantity and quality, respectively.

Methods Using a cross-sectional design, this study was carried out based on the data collected during the BEH Program, stage II. MetS was defined according to NCEP-ATP III criteria. BMD (at the lumbar spine and the hip) and lumbar spine TBS were assessed by dual-energy X-ray absorptiometry device.

Results The data of 2380 participants (women = 1228, men = 1152) aged ≥ 60 were analyzed. In the fully adjusted regression models (including BMI), significant associations between MetS and mean BMD were observed across all locations in men (P values ≤ 0.001) and in the lumbar spine in women (P value = 0.003). In addition, the prevalence of osteoporosis (based on BMD) was significantly lower in those with MetS than those without MetS in both sexes, even after full adjustments (women, OR = 0.707, P value = 0.013; men, OR = 0.563, P value = 0.001). In contrast, in age-adjusted regression analyses, the prevalence of degraded bone microarchitecture (TBS ≤ 1.2) was significantly increased in those with MetS than those without, irrespective of the participants' sex (P values < 0.05). The mean TBS was also negatively associated with MetS in women ($\beta = -0.075$, P value = 0.007) but not in men ($\beta = -0.052$, P value = 0.077), in age-adjusted regression models. However, after including BMI in the adjusted models, all significant associations between TBS values and MetS disappeared.

Conclusion It seems that a positive association exists between MetS and BMD, while MetS is either not associated or negatively correlated with bone quality as measured by TBS.

Keywords Metabolic syndrome · Trabecular bone score · Bone mineral densitometry · BMD · TBS

Introduction

Osteoporosis is a skeletal disorder in which the density and quality of bone are reduced, resulting in an increased risk of fragility fracture [1]. According to current estimates, osteoporosis affects more than 200 million people across the world and causes 8.9 million fractures each year [1]. Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis [2, 3]. However, numerous studies have indicated that the assessment of bone quantity by BMD alone cannot predict all the fragility fractures, and therefore, other factors such as microarchitecture of the bone should be considered for a more accurate fracture risk assessment [2–4]. Several non-invasive techniques have been developed for the evaluation of bone microarchitecture, an index of the bone quality [2, 4–6]. Among these techniques, trabecular bone score (TBS) is a

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more acceptable modality in clinical practice owing to its feasibility and lower costs [2, 7]. TBS is a gray-level texture measurement obtained from lumbar spine DXA images and has been shown to improve the fracture risk prediction of BMD [8].

Metabolic syndrome (MetS) is a medical state defined by the constellation of several metabolic abnormalities, which is predominantly associated with insulin resistance and central obesity [9]. MetS is a prevalent disorder and affects more than 20% of the general population with a growing trend worldwide [9]. The association of MetS with cardiovascular diseases and type 2 diabetes mellitus (DM) is well established [9]; however, there are uncertainties about its effect on bone health [10, 11]. For instance, some studies indicated that MetS and abdominal obesity, one of the main components of MetS, are associated with higher BMD and lower facture risk [12–15]. On the other hand, other studies suggested that these conditions are associated with lower bone density and quality as well as higher incidence of osteoporotic fractures [16–20].

In regard to uncertain and controversial pieces of evidence about the effect of MetS on bone health [10, 21], we aimed to determine the association of MetS and its components with bone quantity (based on BMD) as well as bone quality (based on TBS) in this study.

Materials and methods

Study population

This cross-sectional study was conducted within the framework of Bushehr Elderly Health (BEH) program, stage II (2015). The details and protocol of the BEH program were previously described elsewhere [22, 23]. In summary, the BEH program is a prospective population-based cohort study performed on a representative sample of the elderly (≥ 60 years) in the urban population of Bushehr city, the center of the Bushehr province, located in the south of Iran, with the aim of determining the prevalence and risk factors of noncommunicable diseases (NCD), including cardiovascular disease, musculoskeletal disorders, and cognitive impairment.

Data collection

Demographic and lifestyle data such as physical activity and smoking habits were obtained, using standard self-reported questionnaires [22, 23]. A fixed stadiometer and a digital scale were used for the measurements of height and weight, respectively. The waist circumference (WC) was measured just above the iliac crest using a stretch-resistant tape. All measurements were read with the precision of 0.1 cm and 0.1 kg. Body mass index (BMI) was calculated by the formula weight (kg)/[height (m)]^2. Blood pressure (BP) was measured twice by a standard mercury sphygmomanometer after 15 min of rest in the seated position, and then the mean of the two measurements was considered as the participant's systolic and diastolic blood pressures.

Fasting blood samples were collected from the participants following 8–12 h of overnight fast. Fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by an auto-analyzer using commercial kits (ParsAzmun, Karaj, Iran).

The BMD of the femoral neck, total hip, and lumbar spines (L1-L4) were measured by DXA (Hologic Inc., USA), and the TBS iNsight® software installed on our DXA machine was used for the assessment of L1-L4 TBS.

Definitions

MetS was defined according to the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria by the presence of ≥ 3 of the following criteria: abdominal obesity [WC > 102 cm (men) or > 88 cm (women)]; TG ≥ 150 mg/dl; HDL-C < 40 mg/dl (men) or < 50 mg/dl (women); BP ≥ 130/85 mmHg or on antihypertensive medications; and FPG ≥ 100 mg/dl or on drug treatment for elevated glucose [24].

Current smoker was defined as one who smokes at least one cigarette per day or uses a hookah or pipe once daily at the time of evaluation.

The amount of physical activity was estimated based on metabolic equivalents (METs) score using a validated questionnaire for a single measurement of 24-h physical activity on an average weekday [23, 25].

Based on BMD, osteoporosis was defined as T-score ≤ − 2.5 in the total hip, femoral neck, or lumbar spine [26]. TBS score ≤ 1.200 was considered as degraded bone microarchitecture in both sexes [27–29].

Ethical considerations

This study was approved by the Ethical Research Committee (ERC) of Endocrinology and Metabolism Research Institute, which is affiliated to Tehran University of Medical Sciences and the ERC of Bushehr University of Medical Sciences. Informed consent was obtained from all participants.

Statistical analyses

The Kolmogorov-Smirnov test was used for assessing the normal distribution of continuous variables. Normally distributed variables were presented as mean ± standard deviation (SD) and parametric tests such as independent *t* test or ANOVA were used for comparing means between groups. *P* value for trend was calculated for the assessment of statistical

significance between means and proportions across ordinal groups by χ^2 for trend. Uni- and multivariable linear and logistic regression analyses were used to examine the association between MetS and bone quantity (based on BMD) as well as bone quality (based on TBS). In the fully adjusted regression models, adjustments were performed for age, BMI, physical activity, and current smoking habits in both sexes. All tests were two-sided, and a P value < 0.05 was defined as statistically significant. The Stata 12 software (StataCorp, Texas, USA) was used for all statistical analyses.

Results

Of the initial 2426 included participants, the data of 2380 individuals (1228 women and 1152 men) for the MetS, BMD, and TBS were completed and considered for analysis. The mean ± SD age of the individuals was 69.32 ± 6.35 (69.51 ± 6.40 for men and 69.14 ± 6.30 for women). The diagnosis of MetS was made for 1264 subjects (822 women and 442 men) and the prevalence of MetS was 66.94% in women and 38.37% in men. The baseline characteristics were significantly different between the participants with MetS than those without MetS in both sexes, except for daily physical activity and current smoking in women and age, TC and LDL-C in men (Table 1).

The mean BMD of the femoral neck, total hip, and lumbar spine were significantly higher in subjects with MetS in both sexes in comparison with those without MetS (P values < 0.001). Likewise, the prevalence of osteoporosis (based on BMD) was significantly lower in individuals with MetS (53.77% in women and 13.57% in men) vs. those without MetS (68.47% in women and 29.01% in men) (Table 2). In contrast, the mean lumbar spine TBS in both sexes was not statistically different between participants with and without MetS (P values ≥ 0.05). The prevalence of degraded bone microarchitecture (based on TBS) in women was also not statistically different between the two groups (with MetS, 32.85%; without MetS, 28.33%; P value = 0.108). However, the prevalence of degraded bone microarchitecture in men was significantly higher in patients with MetS (9.05%) compared with those without MetS (4.08%) (Table 2).

In both sexes, there was a significant increase in femoral neck, total hip, and spinal mean BMD with each increment in the number of MetS components (P value < 0.001 for trend). Similarly, the prevalence of osteoporosis significantly decreased when the number of MetS components increased (P value < 0.001 for trend in men and women). When trend analysis was conducted for the mean TBS and the prevalence of degraded bone microarchitecture, the only significant trend observed was the prevalence of degraded bone microarchitecture in men (P value < 0.001 for trend) (Table 2).

In both sexes, the MetS had a significant positive relationship with lumbar spine, femoral neck, and total hip mean BMD in the univariable (unadjusted) linear regression model (P values < 0.001); these significant positive relationships were maintained after adjustments for age, physical activity, and smoking status in all sites and in both sexes (models 1 and 2; P values < 0.001). However, when BMI was added to the model (model 3), the statistical significance was canceled out in femoral neck (P value = 0.071) and total hip (P value = 0.150) in women (Table 3). As demonstrated in Supplementary Table 1, after adding MetS components (when they reached five components), the positive association between MetS and mean BMD in women became significant again in femoral neck (P value = 0.010) and in total hip (P value = 0.049), even after adjustments for several factors, including BMI (fully adjusted model). Univariable and multivariable logistic regression analyses (including BMI) also confirmed a significant reversed relationship between the prevalence of osteoporosis and MetS, irrespective of the participants' sex (P values < 0.05) (Table 4). In addition, after the full adjustment, the reversed relationship between the prevalence of osteoporosis and the number of MetS components still persisted (Supplementary Table 2). Finally, when the data of men and women were pooled, the positive association of MetS with BMD in all sites and the negative association of MetS with the prevalence of osteoporosis remained significant (P values < 0.001) in all the adjusted models (Supplementary Tables 3 and 4).

In the initially unadjusted regression model, MetS was related to increased prevalence of degraded bone in men (OR = 2.337; P value = 0.001). However, no association was observed either between MetS and the prevalence of degraded bone microarchitecture in women or between MetS and mean TBS in both sexes (P values ≥ 0.05). After the adjustment for age (model 1), the prevalence of degraded bone microarchitecture significantly increased in both sexes (in women, OR = 1.349, P value = 0.028; in men, OR = 2.376, P value = 0.001), and also, the MetS became negatively associated with mean TBS in women ($\beta = -0.075$; P value = 0.007). These associations persisted after the inclusion of smoking status and physical activity in the age-adjusted models (model 2; P values < 0.05) (Tables 3 and 4). Moreover, when the number of MetS components increased, the negative association between MetS and mean TBS became significant in both sexes in the unadjusted model (Supplementary Table 1) and remained significant after adjustments for age, physical activity, and smoking status (data not shown). As shown in Supplementary Tables 3 and 4, the pooled data of men and women also confirmed a significantly lower TBS and higher prevalence of degraded bone microarchitecture in those with MetS before and after adjustments for age, sex, smoking status, and physical activity (models 1 and 2; P values < 0.01). However, when BMI was

Table 1 Clinical characteristics of the participants categorized by the presence of MetS

Variables	Total			Women			Men		
	With MetS, $n = 1264$	Without MetS, $n = 1116$	P value	With MetS, $n = 822$	Without MetS, $n = 406$	P value	With MetS, $n = 442$	Without MetS, $n = 710$	P value
Age (years), mean (SD)	68.86 (5.96)	69.84 (6.74)	< 0.001	68.74 (5.82)	69.95 (7.11)	0.002	69.08 (6.20)	69.77 (6.52)	0.072
BMI (kg/m^2), mean (SD)	29.19 (4.75)	25.61 (4.32)	< 0.001	29.73 (5.14)	26.65 (5.09)	< 0.001	28.19 (3.72)	25.02 (3.69)	< 0.001
Daily physical activity (METs), mean (SD)	30.78 (4.91)	31.28 (5.63)	0.021	30.80 (4.66)	30.80 (4.72)	0.995	30.74 (5.35)	31.56 (6.08)	0.021
Current smoker (cigarette, hookah, or pipe), n (%)	237 (18.76)	264 (23.70)	0.003	146 (17.78)	82 (20.25)	0.297	91 (20.59)	182 (25.67)	0.049
TC (mg/dl), mean (SD)	183.65 (47.15)	180.48 (40.88)	0.082	188.68 (48.05)	194.50 (40.53)	0.036	174.30 (43.98)	172.46 (38.89)	0.458
TG (mg/dl), mean (SD)	166.97 (77.45)	100.71 (38.16)	< 0.001	162.78 (76.78)	97.46 (29.54)	< 0.001	174.78 (78.18)	102.57 (42.22)	< 0.001
HDL-C (mg/dl), mean (SD)	42.17 (9.99)	50.20 (11.03)	< 0.001	44.76 (9.77)	56.48 (10.84)	< 0.001	37.37 (8.50)	46.61 (9.43)	< 0.001
LDL-C (mg/dl), mean (SD)	108.44 (40.23)	110.53 (34.90)	0.178	111.66 (41.50)	118.93 (35.99)	0.003	102.44 (37.06)	105.73 (33.35)	0.120
FPG (mg/dl), mean (SD)	119.11 (49.44)	91.81 (26.59)	< 0.001	117.38 (49.87)	88.43 (19.80)	< 0.001	122.33 (48.54)	93.75 (29.63)	< 0.001
WC (cm), mean (SD)	103.07 (10.62)	93.74 (11.55)	<0.001	103.11 (11.07)	94.44 (13.17)	< 0.001	103.00 (9.74)	93.34 (10.50)	< 0.001
SBP (mmHg), mean (SD)	143.09 (18.48)	135.88 (19.48)	0.001	142.44 (18.55)	133.39 (19.21)	< 0.001	144.31 (18.30)	137.30 (19.51)	< 0.001
DBP (mmHg), mean (SD)	82.14 (8.57)	80.94 (8.65)	< 0.001	81.28 (8.52)	79.86 (8.44)	0.006	83.72 (8.45)	81.55 (8.71)	< 0.001

BMI body mass index, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HDL-C* high density lipoprotein-cholesterol, *LDL-C* low density lipoprotein-cholesterol, *MetS* metabolic syndrome, *SD* standard deviation, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *WC* waist circumference

added to the models (model 3 or the fully adjusted model), all significant associations of MetS and the number of MetS components with TBS values disappeared (P values ≥ 0.05) (Tables 3 and 4 as well as Supplementary Tables 1, 2, 3, and 4).

In the multivariable logistic regression model, among the MetS components, abdominal obesity, which was determined by WC, had a strong positive association with osteoporosis (OR = 0.423; P value < 0.001). Other MetS components, including high glucose level (OR = 0.633; P value < 0.001), high TG level (OR = 0.728; P value = 0.013), and high BP (OR = 0.731; P value = 0.004) also had positive association with osteoporosis. In contrast, abdominal obesity (OR = 3.089; P value < 0.001) was the only factor which applied the negative effect of MetS on bone microarchitecture (Table 5).

Discussion

The present study demonstrated that mean BMD in all three sites was significantly higher and the prevalence of osteoporosis (based on BMD) was also significantly lower (more than 14%) in subjects with MetS than those without MetS in both sexes. Moreover, we observed that with the increasing number of MetS criteria, the BMD was further increased in an incremental manner across all locations in men and women. This positive association of MetS with BMD was preserved after several adjustments (including BMI) especially in men. The significant reverse association between the MetS and the prevalence of osteoporosis was also maintained after full adjustments in both sexes. In contrast to the abovementioned findings, depending on the sex and the adjustment model, a negative or no association was observed between MetS and TBS.

Studies have reported inconsistent results about the effects of MetS on BMD [11, 30]. Some of these controversies may arise from differences in ethnicity, baseline characteristics of participants, MetS definition criteria, the BMD measurement methods, and DXA scanner manufacturers, or the adjusting covariates which are used in various studies [10]. In a study conducted by Jeon et al. [31] on 931 postmenopausal women, those with MetS had significantly lower BMD at the femoral neck and lumbar spine before or after adjustments. Hwang

Table 2 Bone health status of the participants based on the presence of MetS and the number of MetS components

Variables	Participants				Number of MetS criteria							
	Total	Without MetS	With MetS	*P* value	No	One	Two	Three	Four	Five	*P* value	*P* value for trend
Women												
	***n* = 1228**	***n* = 406**	***n* = 822**		***n* = 25**	***n* = 107**	***n* = 274**	***n* = 354**	***n* = 311**	***n* = 157**		
Lumbar spine BMD (gr/cm^2), mean (SD)	0.81 (0.14)	0.77 (0.15)	0.83 (0.14)	< 0.001	0.71 (0.11)	0.72 (0.15)	0.79 (0.14)	0.81 (0.14)	0.84 (0.13)	0.87 (0.14)	< 0.001	< 0.001
Femoral neck BMD (gr/cm^2), mean (SD)	0.59 (0.11)	0.57 (0.11)	0.60 (0.11)	< 0.001	0.53 (0.06)	0.54 (0.11)	0.58 (0.11)	0.59 (0.11)	0.60 (0.10)	0.63 (0.12)	< 0.001	< 0.001
Total hip BMD (gr/cm^2), mean (SD)	0.76 (0.13)	0.73 (0.13)	0.77 (0.12)	< 0.001	0.68 (0.10)	0.69 (0.14)	0.74 (0.13)	0.75 (0.13)	0.78 (0.11)	0.80 (0.13)	<0.001	< 0.001
[a]Osteoporosis, *n* (%)	720 (58.63)	278 (68.47)	442 (53.77)	< 0.001	22 (88.00)	82 (76.64)	174 (63.50)	220 (62.15)	160 (51.45)	62 (39.49)	< 0.001	< 0.001
Lumbar spine T-score ≤ −2.5, *n* (%)	507 (41.29)	212 (52.22)	295 (35.89)	< 0.001	16 (64.00)	70 (65.42)	126 (45.99)	161 (45.48)	95 (30.55)	39 (24.84)	< 0.001	< 0.001
Femoral neck T-score ≤ −2.5, *n* (%)	588 (47.99)	233 (57.53)	355 (43.19)	< 0.001	20 (83.33)	68 (63.55)	145 (52.92)	175 (49.44)	128 (41.16)	52 (33.12)	< 0.001	< 0.001
Total hip T-score ≤ −2.5, *n* (%)	219 (17.85)	101 (24.94)	118 (14.36)	< 0.001	9 (37.5)	37 (34.58)	55 (20.07)	64 (18.08)	37 (11.90)	17 (10.83)	< 0.001	< 0.001
TBS (L1-L4), mean (SD)	1.24 (0.09)	1.25 (0.08)	1.24 (0.09)	0.058	1.28 (0.07)	1.24 (0.08)	1.25 (0.08)	1.24 (0.09)	1.24 (0.09)	1.24 (0.09)	0.181	0.175
[b]Degraded bone microarchitecture, *n* (%)	385 (31.35)	115 (28.33)	270 (32.85)	0.108	5 (20.00)	31 (28.97)	79 (28.83)	124 (35.03)	101 (32.48)	45 (28.66)	0.356	0.437
Men												
	***n* = 1152**	***n* = 710**	***n* = 442**		***n* = 81**	***n* = 285**	***n* = 344**	***n* = 274**	***n* = 124**	***n* = 44**		
Lumbar spine BMD (gr/cm^2), mean (SD)	0.99 (0.17)	0.96 (0.16)	1.04 (0.17)	< 0.001	0.92 (0.18)	0.95 (0.16)	0.98 (0.16)	1.03 (0.18)	1.04 (0.18)	1.09 (0.14)	< 0.001	< 0.001
Femoral neck BMD (gr/cm^2), mean (SD)	0.73 (0.13)	0.71 (0.13)	0.76 (0.14)	< 0.001	0.68 (0.13)	0.71 (0.13)	0.72 (0.13)	0.76 (0.13)	0.75 (0.15)	0.81 (0.16)	< 0.001	< 0.001
Total hip BMD (gr/cm^2), mean (SD)	0.94 (0.14)	0.92 (0.14)	0.99 (0.14)	< 0.001	0.88 (0.14)	0.91 (0.14)	0.94 (0.14)	0.98 (0.14)	0.99 (0.14)	1.03 (0.16)	< 0.001	< 0.001
[a]Osteoporosis, *n* (%)	266 (23.09)	206 (29.01)	60 (13.57)	< 0.001	33 (40.74)	92 (32.28)	81 (23.55)	39 (14.23)	18 (14.52)	3 (6.82)	< 0.001	< 0.001
Lumbar spine T-score ≤ −2.5, *n* (%)	178 (15.45)	139 (19.58)	39 (8.82)	< 0.001	26 (32.10)	63 (22.11)	50 (14.53)	27 (9.85)	10 (8.06)	2 (4.55)	< 0.001	< 0.001
Femoral neck T-score ≤ −2.5, *n* (%)	167 (14.51)	128 (18.05)	39 (8.82)	< 0.001	23 (28.75)	58 (20.35)	47 (13.66)	22 (8.03)	15 (12.10)	2 (4.55)	< 0.001	< 0.001
Total hip T-score ≤ −2.5, *n* (%)	20 (1.74)	18 (2.54)	2 (0.45)	0.008	4 (5.00)	10 (3.51)	4 (1.16)	2 (0.73)	0 (0.00)	0 (0.00)	0.008	< 0.001
TBS (L1-L4), mean (SD)	1.35 (0.09)	1.36 (0.09)	1.35 (0.10)	0.123	1.37 (0.07)	1.36 (0.08)	1.35 (0.09)	1.35 (0.10)	1.34 (0.10)	1.34 (0.09)	0.233	0.053
[b]Degraded bone microarchitecture, *n* (%)	69 (5.99)	29 (4.08)	40 (9.05)	< 0.001	2 (2.47)	6 (2.11)	21 (6.10)	23 (8.39)	15 (12.10)	2 (4.55)	0.001	< 0.001

BMD bone mineral density, *MetS* metabolic syndrome, *SD* standard deviation, *TBS* trabecular bone score

[a] Osteoporosis (based on BMD) considered T-score ≤ − 2.5 in the total hip, femoral neck, or lumbar spine

[b] Degraded bone microarchitecture considered lumbar TBS ≤ 1.2

Table 3 Assessing the association of MetS with BMD and TBS using the linear regression analysis in men and women

MetS (yes/no)	Women				Men			
	B	*SE*	*β*	*P* value	*B*	*SE*	*β*	*P* value
Lumbar spine BMD								
Unadjusted	0.062	0.009	0.204	<0 .001	0.077	0.010	0.218	< 0.001
[a]Model 1	0.054	0.008	0.176	< 0.001	0.077	0.010	0.217	< 0.001
[b]Model 2	0.053	0.008	0.175	< 0.001	0.073	0.010	0.207	< 0.001
[c]Model 3	0.023	0.008	0.075	0.003	0.039	0.011	0.111	< 0.001
Femoral neck BMD								
Unadjusted	0.034	0.007	0.142	< 0.001	0.050	0.008	0.180	< 0.001
[a]Model 1	0.025	0.006	0.104	< 0.001	0.046	0.008	0.166	< 0.001
[b]Model 2	0.025	0.006	0.108	< 0.001	0.046	0.008	0.167	< 0.001
[c]Model 3	0.011	0.006	0.046	0.071	0.026	0.008	0.095	0.001
Total hip BMD								
Unadjusted	0.042	0.008	0.156	< 0.001	0.066	0.008	0.226	< 0.001
[a]Model 1	0.031	0.007	0.115	< 0.001	0.063	0.008	0.214	< 0.001
[b]Model 2	0.032	0.007	0.118	< 0.001	0.063	0.008	0.213	< 0.001
[c]Model 3	0.010	0.007	0.035	0.150	0.037	0.009	0.125	< 0.001
TBS								
Unadjusted	− 0.010	0.005	− 0.054	0.058	− 0.009	0.006	− 0.045	0.123
[a]Model 1	− 0.014	0.005	− 0.075	0.007	− 0.010	0.006	− 0.052	0.077
[b]Model 2	− 0.014	0.005	− 0.073	0.009	− 0.005	0.005	− 0.027	0.349
[c]Model 3	− 0.010	0.006	− 0.055	0.059	0.004	0.006	0.024	0.442

β standardized regression coefficient, *B* unstandardized regression coefficient, *BMD* bone mineral density, *MetS* metabolic syndrome, *SE* standard error

[a] Model 1: adjusted for age

[b] Model 2: adjusted for age, physical activity, and smoking status

[c] Model 3 or final model: adjusted for age, physical activity, smoking status, and BMI

Table 4 Assessing the association of MetS with osteoporosis and the degraded bone microarchitecture in men and women using the logistic regression analysis

Sex	Women						Men					
MetS (yes/no)	Osteoporosis*			Degraded bone microarchitecture**			Osteoporosis*			Degraded bone microarchitecture**		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Unadjusted	0.536	0.417–0.688	< 0.001	1.238	0.954–1.606	0.108	0.384	0.280–0.528	< 0.001	2.337	1.426–3.828	0.001
[a]Model 1	0.562	0.433–0.729	< 0.001	1.349	1.033–1.762	0.028	0.392	0.285–0.539	< 0.001	2.376	1.448–3.897	0.001
[b]Model 2	0.550	0.424–0.715	< 0.001	1.319	1.008–1.724	0.043	0.389	0.281–0.538	< 0.001	2.313	1.405–3.807	0.001
[c]Model 3	0.707	0.537–0.930	0.013	1.078	0.816–1.426	0.596	0.563	0.398–0.797	0.001	1.268	0.737–2.182	0.392

CI confidence interval, *MetS* metabolic syndrome, *OR* odds ratio

*Osteoporosis (based on BMD) considered as T-score ≤ −2.5 in the total hip, femoral neck, or lumbar spine

**Degraded bone microarchitecture considered as lumbar TBS ≤ 1.2

[a] Model 1: adjusted for age

[b] Model 2: adjusted for age, physical activity, and smoking status

[c] Model 3 or final model: adjusted for age, physical activity, smoking status, and BMI

Table 5 Multivariable logistic regression analysis between each one of the MetS components and osteoporosis as well as the degraded bone microarchitecture in all subjects

Total						
MetS components*	[a]Osteoporosis			[b]Degraded bone microarchitecture		
	OR	95% CI	*P* value	OR	95% CI	*P* value
[c]Abdominal obesity	0.423	0.325–0.552	< 0.001	3.089	2.242–4.258	< 0.001
[d]High glucose	0.633	0.521–0.770	< 0.001	1.159	0.921–1.457	0.208
[e]High BP	0.728	0.566–0.934	0.013	1.110	0.802–1.537	0.530
[f]High TG	0.731	0.591–0.904	0.004	0.803	0.624–1.032	0.087
[g]Low HDL-C	0.851	0.698–1.037	0.109	0.867	0.686–1.096	0.234

BP blood pressure, *CI* confidence interval, *FPG* fasting plasma glucose, *HDL-C* high density lipoprotein-cholesterol, *MetS* metabolic syndrome, *OR* odds ratio, *TG* triglyceride, *WC* waist circumference

*Adjusted for age, sex, physical activity, and smoking status

[a] Osteoporosis (based on BMD) considered as T-score ≤ −2.5 in the total hip, femoral neck, or lumbar spine

[b] Degraded bone microarchitecture considered as lumbar TBS ≤ 1.2

[c] WC > 102 cm in men or > 88 cm in women

[d] FPG ≥ 100 mg/dl or on drug treatment for elevated glucose

[e] BP ≥ 130/85 mmHg or on antihypertensive medications

[f] TG ≥ 150 mg/dl

[g] HDL-C < 40 mg/dl in men or < 50 mg/dl in women

et al. [16] also reported the same results and showed that the unadjusted and adjusted lumbar spine BMD was significantly lower in those with MetS. Furthermore, they demonstrated that vertebral BMD further declined (*P* value = 0.004) as the number of MetS components increased [16]. However, the results of many studies, especially those which were conducted in the Caucasian population were in line with the present study and indicated a higher BMD in individuals with MetS, at least in crude or age-adjusted analyses [10, 30]. In Rancho Bernardo Study, Von Muhlen et al. [32] evaluated the association of MetS with bone health in 417 men and 671 women. They demonstrated that age-adjusted BMD was significantly higher in total hip and lumbar spine in both sexes. The age-adjusted BMD in femoral neck was also higher in those with MetS but did not reach statistical significance (*P* value = 0.05 for males and *P* value = 0.06 for females). However, they showed that after the addition of BMI to the adjusted factors, these associations were reversed, and MetS was accompanied by lower BMD in all locations (femoral neck, total hip, and lumbar spine) with significant results for the femoral neck in males (*P* value = 0.02) [32]. In another large study, Kinjo et al. [14] examined the relationship between femoral neck BMD and MetS in a population-based US sample from the Third National Health and Nutrition Examination Survey (NHANES III). They demonstrated that the adjusted femoral neck BMD (BMI is not included in adjustment factors) was significantly higher among individuals with MetS than in those in the control group. However, when the adjusted BMD was stratified by BMI, the femoral neck BMD was similar between the two groups. Similar to our results, Kinjo et al. also reported a significant positive trend in femoral neck BMD when the components of MetS increased [14]. In the MINOS Study, Szulc et al. [33] evaluated the association of MetS and bone health in 762 men (aged 50–85) followed up for 10 years. They observed a significantly higher BMD in the lumbar spine, total hip, and femoral neck in those with MetS. However, after adjustments for several factors, including BMI, men with MetS had significantly lower BMD at the total hip and femoral neck. In the fully adjusted model, the lumbar spine BMD was also lower in those with MetS but did not reach statistical significance [33]. Hernandez et al. [34] also demonstrated that MetS was related to higher age-adjusted BMD in femoral neck, total hip, and lumbar spine in postmenopausal women and this positive effect was canceled out after adjustment for BMI at the spine and femoral neck. Nevertheless, the bone mass difference in total hip remained significant even after adjustments for age and BMI in women (*P* value = 0.047). Based on their results, the MetS had no significant effect on BMD in any site before or after adjustments in men [34].

As demonstrated above, many studies concluded that BMI or weight is the main factor that determined the effect of MetS on BMD and after adjustment for it, the positive effect of MetS tended to disappear [30]. On the contrary, our results showed that even after adjustments for several factors, including BMI, the prevalence of osteoporosis (based on BMD) is significantly lower in those with MetS than those without MetS in both sexes. Likewise, in the fully adjusted models, the positive association of MetS with BMD remained with significant results for all sites in males and for the lumbar

spine in females. The reasons for these sex- and site-specific differences in the relationship between MetS and BMD in the fully adjusted model are not known. However, as shown by Felson et al. in Framingham study, the greater effect of BMI on BMD in women than in men may explain some of these sex differences. Felson et al. suggested that BMD in postmenopausal women have greater dependency on estrogen production of adipose tissue than in men with intact gonadal function [35]. Finally, our results showed that besides the strong positive association of WC with BMD, other components of MetS, including high TG, high glucose level, and high BP, also had positive influence on BMD. These findings indicated that MetS may be related to higher BMD irrespective of BMI especially in men.

Most studies have evaluated the effect of MetS on BMD, but the data on its influence on bone quality, especially for TBS, is scarce. Our study indicated that despite the positive association between MetS and BMD, the bone quality (based on TBS) is either not associated or negatively associated with MetS. A study conducted by Povoroznyuk et al. [36] achieved the same results. They showed that postmenopausal women with MetS had significantly higher BMD in all sites and lower mean TBS in comparison with pre-obese females [36]. Our study also showed that the possible negative impact of MetS on bone quality is mainly driven by BMI and/or WC.

The paradoxical effect of MetS on bone quality (no or negative effect) and quantity (positive effect) may be explained by a different way through which obesity may act on bone health. Traditionally, obesity has been considered as a protective factor against osteoporosis, and a positive association between BMI and BMD has been reported [20, 37]. However, recent pieces of evidence proposed that obesity, especially visceral adipose tissue, may have detrimental effects on bone health and may be associated with impaired bone microarchitecture [38]. For instance, Lv et al. investigated the relationship between body fat and its distribution on TBS and BMD. They concluded that fat mass especially visceral fat has a negative impact on TBS and bone microarchitecture, while it improves BMD through mechanical loading [39]. The negative influence of visceral fat on bone quality is also shown at the tissue level in transiliac bone biopsies obtained from healthy premenopausal women with different amounts of central adiposity [19]. Several potential mechanisms have been suggested to account for the complex relationship between abdominal obesity (visceral fat) and bone metabolism. Mechanical loading is the main mechanism by which abdominal obesity contributes to higher BMD in obese individuals [20]. In addition, a higher insulin and 17β-estradiol level caused by abdominal obesity may have positive effects on BMD [14, 40]. Visceral fat may also increase bone mass by the regulation of several adipokines, including leptin and adiponectin [40]. On the other hand, the detrimental effect of central obesity on osteoblast activity and/or the induction of low-grade inflammation by adipose tissue, which affects bone remodeling, may in turn reduce bone quality [19, 41, 42]. Moreover, central adiposity is associated with dysregulation of the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis and lower serum IGF-1 level. Low levels of IGF-1, an anabolic hormone for osteoblast lineage, may adversely affect bone formation and cause poor bone quality [19]. Finally, those with abdominal obesity generally have lower physical activity which has negative effects on bone health [43].

Another possible reason for this discrepancy between the impact of MetS on BMD and TBS is related to the effect of BMI on the TBS measurement accuracy. In other words, TBS is not considered valid for individuals with a high BMI (> 37 kg/m^2) [28]. Based on Langsetmo et al.'s [28] report, despite the fact that TBS is inversely associated with BMI, when compared with lumbar volumetric BMD, it was observed that the bone quality does not decrease as depicted by TBS and therefore TBS may underestimate the bone quality and strength in those with a high BMI. Nevertheless, in our study, after the exclusion of subjects with BMI > 37 kg/m^2, the MetS did not have a positive effect on TBS values (data not shown).

Our study was strengthened by taking a large representative sample of the elderly population from both sexes. Moreover, we assessed the effect of MetS on bone status by both BMD and TBS. However, this research had several limitations, including the cross-sectional design, which did not allow assessing the causality, and also the lack of fracture data. Studies are controversial in regard to the effect of MetS on the risk of bone fracture. However, two published meta-analyses which evaluated the effect MetS on bone fractures concluded that MetS reduced the risk of fracture [13, 44]. If these data are confirmed, the lower rate of fractures in individuals with MetS may be explained by the strong positive effect of MetS on BMD, which offsets its potentially negative impact on bone quality. Another limitation of our study is the possible effect of lumbar spine osteoarthritis, a prevalent disease in old and obese individuals, on spine BMD which may lead to an artifactually elevated spine BMD. However, as both hip (total hip and femoral neck) and lumbar spine BMD were increased in patients with MetS compared with those without, it seems that MetS is actually related to higher BMD. Based on Kolta et al.'s report, TBS is not affected by lumbar spine degenerative changes [45].

In conclusion, our findings suggest that MetS is associated with higher BMD in both sexes. This positive effect on BMD is maintained even after adjustments for several factors, including BMI, especially in men. In addition, after an increase in the number of MetS components, the positive effect of MetS on BMD is further increased. In contrast, MetS may have detrimental or no effect on bone quality as measured by TBS and the possible negative influence of MetS on TBS is mainly driven by BMI and/or WC. Further studies are needed to confirm these paradoxical effects of MetS on BMD and bone quality and to determine the net impact of MetS on bone health and fracture outcome.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethical Research Committee (ERC) of Endocrinology and Metabolism Research Institute, which is affiliated to Tehran University of Medical Sciences and the ERC of Bushehr University of Medical Sciences.

Informed consent Informed consent was obtained from all individual participants included in the study.

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