

# Metabolic syndrome in postmenopausal women with osteoporosis and its relationship with bone density and turnover markers

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## Abstract

**Introduction:** Previous research has explored the uncertain association between metabolic syndrome (MetS) and bone mineral density (BMD). The objective of this study was to determine the prevalence of MetS in postmenopausal Moroccan women with osteoporosis and to examine the relationship between MetS, BMD, and bone turnover markers among this sample.

**Material and methods:** This was a cross-sectional study of 100 postmenopausal women. Anthropometric parameters and biochemical blood tests were assessed. Bone mineral density and *T*-scores in the lumbar spine and femoral neck were screened. Bone mineral density was determined using dual-energy X-ray absorptiometry. National Cholesterol Education Program-Adult Treatment Panel III criteria were used to define MetS. The association between the MetS components, BMD, and bone turnover markers was evaluated by partial correlation and multiple linear regression analysis using SPSS software.

**Results:** Prevalence of MetS in our patients was 44%. The mean age of patients with and those without MetS was  $63.82 \pm 8.65$  and  $60.39 \pm 7.93$ , respectively;  $p = 0.04$ . Lumbar spine BMD correlated significantly with high-density lipoprotein cholesterol (HDL-C;  $r = -0.233$ ;  $p = 0.02$ ). Lumbar spine *T*-score correlated with systolic blood pressure (SBP;  $r = -0.196$ ;  $p = 0.005$ ) and waist circumference ( $r = 0.274$ ;  $p = 0.006$ ). Femoral neck *T*-score correlated with diastolic blood pressure ( $r = -0.218$ ;  $p = 0.02$ ) and waist circumference ( $r = 0.294$ ;  $p = 0.003$ ). Osteocalcin inversely correlated with HDL-C and fasting plasma glucose ( $r = -0.199$ ;  $p = 0.04$  and  $r = -0.238$ ;  $p = 0.01$  respectively). Carboxy-terminal cross-linked telopeptide of type I collagen correlated negatively with HDL-C and SBP ( $r = -0.238$ ;  $p = 0.02$  and  $r = -0.243$ ;  $p = 0.01$  respectively). After linear regression, lumbar spine BMD was associated with age ( $\beta = -2.120$ ,  $p = 0.04$ ), SBP ( $\beta = -0.112$ ,  $p = 0.01$ ) and waist circumference ( $\beta = 0.253$ ,  $p = 0.001$ ). Femoral neck BMD was associated with age ( $\beta = -0.227$ ,  $p = 0.02$ ) and waist circumference ( $\beta = 0.258$ ,  $p = 0.008$ ).

**Conclusions:** The prevalence of MetS was associated with osteoporosis in postmenopausal Moroccan women, predominantly driven by age, blood pressure, and central obesity.

**Key words:** osteoporosis, postmenopausal women, obesity, metabolic syndrome.

## Introduction

Osteoporosis and metabolic syndrome (MetS) are two prevalent conditions with similar pathogenic patterns [1]. In recent decades, an increase of osteoporosis and cardiometabolic syndrome prevalence has been observed [2, 3]. The relationship between these disorders

has been a matter of extensive clinical research and investigation, with conflicting results. It is known that MetS is characterized by a combination of obesity, dyslipidaemia, hyperglycemia, and hypertension [4].

Metabolic syndrome includes serious cardiovascular risk factors that confer a high risk of morbidity and mortality [4]. Moreover, in old age, with the occurrence

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of fractures, osteoporosis constitutes a major health problem [3]. Common pathogenic links have been recently proposed between these two conditions [1].

Bone metabolism, through independent mechanisms, may be affected by MetS components. By inducing inflammation and increasing calcium excretion, MetS can contribute to reduced bone density [5]. On the other hand, obesity may protect against osteoporosis by increasing mechanical loading on the bones. It has been demonstrated that adipose tissue is an endocrine organ; by secreting biological active substances, it may positively influence bone mineral density (BMD) [6–8]. However, studies focusing on the association between MetS and osteoporosis provide disharmonious results. This incoherence can be explained by the balance between beneficial effects of visceral obesity expressed by increased waist circumference versus the detrimental impact of the other components of bone density.

Considering the increasing prevalence of MetS and osteoporosis and the uncertainty regarding their association and the lack of relevant information in Morocco, our aim was to determine the prevalence of MetS in postmenopausal Moroccan women with osteoporosis and to examine the relationship between the individual components of the MetS and bone metabolism in this population.

## Material and methods

We enrolled 100 postmenopausal women with osteoporosis for this cross-sectional study after excluding participants with hyperthyroidism, hyperparathyroidism, bone metastases, osteomalacia, Paget disease, autoimmune disease, multiple myeloma, renal failure and congenital disease of bone formation.

Metabolic syndrome was defined by National Cholesterol Education Program-Adult Treatment Panel III criteria [4]. Metabolic syndrome was retained if 3 or more of the following elements were confirmed: waist circumference  $\geq 80$  cm, high blood pressure [systolic blood pressure (SBP)  $\geq 130$  mmHg or diastolic blood pressure (DBP)  $\geq 85$  mmHg] or hypertension history, high-density lipoprotein cholesterol (HDL-C)  $< 50$  mg/dl, triglycerides (TG)  $\geq 150$  mg/dl, fasting plasma glucose (FPG)  $\geq 100$  mg/dl or a history of diabetes mellitus.

Bone mineral density was measured at the lumbar spine in region L1–L4 and the femoral neck using dual-energy X-ray absorptiometry (Lunar Prodigy vision; GE Healthcare, Madison, WI, USA). Bone density was expressed in absolute BMD values (g/cm<sup>2</sup>) and *T*-scores. Osteoporosis was defined using the World Health Organization (WHO) classification system as *T*-score  $\leq -2.5$  standard deviation (SD) of either the lumbar spine or

femoral neck with the application of the Moroccan female normative data [9, 10]. All our patients had osteoporosis with a *T*-score  $\leq -2.5$  SD.

Other information, including age, educational level (illiterate, primary, secondary, university level), occupation (employed, housewife), matrimonial status (married, divorced, single, widowed), physical activity (all movements produced by the musculoskeletal system with energy consumption including leisure time, work, and domestic activities [yes/no]), monthly household income (less than € 250, € 250–300, more than € 300 €) history of diabetes and hypertension, was also assessed. The body mass index (BMI) was obtained by dividing weight [kg] by height [m<sup>2</sup>]. Waist circumferences were measured in the horizontal plane midway between the lowest rib and iliac crest. The following blood test results were also recorded for each participant: FPG, TG, HDL-C, and bone turnover markers – carboxy-terminal cross-linked telopeptide of type I collagen (CTX) [pg/ml] and osteocalcin [ng/ml].

## Statistical analysis

SPSS Statistics for Windows version 20.0 (IBM, NY, USA) was used to perform statistical calculations. Data are presented using frequencies and percentages for categorical variables and range, mean, and standard deviation for interval variables. The  $\chi^2$  test was used to analyze categorical data. The independent Student's *t* test or Mann-Whitney *U* test was performed to compare continuous variables. Correlations were assessed using Spearman's rank correlation coefficient (*R*). The Kolmogorov-Smirnov test was used to analyze data distribution. The relationships between MetS components and BMD features were analyzed using multiple linear regressions. A *p*-value  $< 0.05$  was considered statistically significant.

## Bioethical standards

In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, the Ethics Committee of Medical University of Rabat approved the study protocol in 2017 (26.09.2017) [11]. Informed consent was obtained from all participants.

## Results

Of the patients, 44% were diagnosed with MetS. Most of the patients were overweight; the mean BMI was  $27.33 \pm 3.86$ . There was no history of smoking or alcohol consumption in any of the patients. The average *T*-score was  $-3.1$  (from  $-3.6$  to  $-2.7$ ) for lumbar spine and  $-1.6$  (from  $-2.1$  to  $-1.1$ ) for femoral neck.

The mean age of patients with and those without MetS was  $63.82 \pm 8.65$  and  $60.39 \pm 7.93$ , respectively;  $p = 0.04$  (Table I). There was no significant difference between the 2 groups regarding BMI, BMD parameters (Table I), and bone turnover markers (Table II). Lumbar spine

BMD correlated significantly with HDL-C ( $r = -0.233$ ;  $p = 0.02$ ). Lumbar spine *T*-score correlated significantly with SBP ( $r = -0.196$ ;  $p = 0.005$ ) and waist circumference ( $r = 0.274$ ;  $p = 0.006$ ). Femoral neck *T*-score correlated with DBP ( $r = -0.218$ ;  $p = 0.02$ ) and waist circumference

**Table I.** Socio-demographic variables of patients and osteoporosis features

Variables	All patients ( <i>n</i> = 100)	Patients without metabolic syndrome ( <i>n</i> = 56)	Patients with metabolic syndrome ( <i>n</i> = 44)	<i>p</i>
Age [years]	61.90 ±8.39	60.39 ±7.93	63.82 ±8.65	0.04
Age of menopause [years]	49.52 ±5.34	49.25 ±5.76	49.86 ±4.80	0.5
Menopause duration [years]	12.38 ±7.77	11.142 ±7.192	13.954 ±8.268	0.07
Number of pregnancies	4 (2–6)	3 (2–6)	4 (1–6)	0.9
Educational level (%)				
Illiterate	64	31 (55.4)	33 (75)	0.2
Primary	20	13 (23.2)	7 (15.9)	
Secondary	11	8 (14.3)	3 (6.8)	
University	5	4 (7.1)	1 (2.3)	
Occupation (%)				
Employed	26	18 (32.1)	8 (18.2)	0.1
Housewife	74	38 (67.9)	36 (81.8)	
Matrimonial status (%)				
Married	58	35 (62.5)	23 (52.3)	0.7
Divorced	5	2 (3.6)	3 (6.8)	
Single	4	2 (3.6)	2 (4.5)	
Widowed	33	17 (30.4)	16 (36.4)	
Monthly household income (%)				
< 250 €	66	36 (64.3)	30 (68.2)	0.4
250–300 €	19	9 (16.1)	10 (22.7)	
> 300 €	15	11 (19.6)	4 (9.1)	
Physical activity (%)	23	11 (19.6)	12 (27.3)	0.3
Height [cm]	154.93 ±6.08	155.59 ±5.43	154.09 ±6.78	0.2
Weight [kg]	65.63 ±9.62	65.57 ±9.81	65.70 ±9.48	0.9
Hip circumference [cm]	101.41 ±9.50	101.64 ±11.10	101.11 ±7.09	0.5
Waist circumference [cm]	94.83 ±9.70	93.62 ±10.66	96.36 ±8.19	0.1
BMI [kg/cm <sup>2</sup> ]	27.33 ±3.86	27.06 ±3.814	27.68 ±3.93	0.4
Normal (< 25)	25	16 (28.6)	9 (20.5)	0.5
Overweight (25–30)	49	27 (48.2)	22 (50)	
Obese (> 30)	26	18 (23.2)	13 (29.5)	
BMD				
Lumbar spine BMD [g/cm <sup>2</sup> ]	0.817 (0.755–0.854)	0.825 (0.762–0.863)	0.815 (0.746–0.850)	0.3
Femoral neck BMD [g/cm <sup>2</sup> ]	0.806 (0.745–0.868)	0.821 (0.769–0.868)	0.791 (0.711–0.868)	0.1
Lumbar spine <i>T</i> -score	–3.1 (from –3.6 to –2.7)	–3.0 (from –3.6 to –2.7)	–3.2 (from –2.7 to –3.6)	0.3
Femoral neck <i>T</i> -score	–1.6 (from –2.1 to –1.1)	–1.6 (from –1.9 to –1.1)	–1.7 (from –2.4 to –1.1)	0.1

Data are presented as mean  $\pm$  standard deviation, median (range), or number (%).

BMD – bone mineral density, BMI – body mass index.

**Table II.** Physical and biochemical characteristics of postmenopausal women with osteoporosis

Variables	All patients (n = 100)	Patients without metabolic syndrome (n = 56)	Patients with metabolic syndrome (n = 44)	p
SBP [mmHg]	131.21 ±21.69	123.18 ±15.30	141.43 ±23.35	< 0.0001
DBP [mmHg]	75.45 ±11.9	71.98 ±8.76	79.86 ±13.87	0.001
HDL-C [mg/dl]	52 (46–59.7)	55 (48–61.7)	48.5 (41.2–54.7)	0.005
TG [mg/dl]	101.5 (80.5–133.2)	96.5 (77.2–115.7)	117.5 (88.2–154)	0.002
FBG [mg/dl]	88 (80.2–99.7)	83 (73–89)	96 (83–118)	< 0.0001
MetS components				
Waist circumference (≥ 88 cm)	98 (98)	54 (96.4)	44 (100)	0.2
Hyperglycemia (≥ 110 mg/dl)	24 (24)	6 (10.7)	18 (41.9)	< 0.0001
Hypertension (≥ 130/85 mmHg)	36 (36)	8 (14.3)	28 (63.6)	< 0.0001
Hypertriglyceridemia (≥ 150 mg/dl)	14 (14)	1 (1.7)	13 (29.5)	< 0.0001
Hypo HDL-C (≤ 50 mg/dl)	43 (43)	16 (28.6)	27 (61.4)	0.001
Bone turnover markers				
Serum CTX [pg/ml]	274.67 ±148.49	254.35 ±131.64	302.63 ±166.59	0.1
Serum osteocalcin [ng/ml]	18.24 ±5.77	18.21 ±5.50	18.27 ±6.18	0.9

Data are presented as number (%), median (range), or mean ± standard deviation.

CTX – C-terminal telopeptide of type I collagen, DBP – diastolic blood pressure, FBG – fasting blood glucose, HDL – high-density lipoprotein cholesterol, SBP – systolic blood pressure, TG – triglycerides.

**Table III.** Univariate analysis of the relationship between metabolic syndrome components and bone mineral density and turnover markers in postmenopausal women with osteoporosis

	SBP	DBP	Waist circumference	HDL-C	TG	FBG
Lumbar spine BMD						
Spearman's R	–0.188	–0.051	0.169	0.198	0.087	–0.075
p	0.06	0.60	0.09	0.04	0.30	0.40
Femoral neck BMD						
Spearman's R	–0.044	–0.136	0.130	–0.015	–0.036	1.187
p	0.60	0.10	0.20	0.80	0.70	0.06
Lumbar spine T-score						
Spearman's R	–0.196	–0.035	0.274	–0.233	0.131	–0.097
p	0.05	0.70	0.006	0.02	0.10	0.30
Femoral neck T-score						
Spearman's R	–0.025	–0.218	0.294	0.016	0.022	–0.149
p	0.80	0.02	0.003	0.80	0.80	0.10
CTX						
Spearman's R	–0.243	–0.029	–0.034	–0.238	0.156	0.120
p	0.01	0.7	0.7	0.02	0.1	0.2
Osteocalcin						
Spearman's R	–0.091	0.087	–0.036	–0.199	0.085	–0.238
p	0.30	0.30	0.70	0.04	0.40	0.01

BMD – bone mineral density, CTX – carboxy-terminal telopeptide of type I collagen, DBP – diastolic blood pressure, FBG – fasting blood glucose, HDL-C – high-density lipoprotein cholesterol, SBP – systolic blood pressure, TG – triglycerides.

**Table IV.** Multivariate linear regression with bone mineral density and turnover markers as dependent variables and metabolic syndrome risk factors as independent variables

Variable	$\beta$ (t)	SE	95% CI	<i>p</i>
Age				
Lumbar spine BMD	-2.120 (-2.087)	0.001	From -0.003 to 0	0.04
Femoral neck BMD	-2.710 (-2.649)	0.001	From -0.006 to -0.001	0.01
Lumbar spine <i>T</i> -score	-0.227 (-2.252)	0.007	From -0.029 to -0.002	0.02
Femoral neck <i>T</i> -score	-0.371 (-3.882)	0.009	From -0.052 to -0.017	< 0.001
CTX	-0.172 (-1.646)	1.835	From -6.668 to 0.627	0.1
Osteocalcin	0.032 (0.294)	0.075	From -0.126 to 0.170	0.7
Waist circumference				
Lumbar spine BMD	0.253 (2.632)	0.001	From 0.0001 to 0.0003	0.001
Femoral neck BMD	0.253 (2.638)	0.001	From 0.001 to 0.005	0.01
Lumbar spine <i>T</i> -score	0.258 (2.713)	0.006	From 0.004 to 0.027	0.008
Femoral neck <i>T</i> -score	0.282 (3.128)	0.007	From 0.008 to 0.037	0.002
CTX	-0.042 (-0.429)	1.497	From -3.619 to 2.334	0.6
Osteocalcin	-0.087 (-0.860)	0.061	From -0.174 to 0.069	0.3
SBP				
Lumbar spine BMD	-0.112 (2.632)	0.0001	From 0.0001 to 0.0003	0.01
Femoral neck BMD	0.016 (0.113)	0.001	From -0.001 to 0.001	0.8
Lumbar spine <i>T</i> -score	-0.128 (-1.072)	0.003	From -0.010 to 0.003	0.2
Femoral neck <i>T</i> -score	0.217 (1.913)	0.004	From 0 to 0.016	0.06
CTX	-0.323 (-2.598)	0.849	From -3.894 to -0.518	0.01
Osteocalcin	-0.169 (-1.320)	0.034	From -0.112 to 0.023	0.1
DBP				
Lumbar spine BMD	-0.035 (-0.299)	0.001	From -0.002 to 0.001	0.7
Femoral neck BMD	-0.100 (-0.850)	0.001	From -0.003 to 0.001	0.3
Lumbar spine <i>T</i> -score	-0.016 (-0.141)	0.006	From -0.012 to 0.010	0.8
Femoral neck <i>T</i> -score	-0.245 (-2.233)	0.007	From -0.030 to -0.002	0.02
CTX	0.032 (0.275)	1.468	From -2.513 to 3.322	0.7
Osteocalcin	0.185 (1.521)	0.059	From -0.028 to 0.208	0.1
FBG				
Lumbar spine BMD	-0.109 (-1.012)	0.016	From -0.047 to 0.015	0.3
Femoral neck BMD	-0.079 (-0.736)	0.024	From -0.067 to 0.031	0.4
Lumbar spine <i>T</i> -score	-0.101 (-0.945)	0.134	From -0.393 to 0.140	0.3
Femoral neck <i>T</i> -score	-0.016 (-0.158)	0.170	From -0.364 to 0.311	0.8
CTX	0.172 (1.513)	35.918	From -17.068 to 125.736	0.1
Osteocalcin	-0.254 (-2.172)	1.454	From -6.049 to -0.269	0.03
HDL-C				
Lumbar spine BMD	0.036 (0.349)	0.026	From -0.042 to 0.060	0.7
Femoral neck BMD	-0.009 (-0.089)	0.040	From -0.084 to 0.076	0.9
Lumbar spine <i>T</i> -score	0.0001 (0.003)	0.221	From -0.438 to 0.039	0.9
Femoral neck <i>T</i> -score	0.0091 (0.934)	0.280	From -0.294 to 0.816	0.3
CTX	-0.125 (-1.056)	154.206	From -469.467 to 143.635	0.2
Osteocalcin	-0.110 (-0.916)	6.089	From -17.677 to 6.521	0.3

Table IV. Cont.

Variable	$\beta$ (t)	SE	95% CI	p
TG				
Lumbar spine BMD	0.135 (1.230)	0.018	From -0.014 to 0.059	0.2
Femoral neck BMD	-0.057 (-0.460)	0.029	From -0.071 to 0.044	0.6
Lumbar spine T-score	0.129 (1.181)	0.158	From -0.127 to 0.499	0.2
Femoral neck T-score	0.158 (1.526)	0.200	From -0.092 to 0.701	0.1
CTX	0.098 (0.889)	42.381	From -46.575 to 121.925	0.3
Osteocalcin	0.005 (0.042)	1.721	From -3.347 to 3.492	0.9
MetS				
Lumbar spine BMD	0.003 (0.023)	0.016	From -0.032 to 0.033	0.9
Femoral neck BMD	-0.019 (-0.154)	0.026	From -0.055 to 0.047	0.8
Lumbar spine T-score	0.017 (0.143)	0.139	From -0.257 to 0.297	0.8
Femoral neck T-score	-0.125 (-1.095)	0.177	From -0.544 to 0.158	0.2
CTX	0.178 (1.318)	40.313	From -27.014 to 133.265	0.1
Osteocalcin	0.065 (0.483)	1.574	From -2.367 to 3.886	0.6

BMD – bone mineral density, CI – confidence interval, CTX – carboxy-terminal telopeptide of type I collagen, DBP – diastolic blood pressure, FBG – fasting blood glucose, HDL-C – high-density lipoprotein cholesterol, MetS – metabolic syndrome, SBP – systolic blood pressure, SE – standard error, TG – triglycerides.

$R^2$  (lumbar spine BMD) = 0.427,  $R^2$  (femoral neck BMD) = 0.425,  $R^2$  (lumbar spine T-score) = 0.441,  $R^2$  (femoral neck T-score) = 0.527,  $R^2$  (CTX) = 0.454,  $R^2$  (osteocalcin) = 0.339.

( $r = 0.294$ ;  $p = 0.003$ ; Table III). Osteocalcin inversely correlated with HDL-C and FPG ( $r = -0.199$ ;  $p = 0.04$  and  $r = -0.238$ ;  $p = 0.01$ , respectively; Table III). C-Terminal telopeptide of type I collagen negatively correlated with HDL-C and SBP ( $r = -0.238$ ;  $p = 0.02$  and  $r = -0.243$ ;  $p = 0.01$  respectively; Table III). In linear regression, lumbar spine BMD was significantly associated with age ( $\beta = -2.120$ ,  $p = 0.04$ ), SBP ( $\beta = -0.112$ ,  $p = 0.01$ ), and waist circumference ( $\beta = 0.253$ ,  $p = 0.001$ ; Table IV). Femoral neck BMD was significantly associated with age ( $\beta = -0.227$ ,  $p = 0.02$ ) and waist circumference ( $\beta = 0.258$ ,  $p = 0.008$ ). Femoral neck T-score was negatively associated with DBP ( $-0.245$ ,  $p = 0.02$ ; Table IV). No association was found between HDL-C, TG, and BMD. Glycemia ( $\beta = -0.245$ ,  $p = 0.03$ ) and SBP ( $\beta = -0.323$ ,  $p = 0.01$ ) remain the significant MetS components influencing osteocalcin and CTx, respectively (Table IV).

## Discussion

The prevalence of MetS in postmenopausal women with osteoporosis in our study was found to be 44%. Age, blood pressure, and waist circumference were significantly associated with BMD. To our knowledge, although there are numerous studies that define the prevalence of MetS in menopausal transition and postmenopausal women, there is a lack, both nationally and internationally, of studies focusing on the prevalence of MetS in postmenopausal women with osteoporosis. Of the patients,

25% of the global population is affected by MetS, highlighting its important public health challenge, especially in elderly patients with fragility fracture risk [2]. Metabolic syndrome has a higher prevalence in postmenopausal Moroccan women (34.9%) than that reported for the general population (26.3%) [12]. An elevated prevalence of MetS estimated at 74.18% was reported in a recent study, in a sample of postmenopausal Moroccan women [13]. Metabolic syndrome prevalence is considerably high in menopausal transition (62.59%) [14]. Moreover, MetS is more prevalent in elderly women and can reach 64.4% [15]. In Mexican postmenopausal women, the prevalence of MetS was 57.2% [16]. In elderly Taiwanese, 33.0% of participants with osteoporosis had MetS [17]. The prevalence of MetS was 48.5% in Korean postmenopausal women [6]. The difference in prevalence can be explained by variety in lifestyle, diet, and social habits and behavior, which can be associated with an increased prevalence of metabolic syndrome, making it a public health problem and a major risk for cardiovascular diseases [2, 3]. In our study, older age was associated with MetS and increased bone loss. In postmenopausal women, the decrease in estrogen level leads to altered body composition and fat distribution, with reduced muscle mass and bone mass. These modifications are associated with the development of MetS. Metabolic syndrome risk factors are diverse and include dyslipidemia, insulin resistance, abdominal obesity, and

elevated blood pressure in a pro-inflammatory state [11]. In our Moroccan context, poor dietary habits (higher carbohydrate intake, poorly planned vegetarian diet, low intake of calcium), sedentary lifestyle, and lack of physical activity lead to metabolic disorders. Moreover, aging, health behaviors (smoking, alcohol intake, nutrient deficiency, low physical activity), clothing habits, as well as endocrine and genetic factors aggravate MetS and induce bone mass decrease. Considering all these risk factors, aging patients may suffer from concomitant MetS and osteoporosis [18].

The present study results of the positive association of MetS with BMD seem to be driven by the component of visceral obesity. Edelstein et al. observed that all BMD sites showed a favorable association with abdominal obesity [19]. The association between MetS and bone density in our study aligns with previous findings. We found that waist circumference was positively associated with BMD, which reflects the effects of mechanical loading on the skeletal system. Kim and Kim [6] and Fodor et al. [8] found that osteoporosis risk was lower with higher waist circumference and that significant abdominal fat was associated with increased bone density. El Maghraoui et al. [15] and Chin et al. [20] reported that women with MetS had higher BMD. Also, MetS was found to have a beneficial influence on BMD of the spine in the meta-analysis of Xue et al. [21]. In older people, obesity is commonly perceived as a protective element against bone mass decrease. Studies have suggested that in spite of increasing risk of other metabolic chronic disorders, obesity, through improving the mechanical loading on bones, boosts the bone metabolism [22]. Obesity is also associated with hyperinsulinemia which leads to increased bone formation. Furthermore, in obese individuals, estrogen is synthesized in adipocytes. Adipocytes enhance BMD by converting androgens to  $17\beta$ -estradiol, the most potent estrogen [23]. Likewise, Prestwood et al. [24] demonstrated that low-dose  $17\beta$ -estradiol medication increased hip, spine, and wrist BMD and also reduced turnover markers of aged women (> 65 years). However, other contradictory results exist. Von Muhlen et al. [5] observed that MetS was linked to lower BMD. Moreover, Lin et al. [15] reported that MetS was not associated with higher BMD in Taiwanese women. Similar results were reported by Terzi et al. [25]. Furthermore, MetS was not associated with reduced osteoporosis risk in women, in a recent meta-analysis and systematic review [26]. Likewise, Salas et al. [16] reported that MetS components were associated with bone loss and increased osteopenia or osteoporosis risk. Later investigations revealed that excess visceral fat mass due to obesity increases osteoporosis risk [27]. Adipocyte hypertrophy and hyperplasia enhance the adi-

pose tissue growth and lead consequently to obesity. Adipocytes and osteoblasts result both from the differentiation of the multipotent mesenchymal stem cells in the marrow, the common progenitor for fat and bone cells. Various signaling pathways modulate the balance of adipocyte and osteoblast differentiation. In addition to energy storage, adipose tissue is a source of pro-inflammatory cytokines such as tumor necrosis factor and interleukin. Osteoclast differentiation and bone resorption are induced through the activation of receptor activator of NF- $\kappa$ B ligand (RANKL)/receptor activator of NF- $\kappa$ B (RANK)/osteoprotegerin pathway. Some studies suggest that minor chronic inflammation adversely impacts bone strength [27]. Even if notable bone health and density are associated with obesity, its unfavorable effects on bone quality may damage bone health [28]. Nevertheless, adverse effects of obesity on bone structure and function occurring in early age may persist into older age. It has been suggested that insulin resistance and inflammation, considered as common obesity metabolic complications, are associated with impaired metabolic health and poor BMD [28]. Regardless of associated higher BMD and obesity, patients with type 2 diabetes have increased fracture risk [29]. However, lifestyle factors or differentiation of stem cells towards adipocytes at the expense of osteoblasts, due to poor metabolic health, may lead to visceral fat accumulation and bone structure and function decline [28, 29]. In addition, the fracture risk associated with visceral adiposity has not been examined [29]. This paradoxical relationship between obesity and bone mass may be interpreted by the various actions of obesity on bones [22]. In fact, central obesity, as a component of MetS reflected by higher waist circumference, is associated with significant  $17\beta$ -estradiol levels, which may inhibit bone resorption and stimulate bone formation. In parallel, visceral fat as an origin of pro-inflammatory mediators may lead to lower BMD [22].

Among MetS components, SBP and DBP correlated negatively with BMD. Similarly to our findings, hypertension increases the risk of lower BMD [1]. However, the effect of increased blood pressure on bone health is a controversial issue with contradictory reports. In a recent systematic review and meta-analysis [30], blood pressure augmented osteoporosis risk by enhancing calcium excretion, elevating parathyroid hormone level and consequently increasing bone resorption [31]. In the findings of Kaplan et al. [32], no relationship was established between blood pressure and BMD in postmenopausal women. Contradictorily, SBP correlated positively with total hip BMD in the report of Chin et al. [20]. It has been suggested that the positive association with BMD and

increased SBP is attributable to increased peripheral vascular resistance due to increased body size [20, 31].

We found in the univariate model that higher HDL-C level was associated with a higher spine BMD, which could be mediated by sex hormones, responsible for lipid regulation and bone formation. A protective effect of bone health by HDL-C was suggested. Oxidized low-density lipoprotein cholesterol (LDL-C) can induce osteoblast apoptosis and increase osteoclast survival, and HDL-C can inhibit LDL-C oxidation [33]. Similarly, Muka et al. [34] and Jeon et al. [35] found that HDL-C was positively associated with lumbar spine BMD in postmenopausal women. However, an inverse association between HDL-C and BMD was reported in postmenopausal Korean women [36].

Other components of MetS, such as fasting blood glucose and TG levels, were not associated with BMD in this study. Similar findings were reported by Chin et al. [20].

However, a positive relationship between BMD and TG in women was reported. Triglycerides increase body weight by being stored in adipocytes and are implicated in bone metabolism by being transported by apolipoprotein E [37].

Given this controversy in the relationship between components of MetS and BMD, we focused on analyzing the circulating bone turnover markers (C-terminal telopeptide of type I collagen, a bone-resorption marker [CTX] and osteocalcin) to determine possible associations with MetS components. We used the reference markers of bone turnover, especially osteocalcin secreted by osteoblasts and CTX, which is released by osteoclasts [38]. In our study, osteocalcin inversely correlated with HDL-C and FPG, whereas CTX negatively correlated with HDL-C and SBP. Osteocalcin level was lower in patients with impaired fasting glucose, which supports other authors' findings [39]. Significantly, osteocalcin and CTX were lower in metabolic syndrome patients in the report of Terzi et al. [25], and lower osteocalcin levels in obese women with impaired fasting glucose levels were reported by García-Martín et al. [40].

Osteocalcin is implicated in calcium homeostasis, bone mineralization, glucose, and fat regulation [41]. Osteocalcin enhances skeletal muscle and adipocyte sensitivity to insulin, consequently abrogating the deleterious effects of a high fat diet on bone metabolism and improving glucose metabolism. Consequently, to predict the increased diabetes risk in postmenopausal women, the authors suggested a potential utility of osteocalcin dosage [41].

The decrease in CTX-1 in patients with MetS was associated with dyslipidemia and systemic inflammation [41]. Interestingly, the data on the influence of MetS in bone turnover markers are also conflicting [8, 42]. In

other research, bone turnover markers were not significantly influenced by any of the MetS components [8].

## Study limitations

However, some limitations of our study must be addressed. Firstly, we assessed BMD in two bone sites, but the relationship between MetS and BMD might differ at other sites. Secondly, regarding the observational nature of the study, a cause and effect relationship between MetS and BMD cannot be established. Thirdly, our selected patients were ambulatory and volunteers, which may affect the Moroccan population representation. Nevertheless, our patients come from many regions of Morocco, so they can be considered a relatively representative sample of Moroccan women. A comprehensive determination of dietary intake (calcium, vitamin D) and the dosage of 25 (OH) vitamin D<sub>3</sub> and C-reactive protein levels was not performed. Also, pro-inflammatory cytokines, adipokines, sex hormones, as well as bone geometry and structure, were not evaluated. Therefore, further pathophysiological investigations are required to confirm our results.

## Conclusions

The study highlights the prevalence of MetS in postmenopausal women in Morocco, as a middle-income developing country, and suggests a positive association between MetS and BMD, prominently due to abdominal obesity. Waist circumference was the most predominant MetS component related to increased BMD. Abdominal obesity, reflected by waist circumference, is associated with significant estrogen levels, reputed to be a bone remodeling inhibitor. In parallel, visceral fat as an origin of pro-inflammatory mediators may lead to lower BMD. Lifestyle, diet, and social habits and behavior should be considered in analyzing the association between MetS and bone mass. The development of therapeutic interventions for both diseases must be preceded by a better understanding of the association between MetS and osteoporosis. Consequently, the effect of intentional weight loss on bone density and quality must be examined. Further studies using carefully designed *in vivo* animal models mimicking a MetS-inducing diet are required to clarify the association between visceral fat, bone density and strength, and fracture risk.

## Disclosures

*Conflict of interest:* The authors declare no conflict of interest.

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*Ethics approval:* The study protocol was approved by the Ethics Committee of Rabat University Mohamed V in 2017 (26.09.2017).

*Data availability:* The data that support the findings of this study are available on request from the corresponding author (B.M.).

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