European Review for Medical and Pharmacological Sciences 2022; 26: 7616-7622

Associations of coronary plaque characteristics and coronary calcification with bone mineral density in postmenopausal women

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Abstract. – OBJECTIVE: We aimed at investigating the association of postmenopausal osteoporosis in different measurement locations, with the coronary plaque burden and morphology detected by coronary computed tomography angiography (CCTA).

PATIENTS AND METHODS: We analyzed a total of 223 postmenopausal women who had undergone both dual-energy X-ray absorptiometry (DXA) and CCTA. Coronary plaque characteristics were analyzed using CCTA.

RESULTS: The number of burdens was higher in the osteoporosis/osteopenia group of patients than in the normal group. Agatston score and BMI were not significantly different between the two groups. T-score femur and bone mineral density (BMD) femur were higher in patients with severe coronary artery disease (CAD as compared to those with mild CAD (p=0.036 and p=0.049, respectively), whereas T-score lumbar and BMD lumbar were not significantly different. Non-calcified/mixed plaque burden was an independent predictor of osteopenia/osteoporosis (OR: 1.396, 95% CI 1.007-1.934; p=0.045) together with age (OR: 1.053, 95% CI 1.015-1.093; p=0.006).

CONCLUSIONS: Non-calcified/mixed plaque burden was significantly and independently associated with osteoporosis/osteopenia at femoral neck but not at lumbar spine. Osteopenia/osteoporosis was not significantly associated with CAC.

Key Words:
Osteopenia, Osteoporosis, Coronary plaque characteristic, Postmenopausal women.

Introduction

Coronary artery disease (CAD) is the main cause of mortality in women, with increasing prevalence after menopause[1]. Osteoporosis (OP) is a systemic skeletal disease that is characterized by low bone mass and the most common type of OP is postmenopausal[2,3]. Endogenous estrogens have protective effect against both CAD and OP[4]. Decrease in estrogen affects bone metabolism through increasing osteoclast resorption activity, resulting in osteoporosis. Risk factors of coronary atherosclerosis (CA), such as inflammation, dyslipidemia, menopause, hypertension, smoking, and diabetes mellitus, are also linked to OP[5,6]. Endothelial dysfunction plays a key role in development of atherosclerosis and is also an important regulator of bone metabolism[7].

Coronary computed tomography angiography (CCTA) allows accurate evaluation of CA, including lesion location, severity, and also provides additional information about plaque morphology[8]. Two recent studies[9,10] found a significant association between postmenopausal OP and CAD detected by CCTA. Moreover, a recent study[11] found that women who have higher risk coronary plaque types detected by CCTA than men suggest that distinguished coronary plaque analysis may improve the risk stratification for both sexes. Recently, Wang et al[12] reported that femoral neck bone mineral density (BMD) may predict the risk of CAD better than the lumbar spine BMD. However, the association between CAD and postmenopausal OP has been previously determined, while the association between postmenopausal OP and coronary plaque characteristics has not yet been studied. Therefore, we aimed at investigating the association of postmenopausal OP different measurement locations, with the coronary plaque burden and morphology detected by CCTA.

Patients and Methods

Study Population

The study was approved by the Research Ethics Board of Muğla Sitki Koçman University

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School of Medicine in Muğla, Turkey (approval number: 200213). Patients who underwent CCTA between March 2018 and January 2021 were considered for possible inclusion in the study. Patients admitted to cardiology ward or referred to our cardiology outpatient clinics with chest pain or any symptoms related to stable CAD were included in the study. The other inclusion criterion for our study was the evaluation of asymptomatic patients who had intermediate to high-risk score, according to Framingham risk assessment. Patients with previous coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, acute coronary syndrome (ACS), concomitant inflammatory diseases, and neoplastic diseases were excluded. CCTA was performed because of symptoms related to stable CAD or evaluation of asymptomatic patients who had intermediate to high Framingham risk score.

Image Analysis

All scans were interpreted by using the three-dimensional Syngo.via workstation (dual-source CT, Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany) by a pair of level 3 certified cardiologist and radiologist who were blinded to the individual's clinical findings. The final CCTA diagnosis was determined by consensus interpretation. The identification of plaque and stenosis, as well as the number of plaques per segment, was determined by highly trained cardiologist and radiologist, as proposed by the modified American Heart Association classification[13].

Coronary artery calcium (CAC) score was measured by means of Agatston method[14]. The Agatston score was computed as the integral (sum) of all Hounsfield values in a lesion multiplied by the voxel volume in mm^3. Plaques were defined as calcified when containing calcified tissue involving ≥ 50% of the plaque area (density > 130 Hounsfield units), calcified plaque (CP) and non-calcified plaque (NCP) when containing no calcification. Plaques having both calcified (comprising < 50% of the plaque) and non-calcified elements within a single plaque were categorized as mixed plaque (MP). The total plaque burden, total CP burden and total NCP/MP burden were calculated for each patient. Plaque burden, CP burden, and NCP burden were measured by summing the number of coronary artery segments that possessed each respective plaque type. The NCP/MP burden which are more vulnerable than CP burden were calculated together. The presence of less than 50% of luminal narrowing plaque during the CCTA examination was defined as non-obstructive coronary atherosclerosis (NOCA). The presence of 50% or more luminal of narrowing plaque during the CCTA examination was defined as obstructive CAD.

Bone mineral density (BMD) of the left femoral neck and lumbar spine (L1-L4) bone densitometry was measured using a dual-energy X-ray absorptiometry using a QDR 4500A fan beam bone densitometer (Bedford, MA, USA) according to the manufacturer's instructions within the previous 12 months. T-score was calculated using Hologic reference databases. T-scores were categorized into three groups, based on the World Health Organization (WHO) criteria for diagnosing osteoporosis: normal BMD (T-score ≥ -1 SD), osteopenia (-1 SD > T > -2.5 SD), and osteoporosis (T-score ≤ -2.5 SD).

Statistical Analysis

All analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Comparison of parametric values between the two groups was performed with an independent samples *t*-test. Comparisons of nonparametric values between the two groups were performed with the Mann-Whitney U test. Categorical variables were compared by the Chi-squared test. The study group was divided into 3 subgroups based on the complexity of CAD. We used Kruskal-Wallis' test to compare BMD and study population characteristics in groups, according to 3 subgroups based on the CAD complexity. Variables with a *p*-value < 0.1 determined by univariate analysis were included in the backward stepwise multivariate logistic regression analysis model. Binary logistic regression analysis was used to assess the predictors of the postmenopausal OP**.** A two-tailed *p*-value < 0.05 was considered statistically significant.

Results

Among the 223 patients, 75 patients had osteopenia or osteoporosis. Detailed analysis of the data between two groups is given in Table I. Patients with osteoporosis or osteopenia were older than the normal group. The number of NCP/MP burden was higher in the osteoporosis or osteopenia group of patients than the normal group. Patients with osteoporosis or osteopenia had a higher prevalence of hypertension. Agat-

Table I. Characteristics of the study population.

	Normal (n = 148)	Osteopenia + Osteoporosis (n = 75)	*p*-value
HT (%)	75 (50.6)	48 (64)	0.031
Smoking (%)	8 (5.4)	4 (5.3)	0.634
Age (years)	61.1 ± 8.6	65.9 ± 8.6	< 0.001
CAC score, mean ± SD	60.59 ± 181.15	69.92 ± 175.31	0.711
Plaques	1.34 ± 2.05	1.87 ± 1.98	0.069
NCP burden mean ± SD	0.29 ± 0.62	0.45 ± 0.68	0.075
CP burden mean ± SD	0.80 ± 0.16	0.92 ± 1.32	0.571
MP burden mean ± SD	0.24 ± 0.49	0.52 ± 0.64	0.001
T-score femur neck	-0.125 ± 0.905	-1.268 ± 0.888	< 0.001
BMD femur neck	1.0132 ± 0.110	0.8036 ± 0.072	< 0.001
T-score lumbar spine	-1.138 ± 1.238	-2.080 ± 1.196	< 0.001
BMD lumbar spine	0.9387 ± 0.151	0.8036 ± 0.120	< 0.001
25(OH)D (ng/ml)	23.26 ± 11.2	22.26 ± 10.1	0.508
WBC (×10^3/µL)	7.29 ± 1.9	6.82 ± 1.8	0.079
Hemoglobin (g/dl)	12.8 ± 1.2	12.5 ± 1.3	0.058
Platelet (×10^3/µL)	284.351 ± 71.6	282.513 ± 67.7	0.852
Plateletcrit (%)	0.302 ± 0.06	0.303 ± 0.65	0.964
RDW-SD (fL)	42.16 ± 3.4	43.07 ± 6.1	0.160
TC (mg/dl)	206.3 ± 43.3	218.8 ± 49.1	0.058
LDL-C (mg/dl)	119.4 ± 37.0	129.51 ± 44.0	0.079
HDL-C (mg/dl)	54.89 ± 13.3	57.93 ± 17.3	0.155
TG (mg/dl)	162.25 ± 108.5	156.15 ± 69.8	0.616
FPG (mg/dl)	107.48 ± 28.4	110.59 ± 40.0	0.505
Urea (mg/dl)	29.24 ± 9.80	32.33 ± 14.0	0.058
Creatinine (mg/dl)	0.724 ± 0.12	0.874 ± 1.28	0.162
Uric acid (mg/dl)	4.78 ± 1.0	5.03 ± 1.2	0.146
Ferritin (ng/ml)	43.28 ± 39.1	58.28 ± 50.9	0.019
Calcium (mg/dl)	9.49 ± 0.5	9.47 ± 0.5	0.741
BMI (kg/m^2)	31.5 ± 6.0	30.6 ± 5.2	0.287
NCP/MP burden mean ± SD	0.533 ± 0.86	0.973 ± 0.95	0.001

BMD, bone mineral density; BMI, body mass index; CAC, coronary artery calcium; CP: calcified plaque; FPG, Fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HT, Hypertension; LDL-C, low-density lipoprotein cholesterol; NCP, non-calcified plaque; MP: mixed plaque; RDW-SD, red blood cell distribution width standard deviation; RDW- CV, red blood cell distribution width coefficient of variation; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

ston score and body mass index (BMI) were not significantly different between the two groups. Serum fasting blood glucose, TC, triglycerides (TG), LDL-C, hemoglobin A1c, hemoglobin, white blood cell (WBC) counts, creatinine and uric acid levels were not significantly different.

We divided the study population into 3 subgroups according to tertiles of CAD severity. Among the 223 participants, 114 patients had almost normal coronary arteries, 60 had NOCA (< 50% luminal diameter narrowing) and 49 patients had obstructive CAD (≥ 50% luminal diameter narrowing), as detected by CCTA (Table II). Patients with severe CAD more commonly have a history of hypertension and diabetes mellitus. Similarly, serum fasting blood glucose, TG, RDW and hs-CRP values were higher in the severe CAD patients, whereas HDL-C and creatinine were not significantly different between three groups. Furthermore, CP, NCP, MP burden and Agatston score were higher in the severe CAD patients. T-score femur and BMD femur were higher in the severe CAD patients ($p = 0.036$ and $p = 0.003$, respectively), whereas T-score lumbar and BMD lumbar were not significantly different.

The NCP/MP burden was positively correlated with age (r = 0.38; $p < 0.001$), creatinine (r = 0.19; $p = 0.005$), uric acid (r = 0.16; $p = 0.020$), BMI (r = 0.13; $p = 0.043$) and TG (r = 0.15; $p = 0.028$) and was negatively correlated with HDL-C (r = - 0.14; $p = 0.033$). There was a weak negative correlation between NCP/MP burden and T-score femur (r = - 0.15; $p = 0.025$) and BMD femur (r = - 0.14; $p = 0.041$) (Figure 1A, 1B). No significant correlation was detected between NCP/MP burden and T-score lumbar and BMD lumbar.

Table II. Characteristics of the population according to CAD severity.

	Normal (n = 114)	NOCA (n = 60)	Obstructive CAD (n = 49)	*p*-value
HT (%)	49 (42.9)	38 (63.3)	36 (73.4)	0.001
DM (%)	24 (21)	22 (36.6)	22 (44.8)	0.005
Smoking (%)	7 (6.1)	3 (5)	2 (4)	0.857
Age (years)	58.2 ± 7.4	66.7 ± 7.3	68.3 ± 8.1	< 0.001
CAC score, mean ± SD	0.0 ± 0.0	40.33 ± 82.7	239.84 ± 312.2	< 0.001
NCP burden mean ± SD	0.0 ± 0.0	0.52 ± 0.59	0.92 ± 0.90	<0.001
CP burden mean ± SD	0.0 ± 0.0	1.10 ± 1.36	2.47 ± 2.06	< 0.001
MP burden mean ± SD	0.0 ± 0.0	0.61 ± 0.61	0.78 ± 0.65	< 0.001
T-score femur	-0.34 ± 1.10	-0.71 ± 0.95	-0.71 ± 1.00	0.036
BMD femur	0.973 ± 0.13	0.910 ± 0.14	0.909 ± 0.12	0.003
T-score lumbar	-1.53 ± 1.29	-1.50 ± 1.45	-1.20 ± 1.23	0.341
25(OH)D (ng/ml)	22.36 ± 9.2	23.65 ± 12.2	23.15 ± 12.3	0.746
WBC ($\times 10^3 \mu L$)	7.02 ± 1.9	7.06 ± 1.8	7.49 ± 1.7	0.327
Hemoglobin (g/dl)	12.8 ± 1.2	12.7 ± 1.3	12.6 ± 1.3	0.756
Platelet ($\times 10^3/\mu L$)	286.433 ± 73.01	281.491 ± 73.49	279.530 ± 59.10	0.818
RDW-SD (fL)	41.63 ± 3.0	43.09 ± 5.9	43.68 ± 5.1	0.014
RDW-CV (%)	13.7 ± 1.5	14.1 ± 1.4	14.5 ± 2.0	0.036
TC (mg/dl)	206.6 ± 39.6	219.0 ± 49.9	1209.1 ± 51.9	0.234
LDL-C (mg/dl)	120.2 ± 34.4	133.6 ± 44.1	115.5 ± 43.1	0.040
HDL-C (mg/dl)	58.5 ± 15.8	53.8 ± 12.6	52.4 ± 13.7	0.025
TG (mg/L)	141.9 ± 73.5	158.7 ± 68.3	203.3 ± 149.2	0.001
FPG (mg/dl)	101.3 ± 19.9	114.2 ± 31.1	117.5 ± 50.3	0.004
Urea (mg/dl)	28.2 ± 7.7	32.1 ± 8.9	32.8 ± 18.6	0.021
Creatinine (mg/dl)	0.70 ± 0.1	0.74 ± 0.1	0.97 ± 1.5	0.106
Uric acid (mg/dl)	4.70 ± 1.0	5.05 ± 1.2	5.00 ± 1.1	0.115
Calsium (mg/dl)	9.43 ± 0.42	9.51 ± 0.41	9.57 ± 0.83	0.267
BMI (kg/m^2)	30.8 ± 5.4	31.4 ± 6.76	31.9 ± 5.23	0.532
NCP/MP burden mean ± SD	0.0 ± 0.0	1.13 ± 0.6	1.69 ± 0.9	< 0.001

BMD, bone mineral density; BMI, body mass index; CAD, coronary artery disease; DM, Diabetes Mellitus; FPG, Fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HT, Hypertension; LDL-C, low-density lipoprotein cholesterol; NOCA, non-obstructive coronary atherosclerosis; RDW-SD, red blood cell distribution width standard deviation; RDW- CV, red blood cell distribution width coefficient of variation; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

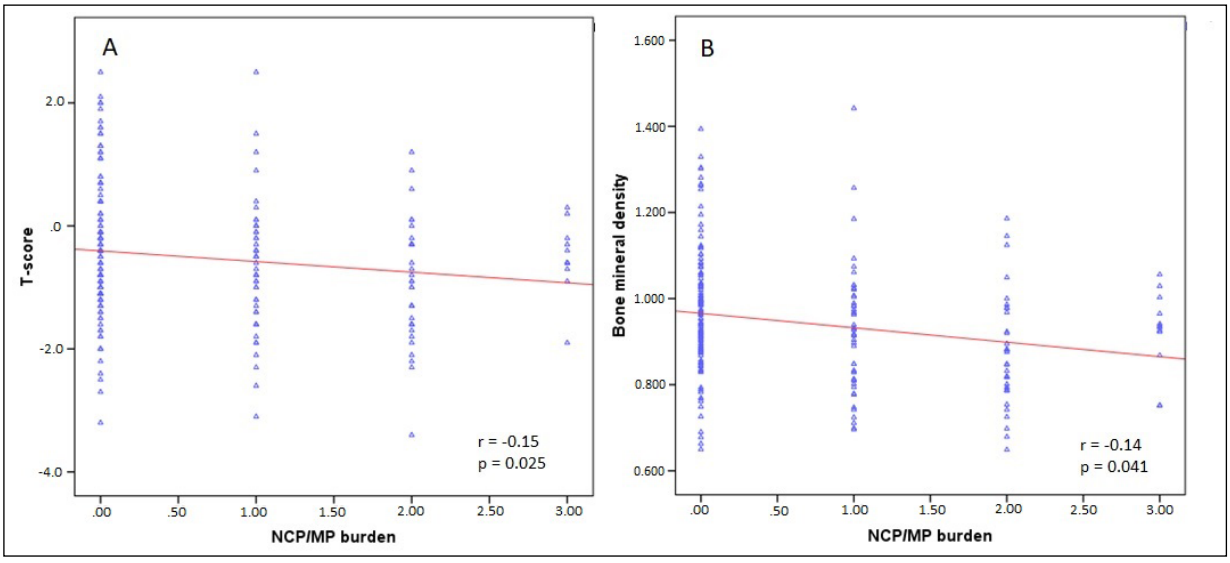

Figure 1. Correlation graph of femoral neck T-score (**A**) and bone mineral density (**B**) with NCP/MP burden.

To further analyze the independent contribution of osteopenia and osteoporosis at the femoral neck to the NCP/MP burden, we performed multiple regression analysis. Table III shows the multivariate predictors of osteopenia/osteoporosis identified by logistic regression. NCP/MP was an independent predictor of osteopenia/osteoporosis (OR: 1.396, 95% CI 1.007-1.934; $p = 0$ .045) together with age (OR: 1.053, 95% CI 1.015-1.093; $p = 0.006$).

Discussion

In our study, we found a significant association between the severity of CAD, as detected by CCTA, and osteopenia or osteoporosis only at the femoral neck. NCP/MP burden was an independent predictor of osteopenia or osteoporosis. CAC was not significantly associated with osteopenia or osteoporosis.

Liu et al[15] investigated the association between low bone mass and change of bone biomarkers carotid and cardiac calcified plaques in Chinese elderly population. Their 5-year prospective study suggested that bone mass density and bone metabolism markers, such as osteoprotegerin (OPG), osteocalcin (OC), and C-terminal cross-linked telopeptide of type I collagen (CTX), were associated with increased risk of carotid and cardiac calcified plaque development. Sex-, age- and/or ethnicity-specific differences may influence the coronary artery plaque composition[11]. Coutinho et al[16] reported that lower arterial compliance was associated with higher percent plaque score detected by CCTA in women, but not in men. Their study suggests that higher ACS mortality in women may be attributed to greater burden of coronary artery plaque in women. Lee et al[10] investigated the association between postmenopausal OP and CAD detected by CCTA. They found a significant association between OP and CAC score and obstructive CAD in asymptomatic postmenopausal women in their study. Arterial stiffness as a marker of subclinical atherosclerosis has been linked with low BMD in postmenopausal women[17-19]. Furthermore, the association between CAD and OP has also been shown in Chinese postmenopausal women[15].

Recently, postmenopausal OP at the femoral neck has been linked with severity of coronary lesions assessed by Gensini score[20]. By contrast, Tekin et al[21] found no significant association between low BMD and CAD in post-menopausal women undergoing coronary angiography. Recently, Wang et al[12] have investigated the relation between different measurement sites of BMD with CAD. They reported that femoral neck BMD may be superior to the lumbar spine BMD for identifying the risk of CAD. Their study suggests that the femoral neck and hip BMD, rather than lumbar spine BMD may be used as a BMD screening site for CAD risk prediction. The femoral neck has the lowest BMD and has not arterial collateral circulation like the vertebra, therefore atherosclerosis in the medial femoral circumflex artery more commonly affects the blood supply of the femoral neck[22]. On the same line with our study, we found a significant inverse association between the severity of CAD and at the femoral neck T-score, but we found no significant association between T-score lumbar and CAD.

OP and coronary atherosclerosis share common pathogenetic mechanisms. MatrixMetalloproteinase 9 (MMP-9), as a regulator of osteoclastogenesis, may also play an important role in development and progression of atherosclerosis[23]. Osteoprotegerin influences both bone resorption and endothelial function by inhibiting osteoclast differentiation, regulating bone remodeling, and protecting endothelial cells against TRAIL-inducedcelldeath[24]. Fibroblast growth factor-23 as a bone-derived hormone, may also play role in CA[25]. Vitamin D known as an essential steroid hormone for calcium absorption and bone mineralization has also been linked with CA and coronary plaque vulnerability[26]. Inflammation plays a key role in the pathophysiology of both in OP and CA[27]. The association between these bone markers and CAD may be possible explanations underlying the progression of atherosclerosis in postmenopausal OP patients.

Several studies[28-33] have investigated the association between BMD and CAC measured by CCTA in postmenopausal women and the results of these studies were inconsistent. Some of these studies[28,29] showed a significant correlation be-

Table III. Multivariate predictors of osteopenia/osteoporosis identified by logistic regression.

	OR	95% CI	*p*-value
Age	1.053	1.015-1.093	0.006
NCP/MP burden	1.396	1.007-1.934	0.045
HT	1.331	0.720-2.458	0.361

CI, confidence interval; HT, Hypertension; OR, odds ratio.

tween BMD and CAC. Chuang et al[28] found no significant association between BMD and CAC, but in their OP group patients BMD in the lumbar spine was independently associated with moderate CAC. By contrast, other studies[30,31] found no significant association between BMD and CAC. Two recent studies[32,33] investigating the association between BMD and CAC reported that lower BMD was significantly associated with higher CAC in women but not in men. In our study we have not found a significant correlation between BMD and CAC. Sex- and/or ethnicity-specific differences may be an explanation for these inconsistent results.

Limitations and Strengths

This study has several limitations. The sample size in our study was relatively small. The NCP/MP burden, which is more vulnerable than CP burden, was calculated together due to small amounts of NCP burden. Our study included only postmenopausal women from Turkey; therefore, the generalizability of our findings to other gender, ages and regions is unknown. Nevertheless, this is the first study that demonstrates an association between postmenopausal OP, and coronary plaque characteristics and utilizes CCTA with an adequate detection of coronary vessels and plaque morphology analyzed by a level 3 certified cardiologist and a level 3 certified radiologist.

Conclusions

NCP/MP burden was independently associated with osteoporosis/osteopenia at femoral neck but not at lumbar spine, suggesting that femoral neck BMD may predict the risk of CAD. Osteopenia/osteoporosis was not significantly associated with CAC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the Research Ethics Board of Muğla Sitki Koçman University School of Medicine in Muğla, Turkey (approval number: 200213).

Funding

None.

Data Availability

Data supporting the findings of this study are available within the paper.

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Informed Consent

The informed consent is not required since this is a retrospective study.

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