Association between mean platelet volume and bone mineral density in postmenopausal women

Cenk Aypak, MD1*, Özlem Türedi, MD1, Mustafa A. Bircan, MD3, Gülnar Civlek, MD2, Mine Araz, MD3

1) Family Medicine Clinic, Diskapi Yıldırım Beyazıt Training and Research Hospital: 06110 Ankara, Turkey
2) Physical Medicine and Rehabilitation Clinic, Ankara Children’s Hematology Oncology Training and Research Hospital, Turkey
3) Division of Nuclear Medicine, Diskapi Yıldırım Beyazıt Training and Research Hospital, Turkey

Abstract. [Purpose] Osteoporosis is an inflammatory disease, and platelets play a critical role in bone remodeling. Mean platelet volume has been shown to be influenced by inflammation. Our aim was to evaluate the relationship between mean platelet volume and bone mineral density in postmenopausal women. [Subjects and Methods] The records of female patients who had been referred to a tertiary hospital for bone mineral density analysis were retrospectively reviewed. [Results] A total of 175 patients (mean age: 61.3 ± 9.0 years) were enrolled. Overall, 72% (126/175) of patients met the criteria for osteoporosis. Mean platelet volume was found to be inversely correlated with body mass index. There was a significant positive correlation between mean platelet volume and femoral neck bone mineral density in our normal weight osteoporotic group, whereas there was a significant negative correlation in our overweight-obese osteoporotic group. The negative correlation between mean platelet volume and femoral neck bone mineral density in the overweight-obese osteoporotic group persisted after adjustment for confounding factors. Multivariate analyses revealed that mean platelet volume was significantly associated with femoral neck bone mineral density in osteoporotic patients in both our normal weight and overweight-obese groups. [Conclusion] Regardless of mechanisms, mean platelet volume might be used as a biomarker for osteoporosis in clinical settings. Key words: Bone mineral density, Mean platelet volume, Osteoporosis

INTRODUCTION

Osteoporosis (OP) is defined as systemic skeletal disease characterized by bone fragility resulting from low bone mass and deterioration of the bone microstructure1-3). OP and cardiovascular diseases (CVD) are major public health concerns in aging populations4, 5). In agreement with accumulating evidence supporting the association of OP with CVD including carotid atherosclerosis, peripheral arterial disease, and stroke, it was postulated that OP is an independent predictor of cardiovascular mortality6, 7).

Emerging evidence has shown that mean platelet volume (MPV), which can be obtained along with routine blood counts, correlates with platelet (PLT) function. MPV has been found to be influenced positively by low-grade inflammation, which has been well documented in hypertension, diabetes, dyslipidemia, insulin resistance, metabolic syndrome, and CVD5). Consequently, some investigators have argued MPV may be used in detection and evaluation of CVD6, 10).

OP is mostly seen in the postmenopausal period and is associated with lowered quality of life11, 12). Aging is a well-known risk factor for OP. MPV was found to be increased with aging in previous studies13). In addition, megakaryocytes are elevated in bone marrow with aging, leading to an imbalance between osteoblastic and osteoclastic functions14, 15). Megakaryocytic...
changes are related to platelet number and size. Furthermore, PLTs were found to have adenosine diphosphate (ADP) and vitamin D receptors, which are important in bone remodeling\(^{16, 17}\). Therefore, it was postulated that PLTs might have a contribution in the pathogenesis of OP.

Although there are studies that have investigated the relation between PLT functions and OP, studies that have investigated the relationship between MPV and OP are limited\(^{18, 19}\). The main limitations of these previous studies was that not excluding patients with conditions affecting PLT functions such as chronic diseases and drug use. Therefore, the aim of this study was to evaluate the relationship between MPV and OP among postmenopausal women.

**SUBJECTS AND METHODS**

The medical records of postmenopausal female patients (n=1,199) who had been clinically referred from polyclinics to nuclear medicine division of a tertiary hospital for bone mineral density (BMD) analysis between May 2014 and October 2014 were retrospectively reviewed. The study was approved by the Ethics and Research Committee for research involving human beings of the institution.

Patients with diagnoses of hematological disorders (n=14), autoimmune diseases (n=19), valvular diseases (n=8), thyroid (n=39) or parathyroid disorders (n=6), diabetes mellitus (n=162), rheumatoid arthritis (n=11), cancer (n=10), or chronic liver (n=16), kidney (n=18) or pulmonary diseases (n=21) were excluded. In addition, patients receiving medical treatment with lipid-lowering agents (n=131), antihypertensive agents (n=298), anticoagulant (n=12) or glucocorticoid drugs (n=14), antiepileptic drugs (n=3), hormone replacement therapy (n=1), PLT function modifying medications (n=86), or other medications known to affect glucose and lipid metabolism (n=9) and patients having white blood cell (WBC) counts of less than 4 × 10^3/μl (n=12) or more than 10 × 10^3/μl (n=38); PLT counts of less than 150 × 10^3/μl (n=9) or more than 400 × 10^3/μl (n=4); or anemia (hemoglobin ≤12 g/dl) (n=46) were excluded. Incompleteness of records (n=37) was another exclusion criterion.

Age, height, weight, body mass index (BMI), lumbar spine BMD (LSBMD), and femoral neck BMD (FNBMD) were noted from records and laboratory tests performed on the day of BMD measurements including complete blood count (CBC), calcium, phosphorus, serum 25 hydroxyvitamin D (25OHD), and intact parathormone (iPTH), and information about utilized drugs was collected from a computerized patient database.

BMI was measured using weight (kg) divided by height squared (m^2). Normal was defined as a BMI between 18.5 kg/m^2 and 25 kg/m^2, and overweight-obesity was defined as BMI≥25 kg/m^2. The patients with OP were divided into groups according to BMI (group 1, normal weight; group 2, overweight-obese).

BMD (g/cm²) was measured at the lumbar spine (L1–L4), femoral neck, and total hip in the anterior-posterior projection using dual-energy x-ray absorptiometry (DXA, QDR Explorer fan-beam X-ray bone mineral densitometer, Hologic, Inc., Bedford, MA, USA). All measurements were taken by the same experienced operator on the same machine using standardized procedures for participant positioning. Daily phantom scans were performed each morning for proper quality control. The BMD data of the patient were compared with the BMD data of the young normal population and an age-matched control group provided by the manufacturer, and T-scores were automatically calculated by the software. Diagnostic classification was based on World Health Organization (WHO) criteria: a BMD T-score ≥−1.0 is normal; >−2.5 and <−1.0 indicates osteopenia; and ≤−2.5 indicates OP. These diagnoses were defined at the site with the lowest T score\(^{20}\).

The CBC is routinely measured in the hospital with a Siemens Healthcare Diagnostic ADVIA 2120i system. CBC samples were measured with potassium-ethylenediaminetetraacetic acid, and then were analyzed one hour after venipuncture. The normal MPV value in the laboratory ranges between 7.0 and 11.1 fl. Calcium and phosphorus were measured using an enzyme method with an autoanalyzer (ADVIA 2400, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). iPTH and 25OHD was measured by immunochemiluminescent assay (Siemens ADVIA Centaur XP, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

Since variables were normally distributed, data were expressed as the mean ± standard deviation (SD). Mean differences were compared with Student’s t-test between groups. Pearson correlation coefficients were computed between BMD and other parameters. Partial correlation analyses between BMD and other variables were adjusted for age, BMI, and PLT. Multiple linear analyses were used to explore independent associations between FNBMD and LSBMD with MPV in osteoporotic patients. Age, weight, and PLT count were included in the model as potential confounders. Data were evaluated using the Statistical Package for Social Sciences (SPSS) 17.0 program for Windows (SPSS Inc., Chicago, IL, USA). All p-values were 2-tailed, and statistical significance was set at p<0.05.

**RESULTS**

A total of 175 (mean age=61.3 ± 9.0) postmenopausal women were enrolled in the study and included in the final analyses. Mean age, time after menopause, and iPTH increased gradually as LSBMD decreased (r=−0.307, p=0.000; r=−316, p=0.000; and r=−0.318, p=0.006, respectively). Mean age and time after menopause increased gradually, while BMI decreased as FNBMD decreased (r=−0.350, p=0.000; r=−305, p=0.000; and r=0.423, p=0.000, respectively).

All of the patients except 12 (6.9%) had osteopenia (n=137) or OP (n=126) according to the diagnostic classification of the WHO. A comparison of clinical and laboratory characteristics of the osteopenic and osteoporotic patients is shown in Table 1.
There was an inverse correlation between MPV and BMI ($r=-0.175, p=0.021$). The patients with OP (n=126) were divided into groups according to BMI [group 1, normal weight (n=33); group 2, overweight-obese (n=93)]. The analyses revealed that there was a significant positive correlation between MPV and FNBMD in the normal weight group, whereas there was a significant negative correlation in the overweight-obese group ($r=0.398, p=0.022$; and $r=-0.237, p=-0.025$, respectively). In addition, there was a positive correlation between MPV and LSBMD in the overweight-obese group ($r=0.222, p=0.038$) (Table 2). After adjusting for age, BMI, and PLT, there was an inverse correlation between FNBMD and MPV in the overweight-obese group ($r=-0.229, p=0.036$).
Multivariate analyses between age, weight, MPV, and BMD revealed that MPV was related to FNBMD in osteoporotic patients in both the normal weight and overweight-obese groups ($r=0.329$, $p=0.039$; and $r=-0.238$, $p=0.238$, respectively) (Table 3).

**DISCUSSION**

This study focused on the association between MPV and OP in postmenopausal women. CVD and OP are the most common diseases and the main causes of morbidity and mortality among postmenopausal women. In spite of sharing many risk factors, OP and CVD are thought to have common pathophysiological pathways (e.g., decreased estrogen and 25OHD and increased age). Individuals with CVD have a higher risk of fragility fractures, and individuals with low BMD have more serious CVD and higher mortality. Postmenopausal women with OP are at increased risk for acute cardiovascular events independent of their age and cardiovascular risk profile. The increase in risk is proportional to the severity of OP at the time of diagnosis. Although the exact mechanism of the relationship between OP and CVD is not yet completely understood, chronic inflammation has been suggested to be the main underlying mechanism. For example, in chronic inflammation, inflammatory cytokines cause a decrease in osteoprotegerin (OPG), and this decrease results in osteoclast activation. OPG is produced by endothelial cells in the cardiovascular system and plays a protective role for the vascular system. Previous research has shown that when used in concentrations inhibiting bone resorption in rats, OPG also prevents vascular calcification.

Previous studies suggested that MPV has an important role as a marker of inflammation, disease activity, and efficacy of anti-inflammatory treatment in several chronic inflammatory disorders. However, data concerning the relationship between MPV and OP are limited. Xue song Li et al. found a negative correlation between MPV and LSBMD and FNBMD. The results of our study were partly in concordance with this report. A negative correlation between MPV and FNBMD was found only in the overweight-obese osteoporotic group. In addition, contradictory to our results, they found a positive correlation between MPV and BMI. In fact, it has been reported that elevated values for MPV are positively correlated with obesity, but the findings of our study were not in agreement with those of previous studies. This discrepancy could be due to age, ethnic, and obesity degree differences among the study populations. Furthermore, it may be mainly due to the failure of the previous studies to rule out factors that could directly affect MPV such as comorbidities or drugs being used by adult patients. It is noteworthy that drugs such as statins, clopidogrel, and angiotensin-converting enzyme inhibitors (ACEIs), which are widely prescribed to adult patients, can influence MPV levels. In addition, decreased MPV was regarded as an enhanced consumption of large PLTs in inflammatory states. In fact, the results of our study were in concordance with the results of two recent studies. In those studies, the researchers also found that MPV was significantly lower in obese female subjects and showed that MPV was inversely associated with the degree of obesity, independent of confounding factors. Although they could not find the reason for the discrepancy in the association of MPV with obesity, they offered some explanatory biological mechanisms that may also account for the results of this study. Adipose tissue secretes various hormones and cytokines, such as leptin, IL-6, and TNF-α, that are generally higher in postmenopausal obese females, and all these factors are correlated with hematological parameters. In addition, many of the hormonal regulators, such as vitamin D, PTH, estrogen, and leptin, also have a direct effect on both bone and the cardiovascular system. Low 25OHD, high PTH, and high leptin levels, which were usually observed in obese adults, were reported to be correlated with increased risk of CVD and OP.

In previous studies, an independent relationship was found between low BMD values in the cortical areas and vascular calcification. Moreover, studies show that the rate of demineralization at the hip is significantly associated with the rate of atherogenesis and even future risk of cardiovascular events. However, studies that primarily measure trabecular (spine) BMD are unsuccessful in demonstrating this relationship. Hence low hip BMD could be a surrogate marker of the atherosclerotic burden in women. Consistent with these reports, we found a correlation between BMD and MPV only at the femur neck.

Although this is the first study to focus on the relationship between MPV and OP in a sample of postmenopausal Turkish women, it has several limitations. Firstly, it has a retrospective design. Therefore, it does not show causality. Secondly, we did
not have a chance to collect information about biochemical markers of inflammation (e.g., C-reactive protein levels). Thirdly, the vast majority of patients had abnormal BMDs (osteopenia or osteoporosis), so there is a lack of information on normal subjects. On the other hand, the main strong point of our study is that it was conducted with a careful selection of subjects in compliance with comprehensive exclusion criteria.

In conclusion, this study shows that MPV is correlated with FNBMD in postmenopausal osteoporotic women. The direction of the association depends on BMI. Regardless of mechanisms, these findings might suggest that MPV could be potentially used as a readily available biomarker for osteoporosis in clinical settings.

REFERENCES

1) Karakas EY, Yetisgin A, Cadirci D, et al.: Usefulness of ceruloplasmin testing as a screening methodology for geriatric patients with osteoporosis. J Phys Ther Sci, 2016, 28: 235–239. [Medline] [CrossRef]

2) Joo SH, Kim MT, Cho JH, et al.: Blood levels related to the Z-score of bone mineral density in young males and females. J Phys Ther Sci, 2015, 27: 1117–1120. [Medline] [CrossRef]

3) Cho JH, Kim JH, Lee HK: The relationship between breast density and bone mineral density after menopause. J Phys Ther Sci, 2015, 27: 1243–1246. [Medline] [CrossRef]

4) Cho JH, Kim MT, Lee HK, et al.: Factor analysis of biochemical markers associated with bone mineral density in adults. J Phys Ther Sci, 2014, 26: 1225–1229. [Medline] [CrossRef]

5) Liang DK, Bai XJ, Wu B, et al.: Associations between bone mineral density and subclinical atherosclerosis: a cross-sectional study of a Chinese population. J Clin Endocrinol Metab, 2014, 99: 469–477. [Medline] [CrossRef]

6) Sumino H, Ichikawa S, Kasama S, et al.: Relationship between carotid atherosclerosis and lumbar spine bone mineral density in postmenopausal women. Hypertens Res, 2008, 31: 1191–1197. [Medline] [CrossRef]

7) Tankö LBB, Christiansen C, Cox DA, et al.: Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res, 2005, 20: 1912–1920. [Medline] [CrossRef]

8) Gasparian AY, Ayvazyan L, Mikhailidis DP, et al.: Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des, 2011, 17: 47–58. [Medline] [CrossRef]

9) Nebeck K, Gelaye B, Lemma S, et al.: Hematological parameters and metabolic syndrome: findings from an occupational cohort in Ethiopia. Diabetes Metab Syndr, 2016, 2: 22–27. [Medline] [CrossRef]

10) Ellinger VC, Carlini LT, Moreira RO, et al.: Relation between insulin resistance and hematological parameters in a Brazilian sample. Arq Bras Endocrinol Metabol, 2006, 50: 114–117. [Medline] [CrossRef]

11) Civelek GM, Pekyavas NO, Cetin N, et al.: Association of vitamin D deficiency with muscle strength and quality of life in postmenopausal women. Climacteric, 2014, 17: 472–477. [Medline] [CrossRef]

12) Kim KJ, Jun HJ, Jeong HS, et al.: The relationship between fracture and quality of life in Korean adults receiving treatment for osteoporosis based on the 2010 Korean Community Health Survey. J Phys Ther Sci, 2015, 27: 2083–2086. [Medline] [CrossRef]

13) Lippi G, Meschi T, Borghi L: Mean platelet volume increases with aging in a large population study. Thromb Res, 2012, 129: e159–e160. [Medline] [CrossRef]

14) Ciovacco WA, Cheng YH, Horowitz MC, et al.: Immature and mature megakaryocytes enhance osteoblast proliferation and inhibit osteoclast formation. J Cell Biochem, 2010, 109: 774–781. [Medline] [CrossRef]

15) Beeton CA, Bord S, Ireland D, et al.: Osteoclast formation and bone resorption are inhibited by megakaryocytes. Bone, 2006, 39: 985–990. [Medline] [CrossRef]

16) D’Amelio P, Cristofaro MA, De Vivo E, et al.: Platelet vitamin D receptor is reduced in postmenopausal patients. Panninerva Med, 2012, 54: 225–231. [Medline]

17) Sa X, Floyd DH, Hughes A, et al.: The ADP receptor P2RY12 regulates osteoclast function and pathologic bone remodeling. J Clin Invest, 2012, 122: 3579–3592. [Medline] [CrossRef]

18) Resorlu H, Resorlu M, Gokmen F, et al.: Association between mean platelet volume and bone mineral density in patients with ankylosing spondylitis and diagnostic value of diffusion-weighted magnetic resonance imaging. J Phys Ther Sci, 2015, 27: 1137–1140. [Medline] [CrossRef]

19) Li XS, Zhang JR, Meng SY, et al.: Mean platelet volume is negatively associated with bone mineral density in postmenopausal women. J Bone Miner Metab, 2012, 30: 660–665. [Medline] [CrossRef]

20) World Health Organization (WHO) scientific group on the prevention and management of osteoporosis. Prevention and management of osteoporosis. https://apps.who.int/iris/bitstream/10665/42841/1/WHO_TRS_921.pdf (Accessed Jun. 17, 2015)

21) Sumino H, Ichikawa S, Kasama S, et al.: Elevated arterial stiffness in postmenopausal women with osteoporosis. Maturitas, 2006, 55: 212–218. [Medline] [CrossRef]

22) Jun HJ, Kim KJ, Lee JS, et al.: Association between osteoporotic fractures and quality of life based on the Korean Community Health Survey of 2010. J Phys Ther Sci, 2015, 27: 3325–3328. [Medline] [CrossRef]

23) Korkmaz N, Tutoglu A, Korkmaz I, et al.: The relationships among vitamin D level, balance, muscle strength, and quality of life in postmenopausal patients with osteoporosis. J Phys Ther Sci, 2014, 26: 1521–1526. [Medline] [CrossRef]

24) Browner WS, Lui LY, Cummings SR: Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. J Clin Endocrinol Metab, 2001, 86: 631–637. [Medline] [CrossRef]

25) Price PA, June HH, Buckley JR, et al.: Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol, 2001, 21: 1610–1616. [Medline] [CrossRef]

26) Jesri A, Okonofua EC, Egan BM: Platelet and white blood cell counts are elevated in patients with the metabolic syndrome. J Clin Hypertens (Greenwich), 2005, 7: 705–711, quiz 712–713. [Medline] [CrossRef]
27) Muscari A, De Pascalis S, Cenni A, et al.: Determinants of mean platelet volume (MPV) in an elderly population: relevance of body fat, blood glucose and ischaemic electrocardiographic changes. Thromb Haemost, 2008, 99: 1079–1084. [Medline]
28) Coban E, Afacan B: The effect of rosuvastatin treatment on the mean platelet volume in patients with uncontrolled primary dyslipidemia with hypolipidemic diet treatment. Platelets, 2008, 19: 111–114. [Medline] [CrossRef]
29) Jagroop IA, Mikhailidis DP: Angiotensin II can induce and potentiate shape change in human platelets: effect of losartan. J Hum Hypertens, 2000, 14: 581–585. [Medline] [CrossRef]
30) Kapsoritakis AN, Koukourakis MI, Sfiridaki A, et al.: Mean platelet volume: a useful marker of inflammatory bowel disease activity. Am J Gastroenterol, 2001, 96: 776–781. [Medline] [CrossRef]
31) Park BJ, Shim JY, Lee HR, et al.: The relationship of platelet count, mean platelet volume with metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists: a focus on gender differences. Platelets, 2012, 23: 45–50. [Medline] [CrossRef]
32) Aypak C, Türedi O, Bircan MA, et al.: Could mean platelet volume among complete blood count parameters be a surrogate marker of metabolic syndrome in pre-pubertal children? Platelets, 2014, 25: 393–398. [Medline] [CrossRef]
33) Priya T, Chowdhury MG, Vasanth K, et al.: Assessment of serum leptin and resistin levels in association with the metabolic risk factors of pre- and post-menopausal rural women in South India. Diabetes Metab Syndr, 2013, 7: 233–237. [Medline] [CrossRef]
34) Clowes JA, Riggs BL, Khosla S: The role of the immune system in the pathophysiology of osteoporosis. Immunol Rev, 2005, 208: 207–227. [Medline] [CrossRef]
35) Wang L, Song Y, Manson JE, et al.: Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes, 2012, 5: 819–829. [Medline] [CrossRef]
36) van der Klift M, Pols HA, Hak AE, et al.: Bone mineral density and the risk of peripheral arterial disease: the Rotterdam Study. Calcif Tissue Int, 2002, 70: 443–449. [Medline] [CrossRef]
37) Hak AE, Pols HA, van Hemert AM, et al.: Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol, 2000, 20: 1926–1931. [Medline] [CrossRef]
38) Bagger YZ, Tankö LB, Alexandersen P, et al. Prospective Epidemiological Risk Factors Study Group: Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med, 2005, 258: 598–605. [Medline] [CrossRef]
39) Kado DM, Browner WS, Blackwell T, et al.: Rate of bone loss is associated with mortality in older women: a prospective study. J Bone Miner Res, 2000, 15: 1974–1980. [Medline] [CrossRef]
40) Tankö LB, Bagger YZ, Christiansen C: Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif Tissue Int, 2003, 73: 15–20. [Medline] [CrossRef]