J. Phys. Ther. Sci. 28: 1753–1758, 2016

The Journal of Physical Therapy Science

Original Article

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

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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

(This article was submitted Jan. 20, 2016, and was accepted Feb. 22, 2016)

INTRODUCTION

Osteoporosis (OP) is defined as systemic skeletal disease characterized by bone fragility resulting from low bone mass and deterioration of the bone microstructure[1–3)]. OP and cardiovascular diseases (CVD) are major public health concerns in aging populations[4, 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 mortality[6, 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 CVD[8)]. Consequently, some investigators have argued MPV may be used in detection and evaluation of CVD[9, 10)].

OP is mostly seen in the postmenopausal period and is associated with lowered quality of life[11, 12)]. Aging is a well-known risk factor for OP. MPV was found to be increased with aging in previous studies[13)]. In addition, megakaryocytes are elevated in bone marrow with aging, leading to an imbalance between osteoblastic and osteoclastic functions[14, 15)]. Megakaryocytic

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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/ml (n=12) or more than 10×10^3/ml (n=38); PLT counts of less than 150×10^3/ml (n=9) or more than 400×10^3/ml (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 thet were analyzed one hour after veinipuncture. 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=37) 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.

Table 1. Clinical and laboratory characteristics of the participants with osteopenia and osteoporosis

	Osteopenia (n=37)	Osteoporosis (n=126)
Age (years)	60.2 ± 6.9	62.4 ± 9.2
Height (cm)	158 ± 6*	156 ± 6
Weight (kg)	76 ± 9*	68 ± 11
BMI (kg/m^2)	30.4 ± 4.1*	28.0 ± 4.3
WBC (10^3/mL)	6.5 ± 1.2	6.4 ± 1.3
RBC (10^6/mL)	4.6 ± 0.4	4.6 ± 0.3
Hgb (g/dl)	13.6 ± 0.8	13.6 ± 0.8
Hct (%)	41.2 ± 2.6	41.2 ± 2.3
Platelet (10^3/mL)	244 ± 49	233 ± 48
MPV (fL)	8.9 ± 0.8	9.0 ± 1.0
PCT (%)	0.20 ± 0.03	0.20 ± 0.03
PDW (%)	17.4 ± 5.8	16.4 ± 5.2
Ca (mg/dl)	9.5 ± 0.3	9.6 ± 0.5
P (mg/dl)	3.4 ± 0.3	3.5 ± 0.5
iPTH (pg/ml)	54 ± 24	78 ± 72
25(OH)D3 (ng/ml)	15.9 ± 8.6	16.6 ± 10.9
Lumbar spine BMD (g/cm^2)	0.85 ± 0.10*	0.68 ± 0.10
Femoral neck BMD (g/cm^2)	0.75 ± 0.08*	0.65 ± 0.09
T-score L1–L4	−1.8 ± 0.6*	−3.3 ± 0.6
T-score Femoral neck	−0.9 ± 0.7*	−1.7 ± 0.8

*p<0.05. BMD: bone mineral density; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; Hgb: hemoglobin; Hct: hematocrit; MPV: mean platelet volume; PCT: platelet crit; PDW: platelet distribution width; Ca: calcium; P: phosphorus; 25(OH)D3: serum 25OH vitamin D3; iPTH: intact parathormone

Table 2. Correlation analyses between bone mineral density (BMD) and other variables in osteoporotic postmenopausal women

	Normal weight (n=33)		Overweight-obese (n=93)	
	Femoral neck BMD (g/cm^2)	Lumbar spine BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Lumbar spine BMD (g/cm^2)
	r	r	r	r
Age (years)	−0.537*	−0.391*	−0.241*	−0.161
Time after menopause (years)	−0.508*	−0.232	−0.216*	−0.278*
Weight (kg)	−0.129	0.176	0.360*	−0.046
BMI (kg/m^2)	−0.146	−0.116	0.267*	−0.047
WBC (10^3/ml)	0.110	0.026	−0.74	−0.195
RBC (10^6/ml)	0.028	−0.10	−0.040	−0.166
Platelet (10^3/ml)	−0.323	−0.069	0.147	−0.246*
MPV (fl)	0.398*	0.170	−0.237*	0.222*

*p<0.05. BMD: bone mineral density; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; MPV: mean platelet volume

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).

Table 3. Multivariate analyses with femoral neck BMD and lumbar spine BMD as the dependent variables

	Femoral neck BMD (g/cm^2)		Lumbar spine BMD (g/cm^2)	
	Normal weight	Overweight-obese	Normal weight	Overweight-obese
	Beta	Beta	Beta	Beta
Age (years)	−0.533*	−0.377*	−0.345	−0.135
Weight (kg)	−0.100	0.331*	−0.202	0.029
MPV (fl)	0.329*	−0.238*	0.220	0.207

*p<0.05. BMD: bone mineral density; MPV: mean platelet volume

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[21, 22]. 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)[23]. 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[7]. 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[21]. 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[24, 25].

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[8]. 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[19]. 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[19]. 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[26, 27]. 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[28, 29]. In addition, decreased MPV was regarded as an enhanced consumption of large PLTs in inflammatory states[30]. In fact, the results of our study were in concordance with the results of two recent studies[31, 32]. 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[33]. 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[34]. 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[35].

In previous studies, an independent relationship was found between low BMD values in the cortical areas and vascular calcification[7, 36, 37]. 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[38, 39]. However, studies that primarily measure trabecular (spine) BMD are unsuccessful in demonstrating this relationship[6]. Hence low hip BMD could be a surrogate marker of the atherosclerotic burden in women[40]. 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.

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