Original Article
Elevated mean platelet volume in patients with primary hyperparathyroidism

Dilek Arpaci1, Fatih Kuzu1, Ali Ugur Emre2, Guldeniz Karadeniz Cakmak2, Mustafa Unal1, Sevil Ilikhan Uygun3, Basak Erol3, Taner Bayraktaroglu1

1Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey; Departments of 2General Surgery, 3Internal Medicine, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey

Received September 23, 2015; Accepted February 26, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Objectives: In patients with primary hyperparathyroidism (PHP), morbidity and mortality due to cardiovascular disease are seen more frequently than the normal population. Platelets play a significant role on the onset and progression of clotting and therefore contribute to the atherosclerotic process. Increased mean platelet volume (MPV) is an indicator of platelet activation. Therefore, it was defined as an independent risk factor for atherosclerotic process. The aim of this study was to compare MPV in patients with PHP and control subjects and also to assess postoperative MPV levels at third months. Materials and methods: We retrospectively reviewed the data of 74 patients with PHP and 71 controls matched for age, gender and presence of diabetes. Results: Age, gender and presence of diabetes were similar between the groups. (P=0.052, P=0.056 and P=0.374 respectively). MPV was found to be higher in patients with PHP compared to controls (8.64±1.20 fL and 7.77±0.88 fL, respectively) (P≤0.01). There was no significant difference between the groups in terms of MPV levels both at the time of diagnosis and third month after surgery (P=0.136). Conclusions: In this study, we found MPV to be higher in patients with PHP than the controls as independent of diabetes. Also, this increase in MPV had been continued until the early stage of postoperative period.

Keywords: Platelet, volume, hyperparathyroidism

Introduction
Parathyroid hormone (PTH) that release from parathyroid glands plays an important role in bone mineral metabolism and the regulation of serum calcium and phosphorus levels. Primary hyperparathyroidism (PHP) is a syndrome with excessive PTH secretion from parathyroid gland and have a broad spectrum of symptoms like elevated serum calcium level, osteoporosis, kidney stones. Etiology of PHP includes parathyroid adenoma (85%), parathyroid hyperplasia (15%) and parathyroid cancer 1% [1, 2]. PHP is closely associated with cardiovascular morbidity and mortality [3, 4].

Platelets are the tiny cells with certain role on coagulation and atherosclerotic processes [5]. In case of overproduction, mean platelet volume (MPV) extends and these large platelets with metabolic and enzymatic hyperactivity, produce tendency towards thrombosis and atherosclerotic disease [6-8]. Accordingly, MPV has been defined as an independent risk factor for cardiovascular disease (CVD), together with cerebrovascular disease and transient ischemic attack [9, 10]. The purpose of this study was to compare MPV patients with PHP to controls, and to evaluate pre- and postoperative MPV level at postoperative third months.

Materials and methods
This is a retrospective study included 74 patients with PHP who was diagnosed with increased PTH despite hypercalcemia and 71 healthy controls matched for age, sex and presence of diabetes. All patients were evaluated for serum calcium (normal range 8.5-10.5 mg/dL), albumin (3.5-5 g/dL), phosphorus (2.5-4.5 mg/dL), PTH (15-65 pg/dL), 25-OH vitamin D (30-60 ng/mL) levels at preoperative and post-
Mean age of patients and control group were 52.77±9.35 and 49.93±9.73 years (P=0.052). There were 48 (64.9%) female and 26 (35.1%) male patients with 37 (52.1%) female and 34 (47.9%) male controls (P=0.056). Diabetes mellitus was diagnosed in 23 (31%) patients and in 23 (26.8%) control subjects (P=0.374).

Mean calcium levels were 11.5±0.87 mg/dL in patients; 8.90±1.08 mg/dL in controls (P≤0.001); Mean phosphorus levels were 2.2±0.05 mg/dL in patients; 3.7±0.80 mg/dL in controls (P≤0.001); serum albumin levels were 4.54±0.41 g/dL in patients; 3.98±0.30 g/dL in controls (P<0.001); serum PTH levels were 336.93±365.76 pg/dL in patients; 46.94±9.34 pg/dL in controls (P<0.001). Mean 25-OH D levels were 20.13±7.67 ng/mL in patients; 29.60±5.04 ng/mL in controls (P<0.001). MPV was determined to be higher in patients with PHP than controls, with mean values of 8.64±1.20 fL and 7.77±0.85 fL, respectively (P≤0.001) (Table 1).

Results

Mean age of patients and control group were 52.77±9.35 and 49.93±9.73 years (P=0.052). There were 48 (64.9%) female and 26 (35.1%) male patients with 37 (52.1%) female and 34 (47.9%) male controls (P=0.056). Diabetes mellitus was diagnosed in 23 (31%) patients and in 23 (26.8%) control subjects (P=0.374).

Mean calcium levels were 11.5±0.87 mg/dL in patients; 8.90±1.08 mg/dL in controls (P≤0.001); Mean phosphorus levels were 2.2±0.05 mg/dL in patients; 3.7±0.80 mg/dL in controls (P≤0.001); serum albumin levels were 4.54±0.41 g/dL in patients; 3.98±0.30 g/dL in controls (P<0.001); serum PTH levels were 336.93±365.76 pg/dL in patients; 46.94±9.34 pg/dL in controls (P<0.001). Mean 25-OH D levels were 20.13±7.67 ng/mL in patients; 29.60±5.04 ng/mL in controls (P<0.001). MPV was determined to be higher in patients with PHP than controls, with mean values of 8.64±1.20 fL and 7.77±0.85 fL, respectively (P≤0.001) (Table 1).

Operative third month time. All patients underwent 99mTc-sestamibi parathyroid scintigraphy and neck ultrasonography for preoperative localization. To assess necessary of parathyroidectomy, 24-hour-urine calcium (normal range 100-300 mg/day) creatinine clearance, renal ultrasound and bone mineral densitometry (BMD) were done. BMD was measured with dual-energy-X-ray absorptiometry (DEXA). According to World Health Organization criteria; BMD T-score >-1.0 is normal; <-1.0 to >-2.5 is osteopenia; ≤-2.5 is osteoporosis. 2009 third workshop was used for indications of parathyroidectomy. These indications are: [11].

1) Serum calcium 1.0 mg/dL or 0.25 mmol/liter (> upper limit of normal). 2) Creatinine clearance is <60 mL/min. 3) Age <50 years. 4) Skeletal BMD at any site (hip, spine and distal radius 1/3) is more than 2.5 standard deviation (T score <2.5) in perimenopausal and postmenopausal women and >50 years male and in premenopausal women and <50 years male: Z score <2.5 and/or fragility fracture.

Patients who had any history of coronary artery disease was excluded.

Table 1. Demographic, biochemical parameters in patients with PTH and healthy controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=74)</th>
<th>Controls (n=71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>52.77±9.35</td>
<td>49.93±9.73</td>
<td>0.052*</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>48/26</td>
<td>37/34</td>
<td>0.056**</td>
</tr>
<tr>
<td>Presences of DM</td>
<td>19/55</td>
<td>23/48</td>
<td>0.374**</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.64±1.20</td>
<td>7.77±0.85</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>11.5±0.87</td>
<td>8.90±1.08</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.54±0.41</td>
<td>3.98±0.30</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PTH (pg/dL)</td>
<td>336.93±365.76</td>
<td>46.94±9.34</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>25-OH D (ng/mL)</td>
<td>20.13±7.67</td>
<td>29.60±5.04</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Mean: average, Abbreviations BMI body mass index, BP blood pressure, HDL-plasma high-density lipoprotein, LDL plasma low density lipoprotein, CRP plasma level of C-reactive protein, DM-diabetes mellitus. *: Mann-Whitney U Test, **: Pearson Chi-Square Test.

Table 2. Pre- and post-operative biochemical parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>11.5±0.87</td>
<td>9.2±0.88</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PTH (pg/dL)</td>
<td>336.93±365.76</td>
<td>61.88±64.23</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.64±1.20</td>
<td>8.97±1.25</td>
<td>0.136*</td>
</tr>
</tbody>
</table>

Mean: average, Abbreviations BMI body mass index, BP blood pressure, HDL-plasma high-density lipoprotein, LDL plasma low density lipoprotein, CRP plasma level of C-reactive protein, DM-diabetes mellitus. *: Mann-Whitney U Test.

SPSS 19.0 was used for all statistical analysis. Descriptive statistics of continuous variables were given with mean, standard deviation and percent for categorical variables. Shapiro Wilk test was used for test of normality. Independent samples t test was used for two independent groups comparisons of normal distributed variables and Mann Whitney U test for non-normal distributed variables. Similarly paired samples t test was used for two dependent group comparisons of normal distributed variabes and Wilcoxon test for non-normal distributed variables. Spearman correlation test was used to determine the relationship between continuous variables. Pearson chi-square, Yates chi-square and Fisher exact chi-square test were used for comparison of categorical variables among groups. For all statistical comparisons with a P value below 0.05 assumed as there is a statistically significance.

Results

Mean age of patients and control group were 52.77±9.35 and 49.93±9.73 years (P=0.052). There were 48 (64.9%) female and 26 (35.1%) male patients with 37 (52.1%) female and 34 (47.9%) male controls (P=0.056). Diabetes mellitus was diagnosed in 23 (31%) patients and in 23 (26.8%) control subjects (P=0.374). Mean calcium levels were 11.5±0.87 mg/dL in patients; 8.90±1.08 mg/dL in controls (P<0.001); Mean phosphorus levels were 2.2±0.05 mg/dL in patients; 3.7±0.80 mg/dL in controls (P<0.001); serum albumin levels were 4.54±0.41 g/dL in patients; 3.98±0.30 g/dL in controls (P<0.001); serum PTH levels were 336.93±365.76 pg/dL in patients; 46.94±9.34 pg/dL in controls (P<0.001). Mean 25-OH D levels were 20.13±7.67 ng/mL in patients; 29.60±5.04 ng/mL in controls (P<0.001). MPV was determined to be higher in patients with PHP than controls, with mean values of 8.64±1.20 fL and 7.77±0.85 fL, respectively (P≤0.001) (Table 1). Mean 24-hours-urine calcium level was 375.64±205.12 mg/day. While we revealed 66 parathyroid adenomas in
MPV in patients with hyperparathyroidism

There were only 19 cases of renal stones in patients with renal ultrasonography. Eleven patients had normal BMD; 35 patients had osteopenia and 28 patients had osteoporosis. Sixty-two patients had parathyroid adenoma, seven patients had parathyroid hyperplasia, four patients had parathyroid carcinoma and one patient had atypical parathyroid adenoma. Despite the persistence of just increased PTH levels in two patients; no parathyroid lesions were seen at ultrasonography. Postoperative mean calcium levels: 9.2±0.88 g/dL; Phosphorus: 3.22±0.77 mg/dL, PTH 61.88±64.23 pg/dL were found. However, there was no statistical difference for MPV level between pre- and postoperative third months (P=0.136) (Table 2).

In the Pearson’s correlation analysis, MPV levels were positive correlated with serum calcium levels (r=0.279; P=0.001) (Figure 1) and PTH (r=0.298; P<0.001) (Figure 2). But MPV was negative correlated with 25-OH vitamin D (r=-0.343; P<0.001) (Figure 3; Table 3).

**Discussion**

This study demonstrated higher levels of MPV in patients with PHP than healthy controls matched for age, gender and presence of diabetes. Nevertheless, remission of the disease did not lead to a decrease in MPV levels at third month. This might be attributed to the short length of remission period.

Increased cardiovascular disease and mortality has been reported in patients suffering from PHP. The exact reason of this has not been demonstrated. But especially coronary artery disease, myocardial, vascular and valvular calcification, myocardial fibrosis, hypertension, left ventricular hyperthyrophy; arrhythmias and endothelial disfunction have been observed [3, 4].

Some studies showed that patients with PHP has significant higher mortality than healthy controls [3, 12]. Vestergaard et al. found that patients with PHP has an increased risk even
MPV in patients with hyperparathyroidism

Figure 3. Correlation of MPV with serum vitamin D levels.

Table 3. Correlation between MPV levels and serum calcium, PTH, 25-OH-D-vitamin

<table>
<thead>
<tr>
<th></th>
<th>Correlation Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>0.279</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>0.298</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-OH-D-vitamin</td>
<td>-0.343</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Platelets play an important role in pathogenesis of every stage of atherosclerosis, such as inflammation, coagulation and thrombosis [14]. Platelets’ activity varies according to size, large platelets are more active than small ones enzymatically and metabolically [15, 16]. Subjects with hypercalcemia had increased cardiovascular disease and mortality compared to age and gender-matched normocalcemic controls [17-19]. In our study we found that serum calcium level was correlated with MPV levels.

MPV is recently defined as a factor considered to predict platelet activity and atherosclerosis [5, 7]. Increase in MPV is associated with the incline in the size and activity of platelets leading to atherosclerotic process [5, 7, 8]. The method of MPV determination is easier, cheaper and more available than the other platelet markers. Several studies in current literature proposed MPV as an independent risk factor for atherosclerosis [20, 21]. The relationship between MPV and cardiovascular disease has also been reported repeatedly [9, 22-25].

Yilmaz et al. [26] found similar results that MPV was increased in patients with PHP compared to controls. In contrast to our results, they found MPV was decreased after surgery at six months. We did not find any decrease in MPV levels after surgery, but we evaluated at third months. Maybe third months could be very early stage for evaluation of decreasing serum MPV levels. Also as like our results, they found that both serum calcium and PTH were correlated with MPV levels. They suggested that increased serum calcium could be induced to increase MPV. Baradaran et al. found similar results; serum PTH correlated with serum MPV levels [27].

Other authors suggested that PTH increases serum calcium, then serum calcium increases platelet calcium and blood pressure [28]. Also serum calcium changes shape and activation of platelets [29]. PHP induces inflammation, oxidative stress and eventually platelets activation [30, 31].

Similar to our results, Cure et al. [32] found negative correlation between MPV levels and 25-OH-D vitamin levels.

The presented data showed that MPV, an indicator of platelet activation, was higher in patients with PHP than the control group irrespective of age, gender and presence of diabetes. However, there was no decrease in MPV levels among patients that were at postoperative third months. Therefore, a further study design with a larger size and longer follow-up period to evaluate MPV is needed.

Disclosure of conflict of interest

None.

Authors’ contribution

DA and FK designated the study and writing. GKC made English editing. MU, SUI and BE col-
lected data from patients. TB made the statistical analysis of the study.

Address correspondence to: Dr. Dilek Arpaci, Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Bülent Ecevit University, Esenköy/Kozlu/Zonguldak, Turkey. Tel: +905072476698; Fax: +903722612502; E-mail: drarpaci@gmail.com

References

MPV in patients with hyperparathyroidism


