

Original Article

Elevated mean platelet volume in patients with primary hyperparathyroidism

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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) ($P\leq 0.01$). 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 abroad spectrum of symptoms like elevated serum calcium level, osteoporosis, kidney stones. Etiology of PHP ncludes 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-

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

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

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

Variable	Preoperative	Postoperative	P
Calcium (mg/dL)	11.5±0.87	9.2±0.88	<0.001*
PTH (pg/dL)	336.93±365.76	61.88±64.23	<0.001*
MPV (fL)	8.64±1.20	8.97±1.25	0.136*

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.

operative third month time. All patients underwent ^{99m}Tc-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.

Statistical methods

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 variables 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

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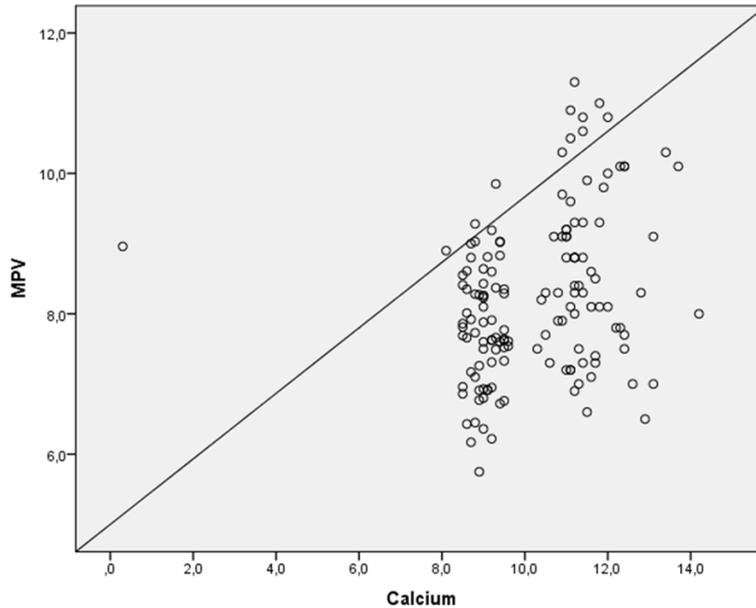


Figure 1. Correlation of MPV with serum calcium level.

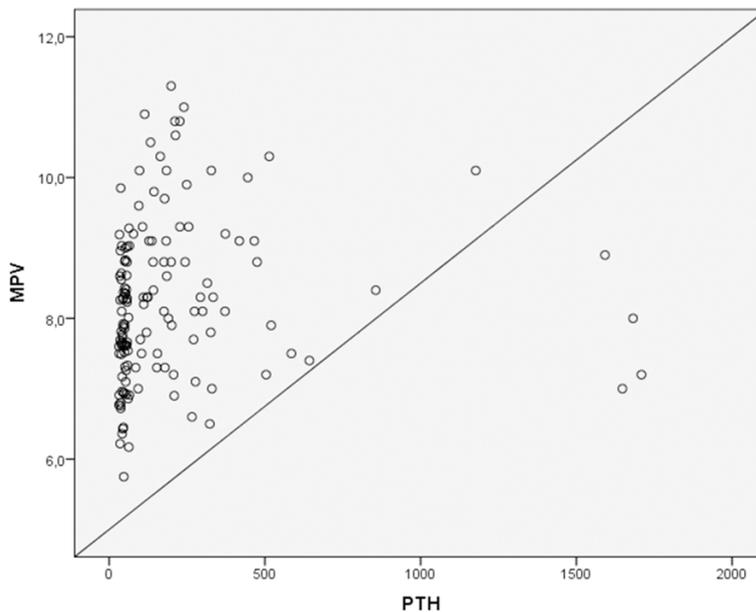


Figure 2. Correlation of MPV with serum PTH levels.

parathyroid ultrasound; 62 cases were determined with parathyroid scintigraphy.

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 hypertrophy; arrhythmias and endothelial dysfunction 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

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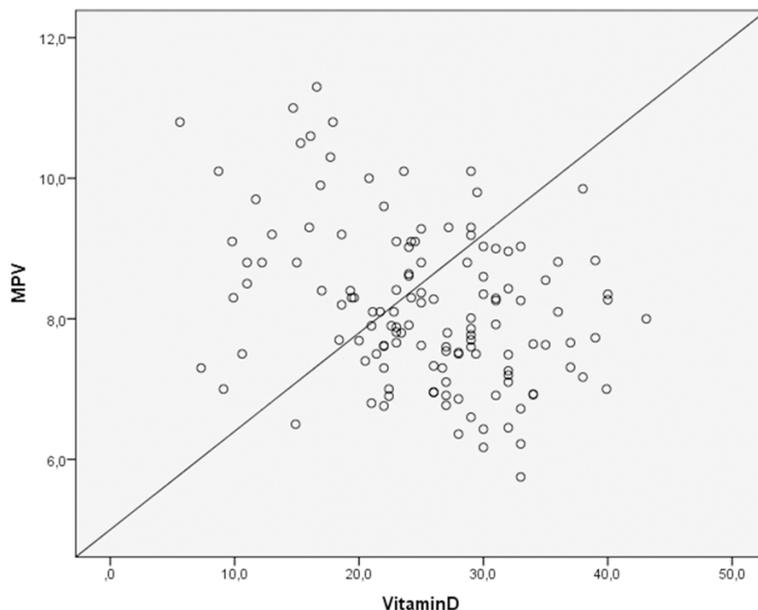


Figure 3. Correlation of MPV with serum vitamin D levels.

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

	Correlation Coefficient	P value
Serum calcium	0.279	0.001
Serum PTH	0.298	<0.001
25-OH-D-vitamin	-0.343	<0.001

after effective surgery [13]. This study may be supported our results. We did not find any decrease in MPV at postoperative third months.

Platelets play an important role in pathogenesis of every stage of atherotrombosis, 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 found 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-

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lected data from patients. TB made the statistical analysis of the study.

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References

- [1] Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000; 21: 343-1863-75.
- [2] Solomon BL, Schaaf M, Smallridge RC. Psychologic symptoms before and after parathyroid surgery. *Am J Med* 1994; 96: 101-6.
- [3] Hedbäck G, Odén A. Increased risk of death from primary hyperparathyroidism-an update. *Eur J Clin Invest* 1998; 28: 277-8.
- [4] Hagström E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundström J. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. *Circulation* 2009; 119: 2765-71.
- [5] Butterworth RJ, Bath PM. The relationship between mean platelet volume, stroke subtype and clinical outcome. *Platelets* 1998; 9: 359-364.
- [6] Van der Loo B, Martin JF. Megakaryocytes and platelets in vascular disease. *Baillieres Clin Haematol* 1997; 10: 109-23.
- [7] Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C, Jordanova N, Christ G, Thalhammer R, Huber K, Sunder-Plassmann R. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. *Br J Haematol* 2002; 117: 399-404.
- [8] Bath PM, Missouri CG, Buckenham T, MacGregor GA. Increased platelet volume and platelet mass in patients with atherosclerotic renal artery stenosis. *Clin Sci (Lond)* 1994; 87: 253-257.
- [9] Jung DH, Lee HR, Lee YJ, Kim JK, Park BJ, Shim JY. The association between coronary artery calcification and mean platelet volume in the general population. *Platelets* 2011; 22: 567-571.
- [10] López-Velasco R, Escobar-Morreale HF, Vega B, Villa E, Sancho JM, Moya-Mur JL. Cardiac involvement in acromegaly: specific cardiomyopathy or consequence of systemic hypertension? *J Clin Endocrinol Metab* 1997; 82: 1047-53.
- [11] Bilezikian JP, Khan AA, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab* 2009; 94: 335-9.
- [12] Hedbäck G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperparathyroidism. *World J Surg* 1990; 14: 829-35.
- [13] Vestergaard P, Mollerup CL, Frøkjær VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg* 2003; 27: 216-22.
- [14] Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood* 2004; 103: 2096-104.
- [15] Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007; 357: 2482-94.
- [16] Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. *Circ Res* 2007; 100: 1261-75.
- [17] Lundgren E, Lind L, Palmér M, Jakobsson S, Ljunghall S, Rastad J. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. *Surgery* 2001; 130: 978-85.
- [18] Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. *J Clin Epidemiol* 1997; 50: 967-73.
- [19] Leifsson BG, Ahrén B. Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab* 1996; 81: 2149-53.
- [20] Mayer FJ, Hoke M, Schillinger M, Minar E, Arbesu I, Kompensteiner R. Mean platelet volume predicts outcome in patients with asymptomatic carotid artery disease. *Eur J Clin Invest* 2014; 44: 22-8.
- [21] Ma H, Lin H, Hu Y, Li X, He W, Jin X, Gao J, Zhao N, Gao X. Mean platelet volume in relation to carotid atherosclerosis in normotensive, euglycemic, and normolipidemic Chinese middle-aged and elderly adults. *Angiology* 2014; 65: 512-8.
- [22] Korkmaz L, Korkmaz AA, Akyüz AR, Ağaç MT, Acar Z, Kırış A. Association between mean platelet volume and coronary artery calcification in patients without overt cardiovascular disease: an observational study. *Anadolu Kardiyol Derg* 2012; 12: 35-9.
- [23] Ozlu MF, Ozturk S, Ayhan SS, Tosun M, Alçelik A, Erdem A. Predictive value of mean platelet

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- volume in young patients with non-ST-segment elevation acute coronary syndromes: a retrospective observational study. *Anadolu Kardiyol Derg* 2013; 13: 57-61.
- [24] Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. *Lancet* 1991; 338: 1409-11.
- [25] Han JY, Choi DH, Choi SW, Kim BB, Ki YJ, Chung JW. Stroke or coronary artery disease prediction from mean platelet volume in patients with type 2 diabetes mellitus. *Platelets* 2013; 24: 401-6.
- [26] Yilmaz H. Assessment of mean platelet volume (MPV) in primary hyperparathyroidism: effects of successful parathyroidectomy on MPV levels. *Endocr Regul* 2014; 48: 182-8.
- [27] Baradaran A, Nasri H. Impact of parathormone Hormone on Platelet Count and Mean Volume in End-stage Renal Failure Patients on regular Hemodialysis. *J Med Sci* 2005; 5: 266-71.
- [28] Fliser D, Franek E, Fode P, Stefanski A, Schmitt CP, Lyons M. Subacute infusion of physiological doses of parathyroid hormone raises blood pressure in humans. *Nephrol Dial Transplant* 1997; 12: 933-8.
- [29] Salzman EW, Ware JA. Ionized calcium as an intracellular messenger in blood platelets. *Prog Hemost Thromb* 1989; 9: 177-202.
- [30] Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates the endothelial nitric oxide synthase through protein kinase A and C pathways. *Nephrol Dial Transplant* 2007; 22: 2831-7.
- [31] Robinson SD, Harding SA, Cummins P, Din JN, Sarma J, Davidson I. Functional interplay between platelet activation and endothelial dysfunction in patients with coronary heart disease. *Platelets* 2006; 17: 158-62.
- [32] Cure CM, Cure E, Yuce S, Yazici T, Karakoyun I, Efe H. Mean platelet volume and vitamin D level. *Ann Lab Med* 2014; 34: 98-103.