Mustafa GÖKSU [1, a]
Hüseyin ALAKUŞ [2, b]

[1] Adiyaman University,
Faculty of Medicine,
Department of General
Surgery,
Adiyaman, TURKIYE

[2] Adiyaman University,
Faculty of Medicine,
Department of Surgical
Oncology,
Adiyaman, TURKIYE

[a] ORCİD: 0000-0002-1807-6957
[b] ORCİD: 0000-0003-2650-7208

RESEARCH ARTICLE

Effects of Successful Parathyroidectomy in Patients with Primary Hyperparathyroidism on Mean Platelet Volume, Which Is An Indicator of Cardiovascular Disease Risk

Objective: Patients with primary hyperparathyroidism (PHPT) have been shown to have an increased risk of cardiovascular mortality, but the mechanisms underlying this increased risk have not yet been elucidated. This research aimed to investigate the changes in preoperative and postoperative serum calcium, serum parathormone, blood platelet count and mean platelet volume (MPV) in patients who underwent parathyroidectomy for PHPT.

Materials and Methods: Four male (11.8%) and 30 female (88.2%) patients who underwent parathyroidectomy for PHPT were included in the study. Preoperative and postoperative sixth-month blood samples were collected, parameters associated with atherosclerosis, namely the serum calcium, serum parathormone, blood platelet count and MPV values were compared.

Results: In this study, there was a statistically significant decrease in the serum calcium level (p<0.001), serum parathormone level (p<0.001), blood platelet count (p<0.001), and MPV (p=0.002) at the sixth month after parathyroidectomy compared to the preoperative period.

Conclusion: In patients with PHPT, successful parathyroidectomy reduces the risk of cardiovascular diseases by providing a decrease in blood parameters associated with atherosclerosis.

Key Words: Parathyroidectomy, primary hyperparathyroidism, mean platelet volume, platelet count, atherosclerosis

Primer Hiperparatiriodide Başarılı Paratiroidektominin Kardiyovasküler Hastalık Risk Göstergesi Olan Ortalama Trombosit Hacmi Üzerine Etkisi

Amaç: Primer Hiperparatiroidizm (PHPT)'li hastalarda kardiyovasküler mortaliteye bağlı risk artışı gösterilmiş ancak bu risk artışının altında yatan mekanizmalar henüz aydınlatılamamıştır. Bu çalışmanın amacı, PHPT nedeniyle paratirodektomi (PTX) yapılan hastalarda preoperatif ve postoperetaif serum kalsiyum, serum parathormon, kan trombosit sayısı ve ortalama trombosit volümü (MPV)'ndeki değişiklikleri incelemektir.

Gereç ve Yöntem: PHPT nedeniyle PTX yapılan 4 erkek (%11.8) ve 30 kadın (%88.2) hasta çalışmaya dahil edildi. Preoperatif ve postoperatif 6. ayda kan örnekleri alınarak ateroskleroz ile ilişkili serum kalsiyum, serum parathormon, kan trombosit sayısı ve MPV değerleri karşılaştırıldı.

Bulgular: Bu çalışmada PTX sonrası 6. ayda serum kalsiyum düzeyi (p<0.001), serum parathormone düzeyi (p<0.001), kan trombosit sayısı (p<0.001) ve MPV (p=0.002)'de azalmalar istatistiksel olarak anlamlı bulundu.

Sonuç: PHPT'li hastalarda başarılı PTX sonrasında koroner ateroskleroz ile ilişkili kan parametreleri değerlerinde azalma sağlayarak artmış ateroskleroz riskini azaltmaktadır.

Anahtar Kelimeler: Paratiroidektomi, primer hiperparatiroidi, ortalama trombosit hacmi, trombosit sayısı, ateroskleroz

Correspondence
Yazışma Adresi

Mustafa GÖKSU
Adiyaman University,
Faculty of Medicine,
Department of General
Surgery,
Adiyaman - TURKIYE

drmustafagoksu@gmail.com

Introduction

Primary hyperparathyroidism (PHPT) is the third most frequent endocrine disease and the most prevalent reason for hypercalcemia seen in outpatients (1, 2). PHPT is a pathological condition characterized by an increase in parathormone (PTH) and calcium levels as a result of impaired calcium metabolism due to autonomous PTH production (2, 3). PHPT causes solitary parathyroid adenomas in 85% of cases and diffuse hyperplasia of the parathyroid glands in most of the remaining cases. In parathyroid gland adenoma and hyperplasia, there is excessive PTH production, which regulates calcium metabolism in the body (4).

Many studies have shown an increased risk due to cardiovascular mortality in patients with PHPT, but the mechanisms underlying this increased risk have not yet been elucidated (5-7). Atherosclerosis is a chronic inflammatory disease that causes cardiovascular diseases, characterized by the accumulation of fibrous material and fat in

the intima layer of the innermost layer of the arteries, and is the main cause of death from cardiovascular diseases (8). Fatty streaks on the arterial walls by stages transform into an atheroma and characteristic plaques. The acute rupture of atheroma induces local thrombosis, leading to the affected artery's partial or complete occlusion (9).

Several modifiable risk factors have been identified for atherosclerosis, including hypercholesterolemia, obesity, hypertension, diabetes mellitus, and smoking (10). Atherosclerosis is a systemic disease affecting the entire arterial system in the body, including the coronary vessels, and the atherosclerotic process stops or even regresses when the factors in its etiology are eliminated with treatment (11). Many studies have reported that PHPT is related to hypertension, disorders in the renin-angiotensin-aldosterone system, cardiac arrhythmia, and also structural and functional changes in the vascular wall (12, 13).

Platelets play an essential role in the etiopathogenesis of atherosclerotic vascular diseases (11). In the development of myocardial infarction, their pathophysiological role has been demonstrated. Large platelets are more active than smaller ones due to their high content of alpha granules and thromboxane A2 and secretion of more glycoprotein (14). Studies have shown that mean platelet volume (MVP) is associated with platelet reactivity and shortening of bleeding time. MVP is a quantitative measure of mean platelet size obtained from a routine blood test. When there is an increase in platelet production, MPV increases (15). Large platelets are considered to be an indicator of increased cardiovascular risk since they are more reactive, and MPV has recently emerged as a potential marker for cardiovascular diseases (15).

This study aimed to evaluate the serum calcium, serum PTH, blood platelet count, and blood MPV levels in patients with PHPT preoperatively and at six months after successful parathyroidectomy (PTX).

Materials and Methods

Research and Publication Ethics: This study was carried out after obtaining the Clinical Research Ethics Committee of Adiyaman University's approval, with the protocol number 2020/6-26 dated 23/06/2020.

The study included 34 patients who underwent PTX for PHPT in the General Surgery Clinic of Our Hospital between 2017 and 2020. The serum calcium, serum PTH, blood platelet count and blood MPV values were retrospectively analyzed preoperatively and at the sixth month after successful PTX. Patients with severe valvular disease, uncontrolled hypertension, cancer history and severe osteoporosis were excluded from the study.

Statistical analyses were performed using the SPSS (version 25.0, SPSS, Chicago, IL, USA) software package. Sample distribution was evaluated with the Kolmogorov-Smirnov test. The paired-Student t-test was used since the data conformed to a normal distribution. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 34 patients that underwent PTX, four (11.8%) males and 30 (88.2%) females, were included in the study. The patients' mean age was 54 ± 14.3 (min: 28, max: 84) years. The mean serum calcium level was 11.5 ± 0.70 mg/dl preoperatively and 9.02 ± 0.59 mg/dl postoperatively, and the difference was statistically significant ($p < 0.001$) (Figure 1). The mean serum PTH levels were 209.6 ± 155.6 pg/ml preoperatively and 40.4 ± 18.0 pg/ml postoperatively, and the difference was statistically significant ($p < 0.001$) (Figure 2). The mean blood platelet count was 254.6 ± 60.8 ($\times 10^3/\mu l$) preoperatively and 240.5 ± 64.1 ($\times 10^3/\mu l$) postoperatively, indicating a statistically significant difference ($p < 0.001$) (Figure 3). Lastly, the mean blood MPV value was 8.35 ± 1.69 fl preoperatively and 7.54 ± 0.81 fl postoperatively, with s statistically significant difference ($p = 0.002$) (Figure 4).
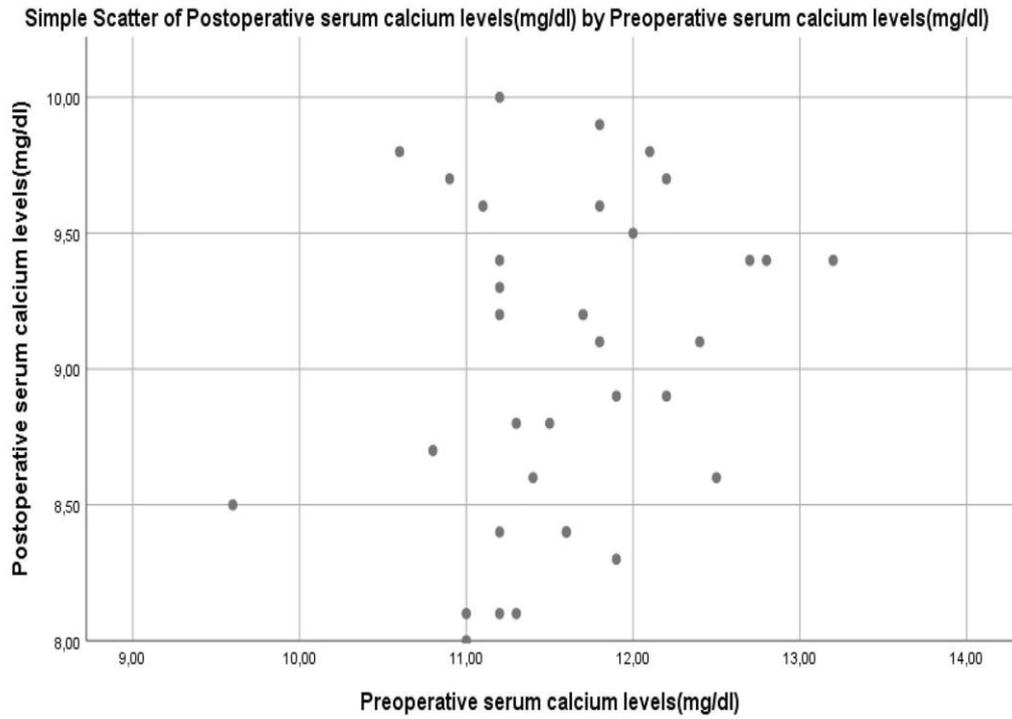
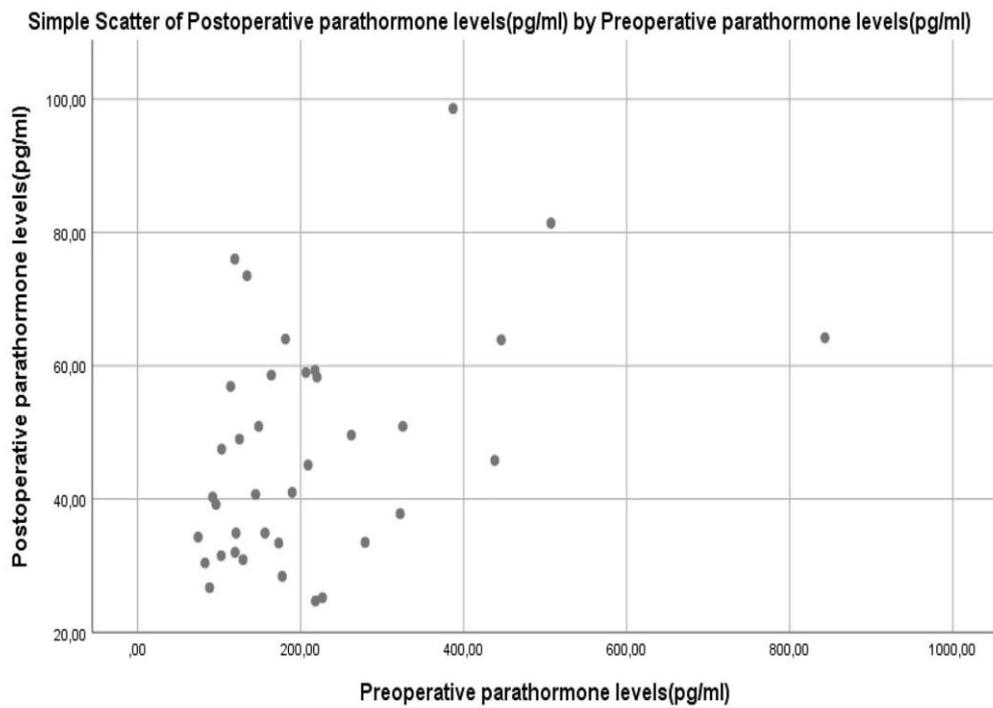**Figure 1.** Comparison of the preoperative and postoperative serum calcium level values

Figure 2. Comparison of the preoperative and postoperative serum parathormone values
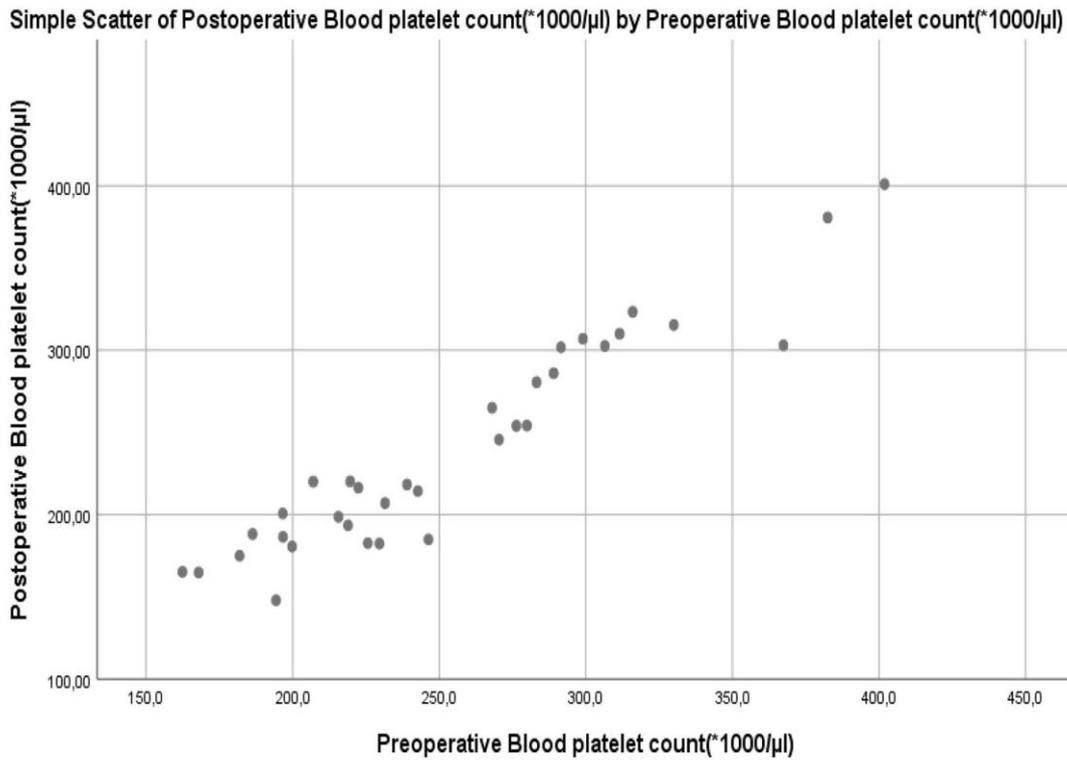
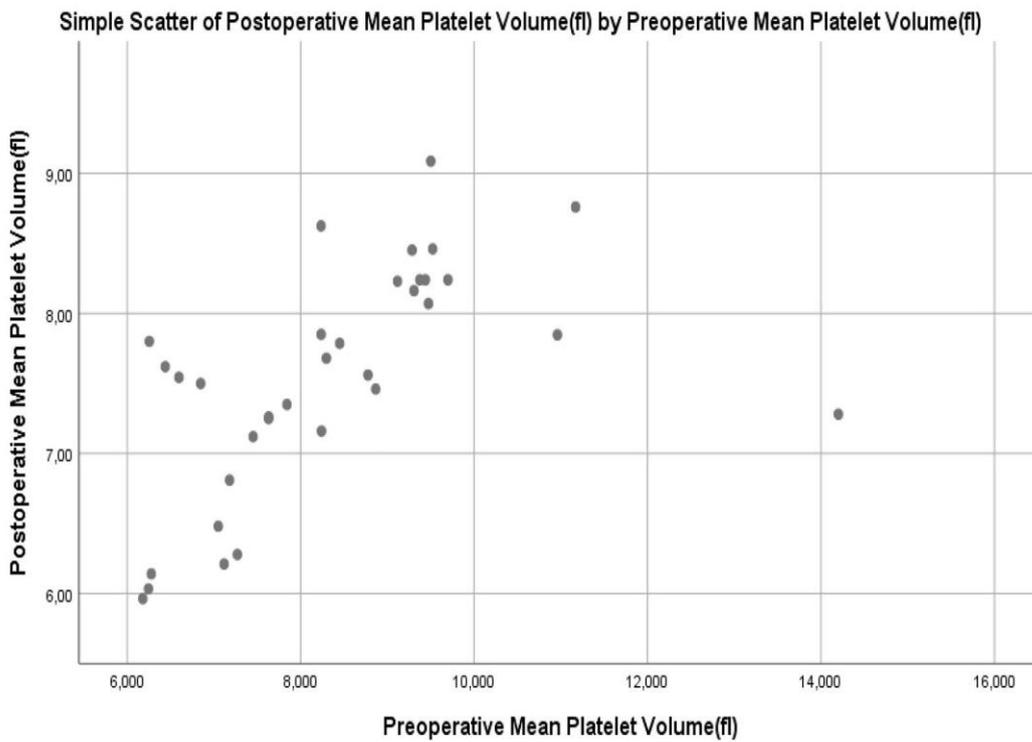**Figure 3.** Comparison of the preoperative and postoperative postoperative blood platelet values

Figure 4. Comparison of the preoperative and postoperative mean platelet volume values

Discussion

Data reported in previous studies show that PHPT leads to a high risk of cardiovascular diseases (16). Atherosclerosis is one of the most important causes of cardiovascular diseases, and platelets play a major role in the etiopathogenesis of atherosclerotic vascular diseases (11).

Hypercalcemia has been shown to be related to increased mortality in patients with PHPT (17). Yu et al. (18) reported that patients with hyperparathyroidism had a standardized mortality rate of 2.62, which was higher than other causes. The authors examined the records of 4461 patients between 1987 and 1994 to investigate the risk of death in those who underwent PTX for PHPT. The risk of death from cardiovascular diseases was found to be increased by 1.71 times among men and 1.85 times among women. Several other studies have similarly shown that PHPT leads to a high risk for cardiovascular diseases (16, 19). Atherosclerosis is one of the main causes of the pathophysiology of cardiovascular diseases in the majority of cases. Platelets play an important role in the etiopathogenesis of atherosclerotic vascular diseases (11). In light of findings indicating that the presence of specific PHPT variables such as serum calcium and PTH constitutes a predictable risk of death, it has been suggested that surgery in patients with PHPT not only relieves signs and symptoms but also improves prognosis (20). Vestergaard et al. (21) evaluated preoperative and postoperative cardiovascular events and postsurgical mortality for PHPT using a historical follow-up design. As a result of the study, it was reported that in patients with moderately high serum calcium levels (mean 1.65 mmol/l), there was an increase in acute myocardial infarction for up to 10 years before surgery, but this decreased to a normal level within the postoperative one year. In a study by Ogard et al. (22) conducted in Denmark, the mortality rates of patients with PHPT due to cardiovascular disease and cancer were investigated compared to the other population. A reduction in the standard mortality rate was observed in women who underwent PTX, while no difference was found in men. Leifsson et al. (23) explored the relationship between high serum calcium values and morbidity and mortality. As a result, they argued that the risk of premature death in men under the age of 50 years increased with high serum calcium levels even in the normal range and that this increase might be largely due to cardiovascular diseases. In this study, the decrease in the serum calcium level was found to be statistically significant in the sixth month after PTX.

Considering that PHPT is related to hypertension, coronary atherosclerosis, and other cardiovascular diseases, Kamycheva et al. (24) evaluated serum PTH levels as an independent risk factor for coronary heart disease in patients with serum calcium values within the reference range and reported that elevated serum PTH increased the risk of coronary heart disease in these individuals and this could indicate the role of PTH in the development of coronary heart disease. Anderson et al. (25) investigated whether elevated PTH was associated with cardiovascular diseases. As a result of their

research, they argued that PTH presented as a complementary and independent predictive value for cardiovascular diseases and mortality. Grandi et al. (26) evaluated the prognostic value of initial PTH for subsequent cardiovascular events and all-cause deaths in a high-risk population with stable coronary heart disease and reported that a PTH value above the normal range was an independent predictive parameter for prognosis in patients with stable coronary heart disease. Recent studies have investigated whether patients with hyperparathyroidism are at the risk of developing different complications such as increased morbidity and mortality from cardiovascular diseases and reported that left ventricular hypertrophy, impaired glucose metabolism, and dyslipidemia could be resolved after surgery and that successful PTX can reduce the higher risk of mortality among patients with PHPT due to cardiovascular diseases (12, 13). In the current study, the decrease in the serum PTH level in the sixth month after PTX was found to be statistically significant.

Platelets are not only essential for primary hemostasis and endothelial repair, but they also play a key role in the development of acute coronary syndromes, and in addition to contributing to cerebrovascular events, they are involved in the creation and expansion of atherosclerotic plaques (27). After separating from the bone marrow, platelets circulate for about ten days. The primary function of platelets is to stop bleeding after tissue trauma and vascular injury. After the initial adhesion of platelets to the extracellular matrix, the repair process requires a rapid response to autocrine and paracrine mediators, including adenosine diphosphate, thrombin, epinephrine, and thromboxane A2. These mediators strengthen and sustain the initial platelet response. Besides, they aggregate platelets in the bloodstream to form a growing hemostatic plug (28). The use of antiplatelet agents in preventing and treating cardiovascular, cerebrovascular and peripheral artery diseases, supported by rich evidence from clinical studies, has confirmed platelets' role in the atherothrombotic process (29). In the present study, there was a statistically significant decrease in the number of blood platelets after PTX.

Platelet volume is a parameter that determines platelet function, and large-volume platelets are more hemostatically active (27, 29, 30). Platelet size, measured as MPV, is a simple and accurate way of predicting platelet activity (27). Bath et al. (31) reported that high MPV was associated with other platelet activation markers, including increased platelet aggregation, thromboxane synthesis, and adhesion molecules. Braunwald (32) determined that mortality and the need for revascularization were higher in patients with myocardial infarction with high MPV values. In contrast, Şahin et al. (33) compared the MPV values of patients with and without coronary artery disease and found no statistically significant difference. In the current study, the decrease in the MPV level after PTX was statistically significant.

The study's limitations concern its be retrospective, small sample size, and no control group to compare the

blood values with PHPT and healthy individuals. The results should be supported by prospective studies with a large sample size and a control group.

As a result, in this study there was a statistically significant decrease in the serum calcium, serum PTH, blood platelet count and MPV values at the sixth month after successful PTX compared to the initials levels that had been elevated due to PHPT. As a result, we consider that PTX can reduce the risk of atherosclerosis and cardiovascular diseases in patients with PHPT.

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