Association between inflammatory markers and primary hyperparathyroidism

İnflamatuar belirteçler ve primer hiperparatiroidi arasındaki ilişki

Selvihan Beysel[1]*, Mustafa Çalışkan[2], Muhammed Kızılgül[3], Murat Çilekar[4], Mustafa Özbek[3], Erman Çakal[3]

1.Afyonkarahisar Health Sciences University, Medicine Faculty, Department of Endocrinology and Metabolism, Afyon, Turkey
2.Ataturk Duzce State Hospital, Department of Endocrinology and Metabolism, Duzce, Turkey
3.University of Health Sciences, Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Training and Research Hospital
4.Afyonkarahisar Health Sciences University, Medicine Faculty, Department of General Surgery, Afyon, Turkey

ABSTRACT

Aim: Primary hyperparathyroidism (PHP) is associated with systemic inflam-mation. The effect of parathyroidectomy (PTX) on inflammatory markers is contro-versial. The aim of our study was to investigate changes in inflammatory markers including C-reactive protein (hs-CRP), platelet-to-lymphocyte ratio (PLR), and red cell distribution width (RDW) before and after PTX.
Patients and **Methods:** PHP patients (n=55) and age and sex matched healthy controls (n=50) were included in the study. The clinical and laboratory results of the PHP and control groups were compared before PTX and 6-months after PTX.
Results: At baseline, serum hs-CRP (4.01±3.44 vs. 2.48±1.73 mg/L), PLR (127.21±25.77 vs. 103.63±32.52), RDW (15.50±2.53 % vs. 13.49±0.70 %) values were higher in the PHP group than in the control group (p<0.05). After PTX, hs-CRP (3.59±3.07 mg/L), PLR (123.03±31.94), RDW (14.25±1.51 %) values did not change (p>0.05). Post-PTX hs-CRP, PLR, and RDW values were higher in the PHP group than in the control group (p<0.05). PTH value was positively correlated with pre-PTX hs-CRP (r2=0.377, p=0.001), PLR (r2=0.234, p=0.023), RDW (r2=0.296, p=0.004).
Conclusion: Before PTX, inflammatory markers were higher in PHP patients compared with healthy controls. After PTX, the inflammatory markers did not significantly decrease; however these postoperative markers were higher than controls. İnflammation occurs in PHP patients, and also shows a partial recovery from inflammation despite successful surgery.

Keywords: primary hyperparathyroidism, platelet-to-lymphocyte ratio, red cell distribution width, inflammatory markers, parathyroidectomy

ÖZ

Amaç: Primer hiperparatiroidizm (PHP) sistemik inflamasyonla ilişkilidir. Paratiroidek-tominin (PTX) inflamatuar b elirteçler ü zerindeki e tkisi tartışmalıdır. Çalışmamızın amacı, PTX öncesi ve sonrası C-reaktif protein (hs-CRP), trombosit / lenfosit oranı (TLO) ve kırmızı hücre dağılım genişliğini (RDW) içeren inflamatuar belirteçlerdeki değişiklikleri araştırmaktı.
Hastalar ve Yöntem: Çalışmaya PHP hastaları (n=55) ve yaş ve cinsiyet eşleştirilmiş sağlıklı kontroller (n=50) dahil edildi. PHP ve kontrol gruplarının klinik ve laboratuar sonuçları PTX'den önce ve PTX'den 6 ay sonra karşılaştırıldı.
Bulgular: Başlangıçta, serum hs-CRP (4,01±3,44'e karşın 2,48±1,73 mg/L), TLO (127,21±25,77'e karşın 103,63±32,52), RDW (15,50±2,53'e karşın 13,49±0,70 %) değerleri PHP grubunda, kontrol grubundan daha yüksekti (p<0,05). PTX'ten son-ra, hs-CRP (3,59±3,07 mg/L), TLO (123,03±31,94), RDW (14,25±1,51 %) değerleri değişmedi (p>0,05). PTX sonrası hs-CRP, TLO ve RDW değerleri PHP grubun-da, kontrol grubundan daha yüksekti (p<0,05). PTH değeri, PTX öncesi hs-CRP (r2=0,377, p=0,001), TLO (r2=0,234, p=0,023), RDW (r2=0,296, p=0,004) ile pozitif olarak korele idi.
Sonuç: PTX'den önce, PHP hastalarında inflamatuar belirteçler sağlıklı kontrollere kıyasla daha yüksekti. PTX'ten sonra, inflamatuar belirteçler istatiksel anlamlı azal-madı; ancak bu ameliyat sonrası belirteçler kontrollerden daha yüksekti. İnflamasyon PHP hastalarında görülür ve aynı zamanda başarılı bir ameliyat olmasına rağmen inflamasyondan kısmen iyileşme gösterir.

Anahtar Sözcükler: primer hiperparatiroidizm, trombosit/lenfosit oranı, kırmızı hücre dağılım genişliği, inflamatuar belirteçler, paratiroidektomi

*Corresponding Authors: Selvihan Beysel. Afyonkarahisar Health Sciences University, Medicine Faculty, Depart-ment of Endocrinology and Metabolism, Afyon, Turkey. Tel: +90 553 7465802 mail: beyselselvihan@gmail.com

ORCID: 0000-0001-6963-1503

INTRODUCTION

Inflammation has a role in the pathogenesis of cardiovascular disease, cancer, and aging [1]. Primary hyperparathyroidism (PHP) is the elevation of serum calcium as a result of excessive parathormone (PTH) production [2]. Inflammatory disorders in the endocrine glands are mostly associated with functional disorders [3]. Hyperparathyroidism increases systemic inflammation as a result of direct or indirect abnormal calcium and phosphate mechanisms [4]. Successful parathyroidectomy cures the clinic findings of PHP; however, the effect of parathyroidectomy on inflammation remains unclear [5]. The reported observations are conflicting with unchanged [6,7] or increased [8] levels of inflammatory markers after parathyroidectomy.

Serum high-sensitivity C-reactive protein (hs-CRP), a low-grade inflammation marker, was found to be positively correlated with serum PTH concentrations in patients with asymptomatic PHP [9]. The platelet-to-lymphocyte ratio (PLR) and red blood cell distribution width (RDW) are markers of inflammation that can be easily obtained from the complete blood count (CBC) test. Serum PTH elevation was reported to be associated with increased inflammatory markers such as hs-CRP, PLR, and RDW in the general population [1]. Serum hs-CRP, PLR, and RDW were considered as markers of inflammation [10,11]; however, there is insufficient evidence on the relationship between PLR and RDW and parathyroid adenoma. In our study, we investigated the levels of inflammatory markers including hs-CRP, PLR, and RDW in patients with PHP before and 6 months after parathyroidectomy, and also compared these parameters with those of a control group. We aimed to show whether there was a relationship between these inflammatory markers and parathyroid adenoma, and also to determine if there was an effect of parathyroidectomy on these inflammatory markers in patients with PHP.

PATIENTS-METHODS

Patients with PHP who were treated in the Department of Endocrinology and Metabolism, Ankara Diskapi Training and Research Hospital, were enrolled in this study. Patients with PHP (n=55) and age- and sex-matched healthy controls (n=50) were included. Patients with elevated calcium concentrations with normal or high PTH values were diagnosed as having PHP. All patients with PHP underwent localization studies such as neck ultrasound, and Tc99-sestamibi and/or single-photon emission-computed tomography. All patients underwent parathyroidectomy. Parathyroid adenoma was confirmed by a single group of pathologists.

Participants with missing clinical and biochemical results were excluded from the study. Patients with renal failure, liver disease, heart disease, autoimmune disease, infection, malignancy, parathyroid cancer, thyroid cancer, and pregnant women were excluded from the study. None of the patients were using steroids or immunosuppressive drugs. Demographic findings, clinical features, and preoperative biochemical results were compared between control and PHP group. Clinical evaluation and laboratory tests were compared before and 6 months after parathyroidectomy. Body mass index (BMI) was calculated as body weight (kg) / height (m2). Office blood pressure (BP) was measured at the level of the heart with the patients in the sitting position.

Serum albumin, total calcium, PTH, phosphorus, creatinine, 25OHvitD, CBC, glucose, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride, and hs-CRP measurements of all participants were performed after 12-hour fasting. Plasma PTH measurements were performed using an intact PTH assay (chemiluminescent immunoassay with an Immulite 2000; normal range 12-65 pg/mL)[12]. The albumin-corrected calcium value was calculated using the following formula: albumin-corrected calcium = [0.8 x (4-serum albumin)] + serum calcium. PLR was calculated as the ratio of platelet count to lymphocyte count.

Carotid artery intima-media thickness (CIMT) testing is a noninvasive method used to detect early atherosclerosis. CIMT is a measure of the luminal-intima and media-adventitia interface of common carotid artery and was assessed using a B-mode imaging high-resolution ultrasound system (EUB 7000 HV, Hitachi, Tokyo, Japan). Each subject gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Diskapi Teaching and Trai-

ning Hospital Local Ethics Committee (24.8.2015-18/31).

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS 18.0 (SPSS, Inc.) software. Descriptive analyses are expressed as mean±standard deviation (SD) and percentages (%). The Kolmogorov-Smirnov or Shapiro-Wilk W test was used to assess the normality of data distribution. The Chi-square test was used for categorical variables. Student's t test was used to compare normally distributed continuous variables or log-transformed variables between two independent groups. The differences between pre-operative and post-operative values were compared using the paired-sample t-test. Logarithmic transformation was used on continuous variables that were not normally distributed. Correlation analysis was performed using Spearman and Pearson tests. Statistical significance was defined as $p < 0.05$.

RESULTS

Sex distribution (female, 78.2% vs. 72.0%), and mean age (51.85±10.21 vs 53.31±7.84 year) were similar between the groups (p>0.05). BMI (30.58±5.14 vs. 28.55±3.71 kg/m2) and BPs were higher in the PHP group compared with the control group (p<0.05). Patients with PHP had higher concentrations of PTH, calcium, and ALP, whereas phosphate and 25(OH) vitamin D values were lower in comparison with the control group. Glucose and lipid profiles were similar between the groups (p>0.05). The characteristics of the control and PHP group are shown in Table 1.

Inflammatory markers at baseline

The white blood cell count (WBC) (6660.42±1492.96 vs. 7323.15±1882.67 x109/μL), and platelet count (259.56±55.24 vs. 239.82±61.16 x103/μL) were similar between the groups (p>0.05). The lymphocyte count was lower in the PHP group compared with the control group (2.44±0.80 vs. 2.12±0.45 x109/μL, p<0.05). The PHP group had greater PLR (127.21±25.77 vs. 103.63±32.52) and RDW (15.50±2.53 vs. 13.49±0.70%) values compared with the control group (p<0.05). Serum hs-CRP (4.01±3.44 vs. 2.48±1.73 mg/L) and CIMT (0.63±0.12 vs. 0.58±0.09 cm) values were higher

in the PHP group compared with the control group (p<0.05).

Changes in inflammatory markers 6 months after parathyroidectomy

Six months after parathyroidectomy, systolic BP, serum PTH, and calcium values were decreased, whereas serum phosphorous and 25OH vitamin D concentrations increased in patients with PHP (p<0.05). Serum lipids, glucose, hs-CRP, and CIMT did not change significantly after surgery (p>0.05). Platelet count, lymphocyte count, WBC, PLR, and RDW did not change significantly after parathyroidectomy (p>0.05). Postoperative hs-CRP, PLR, and RDW values were higher in patients with PHP compared with the control group (p<0.05). Postoperative BMI, BP, and PTH values were higher in patients with PHP compared with the control group (p<0.05) (Table 1).

The serum PTH concentration was positively correlated with preoperative hs-CRP (r2=0.377, p=0.001), PLR (r2=0.234, p=0.023), RDW (r2=0.296, p=0.004), and CIMT (r2=0.239, p=0.021). PTH was not correlated with other inflammatory markers including WBC, platelet count, and lymphocyte count (p>0.05). Postoperative PLR was positively correlated with the postoperative RDW value (r2=0.303, p=0.003). The correlations between serum PTH and inflammatory markers are shown in Table 2.

DISCUSSION

We observed an increase in novel inflammatory markers PLR and RDW in patients with PHP compared with the control group. Six months after parathyroidectomy, these inflammatory markers did not significantly decrease; however, these postoperative markers were higher than in the healthy controls. Our findings suggest that an inflammatory state occurs in patients with PHP, and also only partial reversal of the inflammation observes despite successful surgery.

Previous studies have shown that surgery had no effect on inflammation and cardiovascular risk in patients with PHP [6,7,13], whereas others observed a partial reversal of systemic inflammation [5,14]. The concentrations of CRP increase rapidly after parathyroidectomy in short-term studies,

Table1. Characteristics of groups

	Controls (n=50)	Preoperative PHP (n=55)	Postoperative PHP (n=55)	P*	P**	P***
BMI (kg/m2)	28.55±3.71	30.58±5.14	30.67±4.93	0.038	0.160	0.027
Systolic BP (mmHg)	120.15±10.54	136.67±15.61	129.87±14.79	0.001	0.001	0.001
Diastolic BP (mmHg)	77.56±5.07	84.07±7.19	81.70±7.91	0.001	0.057	0.005
PTH (pg/mL)	54.74±11.63	195.89±103.05	61.77±23.65	<0.001	<0.001	<0.001
Calcium (mg/dL)	9.37±0.36	11.04±0.69	9.50±0.49	<0.001	<0.001	0.193
Phosphorous (mg/dL)	3.46±0.53	2.68±0.41	3.28±0.48	<0.001	<0.001	0.095
Creatinine (mg/dL)	1.02±1.41	0.74±0.16	0.73±0.12	0.153	0.902	0.142
25OHVitD (ng/mL)	17.41±10.96	15.63±13.30	30.82±16.62	0.493	0.001	0.001
hs-CRP (mg/L)	2.48±1.73	4.01±3.44	3.59±3.07	0.017	0.291	0.049
WBC (x109/μL)	7323.15±1882.67	6660.42±1492.96	6724.14±1405.64	0.060	0.642	0.082
Platelet count (x103/μL)	239.82±61.16	259.56±55.24	260.66±57.49	0.106	0.554	0.125
Lymphocyte count (x109/μL)	2.44±0.80	2.12±0.45	2.18±0.51	0.017	0.169	0.063
PLR	103.63±32.52	127.21±25.77	123.03±31.94	0.014	0.232	0.005
RDW (%)	13.49±0.70	15.50±2.53	14.25±1.51	0.018	0.324	0.004
Glucose (mg/dl)	87.77±7.35	89.96±8.55	88.51±8.06	0.198	0.235	0.648
Total cholesterol (mg/dL)	207.12±28.61	221.04±47.59	198.67±35.96	0.107	0.126	0.067
Triglyceride (mg/dL)	148.41±72.17	152.73±67.70	156.14±90.95	0.768	0.639	0.661
HDL-C (mg/dL)	52.49±11.69	51.16±11.32	50.92±10.56	0.583	0.720	0.503
LDL-C (mg/dL)	123.51±22.24	124.52±31.68	130.44±31.61	0.866	0.116	0.243
CIMT (cm)	0.58±0.09	0.63±0.12	0.61±0.81	0.036	0.058	0.416

Abbreviations: BMI, body mass index; BP, blood pressure; PTH, parathyroid hormone; WBC, white blood cell count; hs-CRP, high sensitive C-reactive protein, PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution width; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

p* preoperative vs control

p** preoperative vs postoperative

p*** postoperative vs control

Data are presented as mean±SD.

which can be explained by tissue damage after surgery [8]. Several studies reported patients with PHP who were followed for 18 or 24 months after parathyroidectomy with no benefit of surgical treatment observed on cardiovascular risk factors and inflammatory markers [6,7]. The levels of RDW and PLR did not significantly decrease 6 months after parathyroidectomy; however, postoperatively, these markers were high compared with the controls in our study, which supports this result. Parathyroidectomy develops a partial reversal of the inflammatory processes. Ogard et al. reported that increased markers of inflammation were observed in patients with PHP compared with controls, but inflammatory markers and blood pressure were not decreased after parathyroidectomy, which supports our findings [6]. Parathyroidectomy made no significant improvement in the inflammation marker concentrations. This result may be explained by weight gain in patients undergoing surgery. Patients with mild PHP had subclinical inflammation and endothelial dysfunction after parathyroidectomy, the inflammatory markers increased, whereas subclinical cardiac function decreased [13]. Chirstensen et al. reported an increased inflammatory response in patients with PHP and a partial reversal of the systemic inflammation 6 months after parathyroidectomy, indicating a partial resolution of the systemic inflammation [5]. In the present study, the unchanged serum concentrations of inflammatory markers indicate that PHP is associated with inflammation that persists at least for a year after cure of the parathyroid adenoma. The mechanisms behind the unchanged inflammatory markers after parathyroidectomy have not yet been explained. Some inflammatory processes recover after surgery, whereas other pathways remain activated for as long as 2 years after parathyroidectomy [7].

Increased concentrations of serum PTH were associated with cancer mortality among the general older population [15]. An increased PTH concentration is associated with low-grade inflammation [1]. Cheng et al. showed that CRP, RDW, and PLR values increased with increasing serum PTH con-

centration in the general population [1]. Our study is the first to show the relationship between parathyroid adenoma and hs-CRP, RDW, and PLR, as a marker of inflammation. The increased concentrations of hs-CRP, PLR, and RDW in patients with PHP compared with the healthy controls in our study confirm the increased inflammation of parathyroid adenoma. Systemic inflammation has a role in the progression and recurrence of solid tumors [16]. PLR and RDW values have been shown to be associated with the diagnosis and prognosis of several inflammatory disorders and malignancies [11,17,18]. In patients with secondary hyperparathyroidism, PLR and platelet count decreased after parathyroidectomy; however, these parameters were not significantly decreased in recurrent or persistent hyperparathyroidism [4]. Low PLR values have been found in patients with PHP, which is incompatible with our study [16]. A nonlinear relationship was found between PLR and PTH due to the direct effect of PTH on platelet and lymphocytes [1]. In the general population, increased RDW was independently associated with high hs-CRP [18]. In our study, elevated RDW and PLR correlated with increasing PTH and hs-CRP values, similar to previous studies [1,18], suggesting a positive relationship between increasing PTH and inflammation.

Table 2.Correlation between serum PTH and inflammatory markers

	Preoperative		Postoperative	
	r2	P	r2	p
hs-CRP	0.377	0.001	0.156	0.144
WBC	- 0.113	0.277	-0.069	0.510
Platelet count	0.099	0.343	-0.066	0.528
Lympho-cyte count	- 0.176	0.090	-0.122	0.246
PLR	0.234	0.023	0.109	0.300
RDW	0.296	0.004	0.141	0.177
CIMT	0.239	0.021	0.240	0.022

Abbreviations: PTH, parathyroid hormone; WBC, white blood cell count; hs-CRP, high sensitive C-reactive protein; PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution width; CIMT, carotid intima-media thickness.

Bolds presents significant p-value.

r2 presents correlation coefficient.

There may be a link between inflammation and parathyroid adenoma in the pathogenesis of this endocrine disorder. An upregulation of inflammatory genes was found in adipose tissue obtained from patients with PHP [19]. PTH induces the production of interleukin (IL)-6 in osteoblasts and liver cells. IL-6 regulates the synthesis of acute phase protein production in the liver [1]. Several studies have reported increased subclinical inflammation in parathyroid adenoma [3,9]. Haglund et al. found increased inflammatory infiltrates in the histopathology of parathyroid adenoma, which were associated with an increase in serum PTH level. This is explained as a cytokine-mediated change in the endocrine activity of parathyroid tumor cells [3]. Hyperparathyroidism increases systemic inflammation as a result of an abnormal calcium and phosphate mechanism [4]. PTH-lowering with calcitriol treatment decreased inflammation and contributed to lymphocyte modulation in patients undergoing hemodialysis with secondary hyperparathyroidism [20]. Carcinogenesis causes chronic inflammation. In addition, inflammation and carcinogenesis are related to impaired immunity. The low lymphocyte number was correlated with the suppression of immunity, thereby increased PLR levels are related to low immunity levels in patients with cancer [21]. Moreover, interferon-γ–mediated cellular immune activation occurs in PHP [14]. Granulocyte and monocytes have PTH receptors, which are down-regulated as a result of increasing plasma PTH concentrations. The effects of PTH on the properties of lymphocytes and abnormal PTH stimulation cause the development of disturbances in the immune system. These pathways are not fully explained in patients with PHP, although their influence on inflammatory markers have been reported in previous studies. Six months after parathyroidectomy, the postoperative inflammatory markers PLR and RDW were non-significantly reduced, but remained high compared with the controls in the present study. This result supports a partial recovery of the inflammatory processes.

Serum hs-CRP, PLR, and RDW have been shown to be indicators of inflammation [10,22]. The PLR was positively correlated with hs-CRP [22]. The PLR is a marker of systemic inflammation, which determines the prognosis of neoplastic and cardiovascular disease. It evaluates both thrombotic and inflammatory pathways [1,11]. During systemic inflammation, immune mediators are released, subsequently megakaryocyte proliferation increases the circulating platelet count. Platelets

secrete thromboxane and other mediators, thereby enhancing inflammation [1,4,11,22]. Chronic inflammation is accompanied by reactive thrombocytosis. However, the lymphocyte count is an indicator of physiologic stress, and is inversely related to inflammation. A low lymphocyte count is associated with increased inflammation [17]. RDW is a marker of malnutrition-inflammation syndrome. Zhang at el. reported that elevated RDW presented the condition of inflammation and oxidative stress [23]. An increase in RDW indicates heterogeneity of cell size as anisocytosis [10]. RDW elevation is associated with cancer in the general population, and its value is positively correlated with CRP. Inflammatory cytokines inhibit erythropoietin-induced erythrocyte maturation, which is reflected in increasing RDW [24]. Inflammation and oxidative stress increase RDW values by disrupting iron metabolism and reducing the half-life of red blood cells [10,18]. The increased postoperative PLR was positively correlated with increased RDW values. Elevated PLR was also positively correlated with increasing RDW, which supports our findings [25]. We showed that RDW and PLR value increased with increasing serum hs-CRP and PTH concentrations in patients with PHP compared with the control group, which means that PLR and RDW may be considered for use as markers of inflammation in hyperparathyroidism [10].

In our study, the pathogenic mechanisms in the increased inflammatory response in patients with PHP have not been elucidated, thus further studies are required to evaluate this issue. The effect of parathyroidectomy on inflammation in long-term therapy was not investigated, and long-term studies after surgery are warranted to investigate this further. This is also a retrospective and cross-sectional study with a small sample size. These are the limitations of our study.

CONCLUSION

Our study showed an increase in novel inflammatory markers including PLR and RDW in patients with PHP, confirming a general inflammatory state in patients with PHP. After parathyroidectomy, these inflammatory markers did not decrease significantly; however, the levels of these markers were higher than in the control group, indicating a partial recovery from the inflammatory response. Large population studies are needed to demonstrate the possible relationship between hyperparathyroidism and an inflammatory link and to evaluate the effect of parathyroidectomy on inflammation.

Abbreviations: BMI, body mass index; BP, blood pressure; PTH, parathyroid hormone; WBC, white blood cell count; hs-CRP, C-reactive protein, PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution width; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

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