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Effects of Successful Parathyroidectomy on Clinical, Laboratory, and Cardiovascular Manifestations of Primary Hyperparathyroidism

ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is a disease characterized by excessive parathyroid hormone (PTH) secretion from one or more of the 4 parathyroid glands. The disease affects many organ systems and causes a variety of symptoms. Surgical removal of abnormal parathyroid glands is the most effective treatment for the disease. In this study, we aimed to investigate the effects of parathyroidectomy on the clinical, laboratory, and cardiovascular manifestations of primary hyperparathyroidism.

Methods: Thirty-five patients who underwent parathyroidectomy were included in the study. Biochemical, anthropometric, and bone densitometry results of the patients with PHPT before and after parathyroidectomy were retrieved from the patient's files. In addition, carotid intima–media thickness (CIMT) measured by ultrasonography and epicardial fat tissue (EAT) thickness values measured by transthoracic echocardiography were also included in the study.

Results: A significant improvement was detected in serum calcium, phosphorus, and PTH levels and 24-hour urinary calcium levels in the postoperative period ($P < .001$). A significant decrease was found in CIMT values after parathyroidectomy compared to the preoperative period ($P < .001$). No significant change was detected in EAT thickness after parathyroidectomy ($P = .798$). There was no correlation between EAT thickness and CIMT values measured in the postoperative period and other laboratory and clinical parameters.

Conclusion: It was determined that the CIMT level decreased significantly after parathyroidectomy. No parameter was found to correlate with the CIMT measured in the postoperative period.

Keywords: Carotid intima–media thickness, epicardial adipose tissue thickness, parathyroidectomy, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder that results in the production of more than normal parathyroid hormone (PTH) by one or more overactive parathyroid glands, causing a significant increase in serum calcium level.[1,2] It is the third most common endocrine disease after diabetes mellitus (DM) and thyroid diseases.[3] It occurs mostly after age 50 and is 3 to 4 times more common in women than men.[4] The source of excessive PTH production in PHPT is a single parathyroid adenoma in 80%-85% of cases, a double adenoma in 4%-5%, multiple gland hyperplasia in 10%-15%, and parathyroid cancer in less than 1%.[5] In PHPT, the classical symptoms are associated with hypercalcemia, one of the most important biochemical features of the disease.[6] The clinical presentation of PHPT varies from asymptomatic disease (mostly seen in countries where biochemical screening is routine) to symptomatic disease that can affect multiple organ systems, including the skeletal, kidney, central nervous system, and cardiovascular (CV) system, and manifests with varying degrees of symptoms.[6]

Primary hyperparathyroidism is known to be associated with traditional CV risk factors such as obesity, dyslipidemia, impaired glucose tolerance, DM, and hypertension (HT).[7] Both serum calcium and PTH elevation, the biochemical features of PHPT, individually affect the CV system. It has been suggested in previous studies that hypercalcemia is associated with HT, left ventricular hypertrophy (LVH), arrhythmias, vasoconstriction, and calcification of the myocardium, heart valves, and coronary arteries.[7] Due to all these negative effects, it is suggested that there is an increased CV morbidity and mortality rate in PHPT patients.[8]

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Carotid intima–media thickness (CIMT) is measured by ultrasonography (US), a noninvasive method used for the early detection of atherosclerotic changes.[9] The CIMT is a marker of subclinical atherosclerosis and endothelial dysfunction. Increased CIMT levels are associated with an increased risk of developing cardiovascular disease (CVD).[10]

Epicardial adipose tissue (EAT) is a localized fat accumulation between the myocardial surface and the visceral layer of the pericardium. Epicardial adipose tissue is a risk factor for atherosclerosis and CV events and has become one of the promising new treatment targets for CVD.[11]

Primary hyperparathyroidism must be treated because, if left untreated, it can lead to mortality and morbidity.[1] For those with symptomatic disease, parathyroidectomy is indicated. Recent guidelines for asymptomatic patients have suggested criteria for surgery, but parathyroidectomy may also be considered in patients who do not meet surgical criteria but prefer surgery.[4]

This study aimed to compare anthropometric measurements, laboratory parameters, and subclinical CVD risk indicators such as EAT thickness and CIMT in PHPT patients before and after parathyroidectomy.

Materials and Methods

This retrospective study includes 35 patients who were diagnosed with PHPT at the Department of Endocrinology and Metabolism at the Necmettin Erbakan University (NEU) Faculty of Medicine between 2019 and 2021 and were followed up in the same department after parathyroidectomy. The NEU Clinical Research Ethics Committee approved the study with approval number E-47811134-900-134693 and the date December 30, 2021. Informed consent was obtained from each of the subjects participating in the study. Patients older than 18 years were included in the study. Those with other causes of hypercalcemia, such as cancer-related hypercalcemia, and those diagnosed with secondary or tertiary hyperparathyroidism were excluded from the study. Pre- and postoperative age, gender, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist–hip ratio, systolic blood pressure (SBP), and diastolic blood pressure (DBP), laboratory parameters, and bone mineral density (BMD) data of the patients included in the study were obtained from the patient files. Pre- and postoperative EAT thickness and CIMT measurement data of all subjects were also obtained from patient files.

For all postoperative data of the patients included in the study, the first measurements after the 18th month after surgery were included.

MAIN POINTS

- In this study, a significant decrease was found in carotid intima–media thickness (CIMT) values after parathyroidectomy in patients with primary hyperparathyroidism (PHPT) compared to preoperative values.
- No correlation was found between CIMT values and postoperative changes in any clinical or laboratory parameters.
- In patients with PHPT, epicardial adipose tissue thickness measurements after parathyroidectomy were similar to preoperative values.

The CIMT measurements were performed by the same experienced cardiologist from the common carotid artery using a B-Mode US device. After the patients were supine, 3 measurements were taken 1 cm proximal to the bilateral common carotid artery division, and the average of these measurements was taken.

The same experienced cardiologist performed EAT thickness measurements using transthoracic echocardiography in the parasternal long axis and parasternal short axis windows adjacent to the right ventricle-free wall. EAT was defined as the hypoechoic area between the myocardium and visceral pericardium.

Statistical Analysis

Statistical data analysis was performed with the Statistical Package for the Social Sciences Statistics software, version 18.0 (SPSS Inc., Chicago, Ill, USA). Continuous data were given as mean ± SD if the distribution was normal and as median (minimum–maximum) if the distribution was not normal. Whether the continuous variables were normally distributed or not was determined by the Kolmogorov–Smirnov test and the Shapiro–Wilk test. In comparing differences between 2 dependent samples, the paired samples *t* test was used when parametric test assumptions were provided, and the Wilcoxon signed rank test was used when parametric test assumptions were not provided. The relationship between 2 continuous variables that did not show a normal distribution was examined with Spearman's correlation analysis. The results were evaluated at the 95% confidence interval, and $P < .05$ was considered statistically significant.

Results

Thirty-five patients diagnosed with PHPT and undergoing surgical treatment were included in the study. 32 (91.40%) of the patients were female, and 3 (8.6%) were male. The mean age of the patients was 52.03 ± 9.54 years, and the mean BMI was 30.41 ± 4.63 kg/m^2. Ten (28.60%) of these patients had HT, and 6 (17.10%) had nephrolithiasis. The patients were re-evaluated 28[12-28] months after surgery. Preoperative demographic and clinical characteristics of the patients and follow-up data are shown in Table 1.

It was determined that there was a statistically significant increase in the patients' WC, HC, and SBP values in the postoperative period compared to the preoperative period ($P = .001$; $P = .002$; $P = .010$, respectively). However, there was no significant difference in waist–hip ratio and the BMI values between the preoperative and postoperative

Table 1. Preoperative Demographic and Clinical Characteristics of the Patients and Follow-up Data

Variables	Study Population (n = 35)	Female (n = 32)	Male (n = 3)
Age (years)	52.03 ± 9.54	51.38 ± 9.70	59.00 ± 3.00
BMI (kg/m^2)	30.41 ± 4.63	30.65 ± 4.71	27.89 ± 3.24
WC (cm)	93.51 ± 11.15	93.25 ± 11.62	96.33 ± 2.51
HC (cm)	108.00 (93-146)	109.00 (93-146)	102.00 (98-102)
Waist–hip ratio	0.84 ± 0.06	0.83 ± 0.06	0.95 ± 0.03
Adenoma size (mm)	14.00 (5-36)	14.00 (5-36)	12.50 (9-16)
Time since surgery (months)	28 (19-34)	28.5 (19-34)	27 (27-32)

All values are presented as mean ± SD or median (minimum–maximum).
BMI, body mass index; HC, hip circumference; WC, waist circumference.

Table 2. Anthropometric Measurements and Clinical Data of Primary Hyperparathyroidism Patients in the Preoperative and Postoperative Periods

Variables	Preoperative	Postoperative	*P*
BMI (kg/m^2)	30.41 ± 4.63	30.46 ± 4.68	.883**
WC (cm)	93.51 ± 11.15	99.23 ± 11.24	**.001****
HC (cm)	108.00 (93.00-146.00)	114.00 (97.00-141.00)	**.002***
Waist–hip ratio	0.84 ± 0.06	0.86 ± 0.05	.185**
CIMT (cm)	0.08 (0.03-0.09)	0.06 (0.03-0.08)	**<.001***
EAT thickness (cm)	0.40 (0.05-0.50)	0.30 (0.20-0.70)	.798*
SBP (mm Hg)	127.29 ± 18.4	138.57 ± 19.90	**.010****
DBP (mm Hg)	80.43 ± 14.42	85.11 ± 13.06	.140**

All values are presented as mean ± SD or median (minimum–maximum). Values in bold indicate statistical significance.BMI, body mass index; CIMT, carotid intima–media thickness; DBP, diastolic blood pressure; EAT, epicardial adipose tissue; HC, hip circumference; SBP, systolic blood pressure; WC, waist circumference.
*Wilcoxon signed-rank test
**Paired samples *t*-test.

periods ($P = .185$ and $P = .883$, respectively). EAT thickness and DBP values were similar in the preoperative and postoperative periods ($P = .798$ and $P = .140$, respectively). It was found that the patients' CIMT values decreased in the postoperative period compared to the preoperative values ($P < .001$). The comparison of anthropometric measurements and clinical data of the patients in the preoperative and postoperative periods is shown in Table 2. The distribution of CIMT values in the preoperative and postoperative periods is presented in Figure 1.

According to the dual-energy x-ray absorptiometry (DXA) results of the patients, it was determined that there was a statistically significant increase in the L1-L4 T-score, femoral neck T-score, and total hip T-score values in the postoperative period compared to the preoperative values ($P < .001$; $P = .034$ and $P = .005$, respectively). The distribution of BMD results measured using DXA in the preoperative and postoperative periods of PHPT patients is shown in Table 3.

According to the DXA results in the preoperative period, the BMD of 10 (28.60%) of the patients was normal, the BMD of 18 (51.40%) was compatible with osteopenia, and the BMD of 7 (20.00%) was compatible with osteoporosis. According to the DXA results in the postoperative period, the BMD of 19 (54.30%) of the patients was normal, the

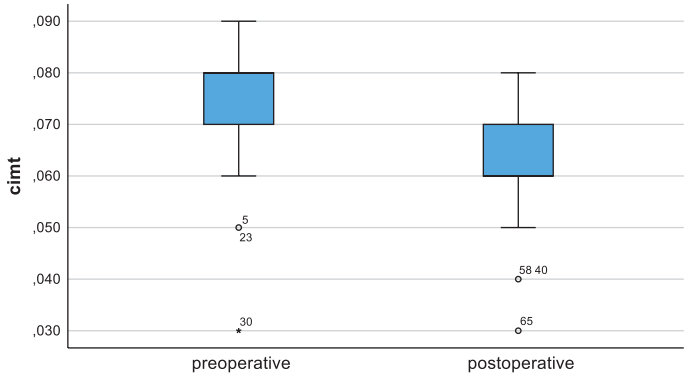

Figure 1. Distribution of carotid intima–media thickness values measured in the preoperative and postoperative periods.

Table 3. Dual-energy X-ray Absorptiometry Results of Primary Hyperparathyroidism Patients in the Preoperative and Postoperative Periods

Variables	Preoperative Mean ± SS	Postoperative Mean ± SS	*P*
L1-L4 T-score	−1.40 (−2.90-1.90)	−0.90 (−2.80-2.90)	**<.001***
Femoral neck T-score	−0.86 ± 1.16	−0.54 ± 1.08	**.034****
Total hip T-score	−0.68 ± 1.07	−0.30 ± 1.04	**.005****

All values are presented as mean ± SD or median (minimum–maximum). Values in bold indicate statistical significance.
*Wilcoxon signed-rank test.
**Paired samples t-test.

BMD of 14 (40.00%) was compatible with osteopenia, and the BMD of 2 (5.70%) was compatible with osteoporosis. None of the patients included in the study received bisphosphonate treatment in the preoperative or postoperative period.

A statistically significant decrease was detected in the fasting plasma insulin, homeostatic model assessment of insulin resistance (HOMA-IR), PTH, serum calcium, 24-hour urinary calcium, and alkaline phosphatase levels of PHPT patients in the postoperative period compared to the preoperative period ($P = .031$; $P = .029$; $P < .001$; $< .001$; $P < .001$; and $P < .001$, respectively). Moreover, an increase in serum phosphorus level was detected in the postoperative period ($P < .001$). A comparison of laboratory parameters of PHPT patients in the preoperative and postoperative periods is shown in Table 4.

The effect of postoperative and preoperative differences in other parameters on the CIMT level was examined by linear regression analysis, and no relationship was found.

Discussion

Primary hyperthyroidism is a metabolic disease in which at least 1 of the 4 parathyroid glands secretes excess PTH, resulting in increased calcium levels in the serum.[1] Primary hyperthyroidism is frequently seen in women after age 50.[4] In our study, consistent with previous studies, 32 (91.40%) patients were female, 3 (8.50%) were male, and the mean age was 52.03 ± 9.54 years.

Parathyroid hormone affects both bone formation and bone resorption. As in PHPT, persistently high serum PTH levels predominate bone resorption.[12] This condition leads to a loss in BMD, leading to osteopenia and osteoporosis.[29] An improvement in BMD is observed after parathyroidectomy.[12,30] Lu et al[29] demonstrated significant increases in lumbar and total hip BMD scores at 6 months, 1 year, and 2 years after parathyroidectomy. In our study, consistent with previous studies, a statistically significant increase was found in L1-L4, femoral neck, and total hip T score levels after parathyroidectomy ($P < .001$; $P = .034$; and $P = .005$, respectively).

The current study evaluated CVD markers such as EAT thickness and CIMT measured before and after surgery in PHPT patients. Dyslipidemia, HT, obesity, and DM are known to be traditional risk factors for CVD.[7] Visceral fat deposition is also a risk factor for CVD.[31] Epicardial adipose tissue is considered the visceral fat tissue of the heart, and determining the amount of visceral fat is important in detecting and treating CVD.[32] Asik et al[33] showed that EAT was significantly increased in patients with PHPT. Kızılgül et al[12]

Table 4. Laboratory Parameters of Primary Hyperthyroidism Patients in the Preoperative and Postoperative Periods

Variables	Preoperative	Postoperative	*P*
HbA1c	5.68 ± 0.34	5.66 ± 0.47	.769**
Fasting plasma insulin (mU/mL)	12.50 (2.00-48.01)	10.80 (3.38-36.40)	**.031***
HOMA-IR	3.00 (0.40-13.50)	2.80 (0.50-9.40)	**.029***
Fasting plasma glucose (mg/dL)	97.38 ± 11.73	96.16 ± 14.59	.597**
Serum urea level (mg/dL)	23.00 (15.00-45.00)	26.50 (14.90-54.20)	.664*
Serum creatinine level (mg/dL)	0.70 (0.17-0.97)	0.73 (0.53-0.93)	.134*
Serum albumin level (g/dL)	46.20 (34.00-51.00)	46.00 (40.60-49.50)	.676*
Triglyceride (mg/dL)	152.00 (55.00-383.80)	153.50 (48.40-527.00)	.322*
HDL (mg/dL)	48.60 (27.50-195.00)	48.70 (35.10-93.10)	.682*
LDL (mg/dL)	128.53 ± 35.15	123.29 ± 31.18	.321**
TSH (mIU/L)	1.50 (0.10-3.59)	1.40 (0.01-30.90)	.857*
Vitamin D (IU)	13.10 (3.00-30.70)	15.50 (6.15-53.20)	.050*
PTH (pg/mL)	179.00 (72.00-653.00)	35.30 (25.30-127.00)	**<.001***
Serum calcium level (mg/dL)	11.18 (10.50-14.10)	9.47 (8.79-10.15)	**<.001***
Serum phosphorus level (mg/dL)	2.46 (1.38-4.10)	3.48 (2.42-4.25)	**<.001***
Serum magnesium level (mg/dL)	2.00 (1.65-2.45)	2.02 (1.18-2.49)	.798*
24-hour urinary calcium (mg)	371.00 (143.00-900.00)	120.00 (19.50-351.92)	**<.001***
ALP (IU/L)	102.00 (43.00-229.00)	78.00 (35.00-145.00)	**<.001***
CRP (mg/dL)	2.00 (0.16-18.00)	2.28 (0.18-18.81)	.589*

All values are presented as mean ± SD or median (minimum−maximum). Values in bold indicate statistical significance. ALP, alkaline phosphatase; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
*Wilcoxon signed-rank test
**Paired samples *t*-test.

included 34 PHPT patients and 28 healthy control subjects in their study investigating the effect of parathyroidectomy on EAT and showed that EAT decreased after parathyroidectomy ($P = .031$). However, the authors found no correlation between the decrease in EAT thickness and CV risk factors.[13] In our study, although there was a decrease in EAT thickness in the postoperative period compared to preoperative values, it was not statistically significant ($P = .798$). No significant difference was found in EAT thickness after parathyroidectomy in our study because there was no statistically significant decrease in the LDL cholesterol level measured in the postoperative period compared to the preoperative LDL cholesterol level.

There is evidence that subclinical CVD may occur in patients with mild PHPT. Previous studies have revealed subclinical carotid vascular changes in patients with mild PHPT, and PHPT patients have increased CIMT and plaque thickness compared to the normal population.[14] Increased CIMT is an early and subclinical marker of atherosclerosis and has been suggested to be clinically associated with CV and cerebrovascular events.[15] In a study including 20 patients with PHPT and 20 healthy control subjects, Nuzzo et al[15] showed that CIMT levels were significantly higher in patients with PHPT. Kosch et al[16] included 19 PHPT patients and 20 healthy control subjects in their study and found no difference between the groups regarding CIMT. The authors also reported no change in CIMT levels after parathyroidectomy.[17] Walker et al[13] evaluated the CIMT level, carotid plaque, and stiffness measurement parameters of 44 PHPT patients at 1 and 2 years after surgery. The authors revealed that carotid stiffness approached the normal range 2 years after parathyroidectomy, and there was no decrease in increased CIMT levels.[15] Cansu et al[17] showed no significant difference in CIMT levels 6 months after parathyroidectomy in normocalcemic PHPT patients compared to preoperative values. However, in hypercalcemic PHPT patients, there was a significant decrease in CIMT values measured in the postoperative period compared to preoperative values.[18] In another study, 53 patients with PHPT and 46 healthy control subjects were included, and it was shown that there was a significant decrease in CIMT levels after parathyroidectomy.[19] In the current study, consistent with previous studies, a decrease in CIMT levels after parathyroidectomy was detected compared to preoperative values, and the difference was found to be statistically significant ($P < .001$). However, our study did not find a correlation between EAT thickness and CIMT levels and the change in laboratory parameters.

According to the results of our study, we think that PHPT patients should be followed up for early diagnosis of CVD due to increased CIMT levels in the preoperative period and that there is an improvement in the development of CVD with a decrease in CIMT levels in the postoperative period.

There are conflicting results in the literature regarding the frequency of HT in patients with PHPT.[20] In our study, there was a significant increase in postoperative SBP levels ($P = .010$), while DBP levels were found to be similar to preoperative levels ($P = .140$). These results in our study were likely due to the length of the postoperative period, the mean age of the patients, and the presence of primary HT.

There are studies on the relationship of symptomatic PHPT with glucose intolerance, obesity, and insulin resistance.[21] While previous studies have shown that parathyroidectomy is associated with improvement[22] or worsening[23] in glucose levels, there are also studies showing that the glucose level does not change after parathyroidectomy.[24,25] Our study shows no significant difference between preoperative and postoperative values in BMI and glucose levels ($P = .883$; $P = .597$, respectively).

In PHPT, increased serum calcium levels result in insulin resistance. In addition, the effect of PTH on suppressing lipolysis causes weight gain and an increase in insulin resistance.[26] Procopio et al[26] showed that HOMA-IR levels were higher in 68 patients with PHPT compared to the control group and were associated with serum calcium levels. Additionally, a randomized, double-blind study showed a significant decrease in HOMA-IR and glucose levels at 12-month follow-up after parathyroidectomy in 150 patients with PHPT.[28] Our study found a

significant decrease in HOMA-IR and insulin levels in the postoperative period ($P = .029$; $P = .031$, respectively). However, a moderately positive correlation was found between HOMA-IR and PTH levels ($r = .441$; $P = .008$).

Our study included data after the 18th month after surgery as postoperative data. An important limitation of our study is that early postoperative data (such as the third month, sixth month, and first year) were not included. Additionally, the small sample size is another important limitation of our study.

In conclusion, in the current study, as expected, a significant improvement was detected in laboratory parameters such as calcium, phosphorus, PTH, and urinary calcium levels measured before and after parathyroidectomy. A significant improvement was detected in L1-L4 and femur T scores measured by DXA in the postoperative period, in accordance with the literature. After parathyroidectomy, EAT thickness, one of the subclinical CVD indicators, was similar to the preoperative period, while a significant decrease was observed in CIMT values. No correlation was found between CIMT values and postoperative changes in any clinical or laboratory parameters. According to the current study, if supported by further large-scale studies with a larger sample size, PHPT should be treated surgically to prevent the development and progression of CVD.

Ethics Committee Approval: The Ethics Committee of the Necmettin Erbakan University (NEU) Meram Medical Faculty approved the study (decision number: E-47811134-900-134693; date: December 30, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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