Effect of parathyroidectomy on epicardial fat thickness as a cardiovascular risk factor in patients with primary hyperparathyroidism

Muhammed KIZILGÜL![ORCID], **Mustafa ÇALIŞKAN**![ORCID], **Selvihan BEYSEL**![ORCID], **Mustafa ÖZBEK**![ORCID], **Erman ÇAKAL**![ORCID]

Department of Endocrinology and Metabolism, University of Health Sciences, Dışkapı Training and Research Hospital, Ankara, Turkey

Background/aim: Several studies demonstrated that primary hyperparathyroidism is related to increased risk for cardiovascular diseases (CVDs), and risk is decreased by parathyroidectomy. Epicardial fat thickness (EFT) has been postulated as a new marker of CVD risk. We evaluated the impact of parathyroidectomy on EFT in patients with primary hyperparathyroidism (PHPT).

Materials and methods: Thirty-four PHPT patients (29 female, 5 male) and 28 age- and sex-matched controls (19 female, 9 male) were included in the study. Demographic, anthropometric, and biochemical data were recorded both before parathyroidectomy and 6 months after the procedure. Epicardial fat thickness was measured by transthoracic echocardiography.

Results: Mean age was 53.15 ± 8.44 years. Mean preoperative EFT was higher than mean EFT in the control group (0.49 ± 0.07 cm to 0.46 ± 0.08 cm, P: 0.0005), and EFT decreased after parathyroidectomy (0.49 ± 0.07 cm to 0.44 ± 0.08 cm, P: 0.0005). Systolic blood pressure and calcium, parathormone, and hsCRP levels decreased after parathyroidectomy (P < 0.05). Vitamin D levels increased (P < 0.05). Diastolic blood pressure, body mass index, carotid intima-media thickness, and HOMA-IR, fasting plasma glucose, and phosphorus levels were unchanged after parathyroidectomy (P > 0.05). Preoperatively, EFT was correlated with SBP (r: 0.360, P: 0.0285) and age (r: 0.466, P: 0.0036). Multiple linear regression used to identify independent predictors of change in epicardial fat did not find any predictor of change in epicardial fat (P > 0.05).

Conclusion: EFT was decreased by parathyroidectomy in patients with primary hyperparathyroidism. However, the decrease in EFT was not correlated with any of the cardiovascular risk factors. More comprehensive studies evaluating the potential relation between PHPT and EFT need to be conducted.

Key words: Primary hyperparathyroidism, epicardial fat thickness, cardiometabolic risk factors

1. Introduction

Primary hyperparathyroidism (PHPT) is described as increased serum calcium and nonsuppressed parathyroid hormone (PTH) levels [1]. The incidence of PHPT is increasing significantly as laboratory screening tests become more widely available [2]. Accumulating data show that even mild PHPT leads to an elevated risk for cardiovascular diseases (CVDs), many of which improve after parathyroidectomy [3–7]. Epicardial fat (EF) is present between the outer layer of the myocardium and the inner layer of the pericardium. EF is metabolically active and may cause inflammation and dysfunction in the myocardium by secreting proatherogenic and proinflammatory cytokines, as well as reactive oxygen radicals. Increasing thickness of EF is related to higher risk of CVD [8]. Epicardial fat thickness (EFT) can be measured by transthoracic echocardiography [9] and is considered a novel marker of CVD risk [10]. We evaluated

the impact of parathyroidectomy on EFT and its relation to cardiometabolic risk factors in patients with PHPT.

2. Materials and methods

2.1. Patient selection

Thirty-four patients (29 female, 5 male) who were diagnosed with PHPT at the Dışkapı Training and Research Hospital between 2012 and 2016 and 28 age- and sex-matched controls (19 female, 9 male) were enrolled in the study. Local ethics committee approval was obtained, and all participants provided written informed consent before the study began. Patients with multiple endocrine neoplasias, parathyroid cancer, thyroid cancer, or hyperparathyroidism-jaw tumor syndrome and patients on drugs that counteract calcium and vitamin D metabolism were excluded from the study. A PHPT diagnosis was made in the case of persistent hypercalcemia with normal or nonsuppressed PTH concentrations. The decision for

1165

surgery was in agreement with guidelines applied at the time of diagnosis [11].

2.2. Clinical, biochemical, and hormonal measurements

Basal demographic data, clinical features, and carotid intima-media thickness (CIMT) measurements were recorded for all participants. Weight, height, waist circumference (WC), body mass index (BMI), and systolic and diastolic blood pressure (SDP and DBP, respectively) were measured. Fasting biochemical and hormonal measurements were taken in the morning using colorimetric methods, and complete blood counts were obtained from all participants. An intact chemiluminescent immunoassay of PTH (Immulite 2000) was used for measuring serum PTH levels, and 25-OH vitamin D concentrations were measured using a radioimmune assay.

EFT was calculated using a Philips IE33, a commercially available device (Philips Electronics, USA), and was described as the distance between the visceral and parietal pericardium on the anterior wall of the right ventricle. EFT was calculated vertically on the free wall of the right ventricle in parasternal long- and short-axis views at end-diastole over 3 cardiac cycles [12]. Three measurements were performed and the average was recorded. High-resolution B-mode ultrasound (EUB 7000 HV; Hitachi, Japan) with a 13-MHz linear array transducer was used to image parathyroids. CIMT was measured by B-mode imaging high-resolution ultrasound (EUB 7000 HV; Hitachi).

2.3. Statistical analysis

All statistical analyses were performed using JMP 13.0.1 software (SAS Institute, USA). Descriptive data are reported as mean ± standard deviation (SD) and percentage (%). Normality of distribution was examined by using the Kolmogorov–Smirnov or Shapiro–Wilk W tests. The chi-square or Fisher's exact test was used when variables were categorical. Student's t-test was used for normally distributed continuous variables, and the Mann–Whitney U-test was used for those that did not fit a normal distribution. Correlations were assessed using Pearson's and Spearman's correlation. A multiple linear regression model was used to identify independent predictors of change in EF and P < 0.05 was accepted as statistical significance.

3. Results

Thirty-four PHPT patients (29 female, 5 male) were included in the study. Mean age was 53.15 ± 8.44 years. The basal demographic, anthropometric, and biochemical parameters of patients are shown in Table 1. Preoperatively, EFT was correlated with SBP (r: 0.360, P: 0.0285) and age (r: 0.466, P: 0.0036) (Table 2). Mean preoperative EFT was higher than mean EFT in the control group (0.49 ± 0.07 cm to 0.46 ± 0.08 cm, P: 0.0005). Mean EFT

Table 1. Clinical and demographic characteristics of patients.

	Mean ± SD
Age (years)	53.15 ± 8.44
BMI (kg/m²)	31.66 ± 7.71
Systolic blood pressure (mmHg)	141.03 ± 19.25
Diastolic blood pressure (mmHg)	86.38 ± 8.64
Calcium (mg/dL)	11.22 ± 0.55
Phosphorous (mg/dL)	2.83 ± 1.20
Parathormone (pg/mL)	226.97 ± 253.61
Vitamin D (ng/mL)	14.27 ± 15.40
Fasting plasma glucose (mg/dL)	93.50 ± 9.44
Creatinine (mg/dL)	0.73 ± 0.20
Albumin	4.54 ± 0.32
Alkaline phosphatase	119.00 ± 42.74
LDL-cholesterol (mg/dL)	126.33 ± 30.04
Triglyceride (mg/dL)	174.82 ± 88.56
HDL-cholesterol (mg/dL)	49.27 ± 12.48
CRP (mg/L)	3.13 ± 2.6
HOMA-IR	2.64 ± 1.50
CIMT (cm)	0.67 ± 0.12

decreased after parathyroidectomy (0.49 ± 0.07 cm to 0.44 ± 0.07 cm, P: 0.031). Systolic blood pressure and calcium, parathormone, and hsCRP levels decreased after parathyroidectomy (P < 0.05). Vitamin D levels increased (P < 0.05). Diastolic blood pressure, BMI, CIMT, and HOMA-IR, fasting plasma glucose, and phosphorus levels were unchanged after parathyroidectomy (P > 0.05) (Table 3). A multiple linear regression model was used to identify independent predictors of change in EF. We did not find a predictor of change in EF (Table 4).

4. Discussion

Our aim was to evaluate the effect of parathyroidectomy on EFT and its relation to cardiovascular risk factors in PHPT patients. We found that EFT decreased after parathyroidectomy and was correlated with SBP and age. We believe that ours is the first study to evaluate the effect of parathyroidectomy on EFT in PHPT.

Adipose tissue is not just considered a primary site for fat storage; it also serves as an endocrine organ by secreting several hormones and adipokines including leptin, adiponectin, and tumor necrosis factor-α (TNF-α), which have proinflammatory, proatherogenic, or protective effects and lead to negative metabolic and cardiovascular outcomes [13,14]. Extraabdominal deposition of fat as epicardial and intraabdominal visceral adiposity are now

Table 2. Correlation of EFT with metabolic and biochemical parameters.

	r²	P
Systolic blood pressure (mmHg)	0.3602	0.0285
Diastolic blood pressure (mmHg)	0.152	0.369
Adenoma volume (mL)	0.1768	0.325
Age (years)	0.4662	0.0036
Calcium (mg/dL)	−0.2057	0.222
Phosphorous (mg/dL)	0.0007	0.996
Parathormone (pg/mL)	−0.0252	0.882
Vitamin D (ng/mL)	−0.2014	0.232
Fasting plasma glucose (mg/dL)	0.3228	0.058
Creatinine (mg/dL)	0.1144	0.5
LDL-cholesterol (mg/dL)	−0.2013	0.239
Triglyceride (mg/dL)	−0.013	0.94
HDL-cholesterol (mg/dL)	0.1408	0.412
Waist circumference (cm)	0.3101	0.062
CRP (mg/L)	−0.0543	0.757
HOMA-IR	−0.0276	0.881
CIMT (cm)	0.0508	0.765
BMI (kg/m²)	0.3068	0.065

suggested as markers of CVD risk [15–17]. Epicardial fat can synthesize and release adipokines and bioactive factors that may extend into the myocardium through vasocrine and/or paracrine pathways. Hence, EF tissue could be considered an endocrine organ [18]. As a result of functional and anatomical proximity, EF has a negative effect on coronary circulation and may lead to myocardial dysfunction and hypertrophy, and finally to coronary artery disease and cardiac insufficiency. EF is related to cardiometabolic disorders such as coronary artery disease, obesity, type 2 diabetes mellitus, and metabolic syndrome and with CVD risk factors such as hyperlipidemia, hypertension, obesity markers, and CIMT [8].

PTH receptors are present in cardiomyocytes, endothelial cells, and smooth muscle cells [19], and elevated PTH levels are related to myocardial fibrosis, calcification, and hypertrophy [20]. Additionally, elevated serum calcium levels are related to a higher rate of mortality, hypertension, left ventricular hypertrophy, and arrhythmias, as well as calcification of the myocardium, coronary arteries, and heart valves [21]. Studies have demonstrated that patients with PHPT had increased cardiovascular events and mortality, and many of these patients improved after parathyroidectomy [3–7,22]. Hypertension, hyperlipidemia, CIMT, CRP, and insulin resistance are all well-known CVD risk factors [23,24]. Numerous cardiovascular risk factors have been shown in patients with PHPT, including hypertension and elevated CIMT, insulin resistance, and CRP [25–28].

Table 3. EFT and metabolic parameters before and after parathyroidectomy.

Variables	Before parathyroidectomy (n: 33)	After parathyroidectomy (n: 33)	Control (n: 28)	P*	P**
Age (years)	53.15 ± 8.44		52.57 ± 6.03		0.755
EFT(cm)	0.49 ± 0.07	0.44 ± 0.08	0.46 ± 0.07	0.0005	0.031
SBP (mmHg)	140.68 ± 19.25	130.99 ± 17.11	122.31 ± 10.32	0.0026	<0001
DBP (mmHg)	86.96 ± 8.64	83.96 ± 8.64	78.95 ± 5.66	0.128	<0001
BMI (kg/m²)	31.76 ± 7.71	31.09 ± 4.88	29.87 ± 3.62	0.504	0.063
Ca (mmol/L)	11.21 ± 0.55	9.55 ± 0.58	9.39 ± 0.38	<0001	<0001
P (mmol/L)	2.82 ± 1.20	3.32 ± 0.60	3.45 ± 0.51	0.050	0.0017
PTH (pg/mL)	226.96 ± 253.61	64.89 ± 33.75	61.97 ± 25.25	0.0006	<0001
25(OH)D₃ (ng/mL)	14.27 ± 15.39	28.97 ± 14.87	15.64 ± 12.07	0.0007	0.767
FPG (mmol/L)	93.50 ± 9.43	94.12 ± 14.08	88.3 ± 8.31	0.733	0.0021
hsCRP (mg/L)	3.13 ± 2.6	3.82 ± 2.16	3.23 ± 2.35	0.052	0.806
CIMT (cm)	0.66 ± 0.11	0.64 ± 0.11	0.61 ± 0.12	0.388	0.049
HOMA-IR	2.63 ± 1.49	2.43 ± 1.25	2.06 ± 1.03	0.256	0.041

*Before vs. after parathyroidectomy; data are represented as mean ± SD.
**Before parathyroidectomy vs. control.

Table 4. Multiple linear regression model to identify independent predictor of change in epicardial fat.

	β	P
Sex	−0.152	0.489
Age	−0.296	0.180
Preoperative CRP	0.172	0.434
Adenoma size	−0.028	0.987
Preoperative PTH	−0.004	0.986
Preoperative calcium	−0.195	0.373
Preoperative BMI	0.058	0.792
Diastolic BP	−0.213	0.329
Systolic BP	−0.263	0.225
CIMT	−0.068	0.759

Asik et al. demonstrated that patients with PHPT had increased EFT. They also found correlations between EFT and CIMT, age, systolic blood pressure, and PTH and serum calcium levels [29]. In light of this information, we aimed to investigate whether EFT could be related to cardiometabolic risk factors and whether these decreased after parathyroidectomy in PHPT patients. In our study, EFT was correlated with some cardiometabolic risk factors such as SBP and age. Additionally, EFT decreased after parathyroidectomy in these patients. However, the decrease in EF thickness was not correlated with any of the cardiovascular risk factors.

Our study has some limitations since it was designed as a cross-sectional prospective study. Additionally, we had a relatively small sample size, and the study was conducted in a single center. We evaluated EF by 2-dimensional echocardiography. Although echocardiography is a relatively simple and cheap method, echocardiography might not fully represent the amount of EF tissue due to its 3-dimensional nature. This could be another limitation of our study.

As a result of the anatomical and functional proximity of EF tissue to coronary circulation, it can exert a direct effect on CVD risk. Our study showed that parathyroidectomy decreased the thickness of EF; however, this decrease was not correlated with any of the cardiovascular risk factors. More comprehensive studies evaluating the potential relation between PHPT and EFT need to be conducted.

References

1. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. British Medical Journal 2015; 350: h2723. doi: 10.1136/bmj.h2723

2. Bilezikian JP, Cusano NE, Khan AA, Liu JM, Marcocci C et al. Primary hyperparathyroidism. Nature Reviews Disease Primers 2016; 2: 16033. doi: 10.1038/nrdp.2016.33

3. Smith JC, Page MD, John R, Wheeler MH, Cockcroft JR et al. Augmentation of central arterial pressure in mild primary hyperparathyroidism. Journal of Clinical Endocrinology and Metabolism 2000; 85 (10): 3515-3519.

4. Yu N, Donnan PT, Flynn RW, Murphy MJ, Smith D et al. Increased mortality and morbidity in mild primary hyperparathyroid patients. The Parathyroid Epidemiology and Audit Research Study (PEARS). Clinical Endocrinology 2010; 73 (1): 30-34. doi: 10.1111/j.1365-2265.2009.03766.x

5. Nilsson IL, Åberg J, Rastad J, Lind L, Clark OH et al. Circadian cardiac autonomic nerve dysfunction in primary hyperparathyroidism improves after parathyroidectomy. Surgery 2003; 134 (6): 1013-1019.

6. Piovesan A, Molineri N, Casasso F, Emmolo I, Ugliengo G et al. Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. Clinical Endocrinology 1999; 50 (3): 321-328.

7. Stefenelli T, Abela C, Frank H, Koller-Strametz J, Globits S et al. Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. Journal of Clinical Endocrinology and Metabolism 1997; 82 (1): 106-112.

8. Katsiki N, Mikhailidis DP, Wierzbicki AS. Epicardial fat and vascular risk: a narrative review. Current Opinion in Cardiology 2013; 28 (4): 458-463. doi: 10.1097/HCO.0b013e3283605fba

9. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. Journal of the American Society of Echocardiography 2009; 22 (12): 1311-1319. doi: 10.1016/j.echo.2009.10.013

10. Lima-Martínez MM, Blandenier C, Iacobellis G. Epicardial adipose tissue: more than a simple fat deposit? Endocrinology 2013; 60 (6): 320-328. doi: 10.1016/j.endonu.2012.08.001

11. Bilezikian JP, Potts JT Jr, Fuleihan GH, Kleerekoper M, Neer R et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. Journal of Clinical Endocrinology and Metabolism 2002; 87 (12): 5353-5361.

12. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obesity Research 2003; 11 (2): 304-310.

13. Mazurek T, Zhang LF, Zalewski A, Mannion JD, Diehl JT et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003; 108 (20): 2460-2466.

14. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends in Endocrinology and Metabolism 2000; 11 (8): 327-332.

15. Sacks HS, Fain JN, Bahouth SW, Ojha S, Frontini A et al. Adult epicardial fat exhibits beige features. Journal of Clinical Endocrinology and Metabolism 2013; 98 (9): E1448-1455. doi: 10.1210/jc.2013-1265

16. Salazar J, Luzardo E, Mejías JC, Rojas J, Ferreira A et al. Epicardial fat: physiological, pathological, and therapeutic implications. Cardiology Research and Practice 2016; 2016: 1291537. doi: 10.1155/2016/1291537

17. Matloch Z, Kotulak T, Haluzik M. The role of epicardial adipose tissue in heart disease. Physiological Research 2016; 65 (1): 23-32.

18. Iacobellis G. Epicardial adipose tissue in endocrine and metabolic diseases. Endocrine 2014; 46 (1): 8-15. doi: 10.1007/s12020-013-0099-4

19. Schluter KD, Piper HM. Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. Cardiovascular Research 1998; 37 (1): 34-41.

20. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. Current Osteoporosis Reports 2008; 6 (2): 77-83

21. Silverberg SJ. Editorial: Cardiovascular disease in primary hyperparathyroidism. Journal of Clinical Endocrinology and Metabolism 2000; 85 (10): 13-14.

22. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease—a review. European Heart Journal 2004; 25 (20): 1776-1787.

23. Akhabue E, Thiboutot J, Cheng JW, Vittorio TJ, Christodoulidis G et al. New and emerging risk factors for coronary heart disease. American Journal of the Medical Sciences 2014; 347 (2): 151-158. doi: 10.1097/MAJ.0b013e31828aab45

24. Cannon CP. Cardiovascular disease and modifiable cardiometabolic risk factors. Clinical Cornerstone 2007; 8 (3): 11-28.

25. Walker MD, Fleischer J, Rundek T, McMahon DJ, Homma S et al. Carotid vascular abnormalities in primary hyperparathyroidism. Journal of Clinical Endocrinology and Metabolism 2009; 94 (10): 3849-3856. doi: 10.1210/jc.2009-1086

26. Ljunghall S, Palmer M, Akerstrom G, Wide L. Diabetes mellitus, glucose tolerance and insulin response to glucose in patients with primary hyperparathyroidism before and after parathyroidectomy. European Journal of Clinical Investigation 1983; 13 (5): 373-377.

27. Almqvist EG, Bondeson AG, Bondeson L, Svensson J. Increased markers of inflammation and endothelial dysfunction in patients with mild primary hyperparathyroidism. Scandinavian Journal of Clinical and Laboratory Investigation 2011; 71 (2): 139-144. doi: 10.3109/00365513.2010.543694

28. Luigi P, Chiara FM, Laura Z, Cristiano M, Giuseppina C et al. Arterial hypertension, metabolic syndrome and subclinical cardiovascular organ damage in patients with asymptomatic primary hyperparathyroidism before and after parathyroidectomy: preliminary results. International Journal of Endocrinology 2012; 2012: 408295. doi: 10.1155/2012/408295

29. Asik M, Sahin S, Temiz A, Ozkaya M, Ozkul F et al. Evaluation of epicardial fat tissue thickness in patients with primary hyperparathyroidism. Endocrine Practice 2014; 20 (1): 26-32. doi: 10.4158/EP13140.OR