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Original Article

The effect of parathyroidectomy on kidney functions in primary hyperparathyroidism

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Abstract

Aim: The purpose of this study is to investigate the changes in renal function of the patients having primary hyperparathyroidism with GFR <60 ml/min/1.73 m^2 and GFR>60 ml/ min/1.73 m^2 before and after PTX. A. Prolonged hypercalcemia leads to impaired renal function and the associated glomerular filtration rate (GFR) decrease. One of the indications of surgery in primary hyperparathyroidism is decreased renal function (GFR <60 ml/min). Discussions about the effect of parathyroidectomy (PTX) on renal function still continue.

Materials and Methods: The archive files of 59 patients diagnosed with primary hyperparathyroidism (PHPT), to whom PTX have been performed between January 2008 and October 2019 at Cumhuriyet University Surgical Oncology Clinic, were reviewed retrospectively. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Patients were divided into two groups according to their GFR values, as GFR<60 ml/min/1.73 m^2 and GFR>60 ml/min/1.73 m^2. Laboratory outcomes of the patients one week before and after PTX were compared. The data of the study were analyzed in SPSS (ver. 23.0) program.

Results: Regarding the patients to whom PTX have been performed, 12 patients (20.3%) were male and 47 (79.7%) were female. The mean age was 54.7 years. In patients with GFR<60 ml/min/1.73 m^2, pre-op mean Parathormone (PTH) value was 1227.36 pg/ml, Calcium (Ca) 10.60 mg/dl, Creatine (Cr) 5.12 mg/dl: while mean PTH value in post-op period was found to be 131.69 (SS: 2.99), Ca: 8.29, Cr: 3.57. In the patient group with GFR>60 ml/min/1.73 m^2, pre-op mean PTH was 309.34, Ca: 11.05, Cr: 0.73 (SD: 0.15); whereas post-op PTH was 48.51, Ca: 8.88, Cr: 0.68. In addition, GFR increased in patients in both groups and statistically significant results were obtained between pre and post PTX values.

Conclusion: In this study, an improvement was observed after PTX in the renal function of the patients with impaired renal function, whereas GFR values of the patients with normal renal function were increased.

Keywords: Glomerular filtration rate (GFR); parathyroidectomy (PTH); primary hyperparathyroidism (PHPT)

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disease characterized by increased parathyroid hormone and associated calcium (Ca) increase (1). It is a relatively common endocrine disorder with a prevalence of 1-7 cases per 1000 adults (2,3). Autonomic secretion of PTH affects the target organs (bone, kidney) and increases the calcium (ca) concentrations in the extracellular area (4,5).

Previously, patients with PHPT used to appear with clinical cases such as brown tumors, osteitis fibrosa cystica, nephrolithiasis, band keratopathy, abdominal noise, excessive fatigue, psychic complaints, bone pain, muscle atrophy and myopathy due to the prolonged duration of the disease (6, 7). These problems are rare nowadays, as most PHPTs are asymptomatic. Regarding the kidney, patients with symptomatic PHPT have hypercalciuria, renal microlithiasis and slightly impaired renal function (5,8).

Kidney is a classic target organ in parathormone (PTH) and the relationship between severe PHPT and kidney damage has been identified years ago (8-12). Prolonged hypercalcemia impairs renal function and low GFR is typical in PHPT (13,14). Reduced glomerular filtration rate (<60 ml/min) is also mentioned in the manuals as a criterion for parathyroidectomy (PTX) (15,16) which can serve to the protection of renal function of these patients (9).

On the other hand, some studies have shown that no improvement occurs in renal function after PTX (13,14,17-19). In addition, recent randomized controlled studies conducted in patients with mild asymptomatic PHPT,

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showed no improvement in renal function after PTX (20-23). Other studies even showed that PTX has a negative effect on renal function, especially in patients with creatinine clearance of 60 ml/min (24,25). Due to different results obtained in different studies, the relationship between PTX and renal function still remains controversial today.

In light of the above information, due to limited data on renal failure predictions in patients with PHPT, in this study, we aimed to investigate GFR values before and after PTX and related changes in renal function of PHPT patients.

MATERIALS and METHODS

The archive files of 59 patients operated for PHPT between January 2008 and October 2019 at Cumhuriyet University Surgical Oncology Clinic were reviewed retrospectively.

For each patient, personal data such as age, sex were collected from these files, and biochemical data such as PTH, Ca, Cr values were collected from the laboratory tests taken before and after the surgery. Estimated glomerular filtration rate of the patients before PTX was calculated. After the diagnosis, PTX diagnostic criteria were consistent with the guidelines (8).

Patients were divided into two groups according to their GFR values: those whose GFR is below 60 ml/min/1.73 m^2 and whose GFR is above 60 ml/min/1.73 m^2. In groups, pre and post-parathyroidectomy laboratory values of the parameters were compared. CKD-EPI creatinine equation for the measurement of glomerular filtration rate is: (141 × min (Scr/κ, 1) α × max (Scr/κ, 1) × 1.209 × 0.993Age × 1.018 [for women] × 1.159 [for blacks]. Where SCr is serum creatinine (in mg / dL); κ is 0.7 for women, 0.9 for men; α is -0.329 for women and -0.411 for men; min (Scr/κ, 1) is minimum serum creatinine or 1; and max (Scr/κ, 1) is maximum serum creatinine or 1 (26). Calculation of GFR was performed according to CKD-EPI equation.

Statistical analysis

Data analysis was performed using SPSS 23.0 software. In our study, non-parametric tests were applied because all variables were not found to have normal distribution as a result of Kolmogorov-Simirnov test. Wilcoxon Signed-Rank test was used to compare PTH, Ca, Cr and GFR values. Chi-square test was used to compare GFR groups. Evaluations were based on 95% confidence level.

RESULTS

20.3% of the patients (12 patients) to whom Primary hyperparathyroidism PTX have been performed, were male and 79.7% (47 patients) were female, and their average age was calculated as 54.7.

As shown in Table 1, regarding mean PTH, Ca, Cr and GFR values of the patients with GFR<60 ml/min/1.73 m^2 before and after PTX, pre-operation mean Parathormone (PTH) value was found to be 1227.36 pg/ml, Calcium (Ca) 10.60 mg/dl, Creatinine (Cr) 5.12 mg/dl, while mean PTH value in post-op period was found to be 131.69, Ca: 8.29, Cr: 3.57. It was found that PTH (Figure 1), Ca, Cr values decreased and GFR value increased after PTX (Figure 2) in this group and the difference between baseline values and post-op values was statistically significant (p <0.001) (Table 1).

Table 1. Mean PTH, Ca, Cr and GFR values of the patients with GFR<60 ml/min/1.73 m^2, before and after PTX (n:15)

	Before PTX	After PTX	
	X + SS	X + SS	p
PTH (pg/ml)	1227.36 + 974. 77	131.69+219.69	< 0.001
Ca (mg/dl)	10.60 + 1.03	8.29+0.91	< 0.001
Cr (mg/dl)	5.12 +2.99	3.57+2.03	< 0.001
GFR (mL/min/1.73 m^2)	18.66 +17.33	26.20+21.39	< 0.001

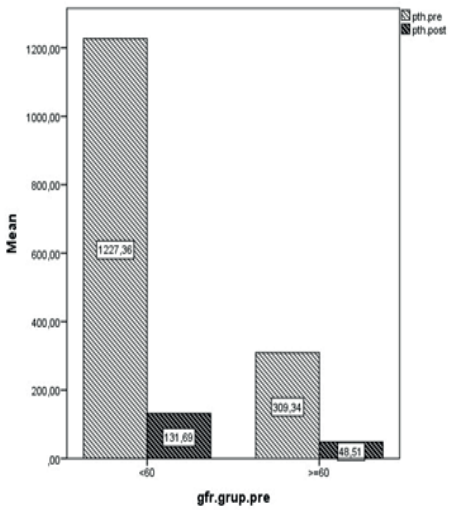

Figure 1. Mean PTH Value Before and After PTX According to GFR

Table 2. Mean PTH, Ca, Cr and GFR values of the patients with GFR>60 ml/min/1.73 m^2, before and after PTX (n:44)

	Before PTX	After PTX	
	X + SS	X + SS	p
PTH (pg/ml)	309.34+376.17	48.51+46.99	< 0.001
Ca (mg/dl)	11.05+0.58	8.88+.54	< 0.001
Cr (mg/dl)	0.73+0.15	0.68+0.15	0.003
GFR (mL/min/1.73 m^2)	95.13+16.41	99.95+1786	0.003

Regarding the mean PTH, Ca, Cr and GFR values of the patients with GFR>60 ml/min/1.73 m^2, before and after PTX (Table 2), pre-PTX mean of PTH was found to be 309.34, Ca: 11.05, Cr: 0.73 (SS:0.15), while post-PTH was found to be 48.51, Ca: 8.88, Cr: 0.68. GFR was (X + SS) 95.13 + 16.41 in pre-op period, whereas it was found to be 99.95 + 1786 in post-op period.

So, it was found that PTH (Figure 1), Ca values of the patients with GFR>60 ml/min/1.73 m^2 decreased and Cr, GFR values increased after PTX (Figure 2) and the difference between pre-op and post-op values was statistically significant (p <0.005).

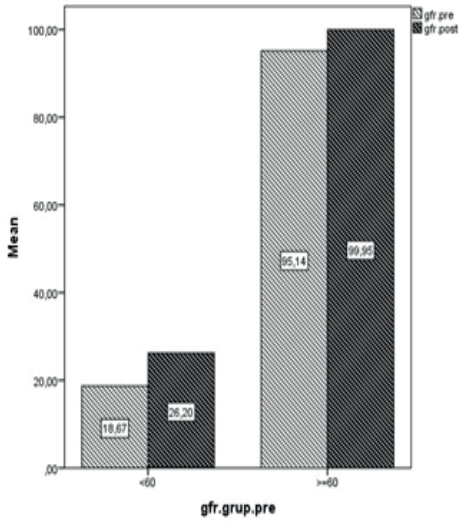

Figure 2. Mean GFR Value Before and After PTX

DISCUSSION

PHPT, caused by excessive and uncontrolled secretion of PTH by parathyroid glands, is the most common cause of hypercalcemia in outpatients and is a common disease in the community (7,27). The increasing number of studies based on serum calcium measurement has led to the progress of PHPT incidence determination studies (9,10). In the population-based prevalence studies of PHPT, different results were obtained due to the variations of the research methods. Today, PHPT incidence in Europe is reported to be around 100-150 cases per million, whereas it was reported as 44 cases per million/year in the United States (27). Similarly, in a recent study in Spain, this rate was estimated as 99.5 cases per million per year (28). In a Swedish study, it was determined as 38 cases per million per year (27).

As is known, prolonged hypercalcemia and decreased GFR are typical in primary hyperparathyroidism and this leads to deterioration of renal function over time. The most important target organ of PHPT is kidney (16, 18). In PHPT, impaired renal function became a PTX indication, which may be due to the addition of secondary HPT to the existing PHPT and the direct impact of serum calcium or PTH on the renal functions or the concern of impaired renal function due to development of nephrocalcinosis nephrolithiasis (9).

In recent years, PHPT can also be diagnosed without clinical symptoms. Studies have shown that 80 percent of patients in developed countries can be diagnosed asymptomatically today (16,29). In the last decade, surgical guidelines for asymptomatic PHPT treatment, which is the predominant form of the disease, reaffirmed that renal failure is an indication of PTX. According to the consensus reflected in these guidelines, GFR threshold value for renal failure was set as 60 mL/min/1.73 m^2 (15,30).

After PTX, patients' blood calcium level and PTH level return to normal, the risk of fracture, lithiasis decreases and bone mass increases. In addition, the risk of developing new complications related to PHPT, which can be treated postoperatively by 95%, is reduced and morbidity and mortality rates decrease (31). In fact, it has been reported that non-treatment of PHPT increases mortality and morbidity (32,33). A recent prospective PEARS study compared 1424 patients with PHPT and 7120 controls and found that individuals with PHPT were under 13.83 times higher risk of developing renal failure over a decade, which increased morbidity and mortality rate (33).

Guidelines based on recent studies in patients with PHPT recommend parathyroidectomy if GFR is below 60 ml/min/1.73m^2 (15).

The purpose of this study was to examine GFR, PTH, Ca^{2+}, and Cr values of the patients with primary hyperparathyroidism, having GFR <60 ml/min/1.73 m^2 and GFR>60 ml/ min/1.73 m^2 before and after PTX. In this study, which was retrospectively conducted with 59 PHPT diagnosed patients to whom PTX has been performed between January 2008 and October 2019, PTH, Ca^{2+}, Cr values of the patients before PTX were found to be high and for 15 patients GFR was below 60 ml/min/1.73 m^2.

After PTX, PTH, Ca^{2+}, Cr values decreased, and GFR increased in both groups separated as GFR<60 ml/min/1.73 m^2 and GFR>60 ml/min/1.73 m^2. Our data show that curative PTX can prevent further impairment of renal function of both PHPT patients with GFR above 60 ml/min/1.73 m^2 and GFR below 60 ml/min/1.73 m^2. In a recent study of Caliskan et al. (34) in which 125 patients with PHPT were included, the comparison of laboratory values and renal functions before and after PTX in patients with GFR above and below 60 ml/min/1.73 m^2, it was reported that the occurrence of more renal failure was prevented after PTX in both groups, which is similar to the results of our study. In another study, Egan et al. (24) analyzed the changes in renal function of 62 patients and found that creatinine increased postoperatively (1.09 to 1.15 mg/dl) and GFR decreased from 78 to 73 ml/min in 8-12 weeks.

However, there are many studies in the literature on renal functions and laboratory values of PTX, in which different results have been obtained (24,25). Although the decrease in GFR is an indicator of PTX (15), there are studies showing that PTX has no beneficial effect on renal function (35,37). In these retrospective studies over a

period ranging from 6 months to 11 years after PTX, there was no evidence suggesting that PTX could change the course of renal failure (35-37).

There are studies in the literature showing that renal functions were impaired after PTX. Two recent studies designed to evaluate the effect of PTX have shown that renal function worsened after PTX (24,25). Egan et al. (24) analyzed the changes in renal function of 62 patients and found that creatinine increased postoperatively (from 1.09 to 1.15 mg/dl) and GFR decreased from 78 to 73 ml/min in 8-12 weeks. Tassone et al. (25) analyzed the changes in renal function of 109 patients (creatinine clearance <60 ml/min) in 6 months after PTX. In this study, serum creatinine increased significantly in patients with creatinine clearance above 60 ml/min, and serum creatinine worsened in 14 patients whose GFR decreased, but this was not statistically significant. A recent study involving 298 patients was performed in Spain. Pre and post-PTX GFR values of the groups with GFR above and below 60 ml/min/1.73 m^2 were compared. Renal function was observed to be worsened in all patients and this fact continued one year after surgery.

Having different results related to renal function after PTX in patients with PHPT may be related to many factors such as the variations of research methods and the differences in patients' clinical status. For this reason, it is thought that more large-scale studies are needed and the factors affecting the results should also be analyzed.

CONCLUSION

In conclusion, in this study, the observed decrease in PTH, Ca^{2+}, Cr and the increase in GFR after PTX in patients with PHPT shows that surgery has positive effects on renal functions.

Conflict of interest: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: In the article, obtaining approval from the institutional Ethics committee was not seen as a requirement because of the reasons that the study was not conducted by collecting biological samples from human participants (blood,urine and seum etc.), that it was not based on investigating any previously collected biological samples, that it did not evaluate any personal information and its relation with spesific diseases, and that it was not a type of study in which any experimental procedures (medication etc.) were applied on humans.

REFERENCES

1. Uludağ M, Aygün N. Primer Hiperparatiroidi: Klinik ve Biyokimyasal bulguların güncel durumu. Şişli Etfal Hastanesi Tıp Bülteni 2016;50:171-80.
2. Yu N, Donnan PT, Murphy MJ, et al. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. Clin Endocrinol (Oxf) 2009;71:485-93.
3. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism.N Engl Med 2011;365:2389-97.
4. Bilezikian JP, Bandeira L, Khan A, et al. Hyperparathyroidism. Lancet 2018;168-78.
5. Torres M, Martín A. Hiperparatiroidismo primario. Med Clin (Barc) 2018:150;226-32.
6. Brunicardi FC, Anderson DK, Billiar TR, et al.Thyroid, parathyroid, and adrenal. Schwartz's Principles of Surgery 10th ed. NewYork McGraw Hill 2015;1522-96.
7. Felger EA, Kandil E. Primary hyperparathyroidism. Otolaryngol Clin North Am 2010;43:417-32.
8. Verdelli C, Corbetta S. Kidney involvement in patients with primary hyperparathyroidism an update on clinical and molecular aspects. Eur J Endocrinol 2017; 176:39-52.
9. Hendrickson CD, Pereira DJ, Comi RJ. Renal impairment as a surgical indication in primary hyperparathyroidism do the data support this recommendation. J Clin Endocrinol Metab 2014;99:2646-50.
10. Valdemarsson S, Lindergård B, Tibblin S, et al. Increased biochemical markers of bone formation and resorption in primary hyperparathyroidism with special reference to patients with mild disease. J Intern Med 1998; 243:115-22.
11. Gianotti L, Tassone, F, Cesario F, et al. A slight decrease in renal function further impairs bone mineral density in primary hyperparathyroidism. J ClinEndocrinol Metab 2006;91:3011-6.
12. Walker MD, Nickolas, T, Kepley A, et al. Predictors of renal function in primary hyperparathyroidism. J Clin Endocrinol Metab 2014;99:1885-92.
13. Jones DB, Lucas PA, Henry Jones J, Lucas PA, Wilkins WE et al. Changes in blood pressure and renal function after parathyroidectomy in primary hyperparathyroidism. Postgrad Med J 1983;59:350-3.
14. Kristoffersson A, Backman C, Granqvist K, et al. Preand postoperative evaluation of renal function with five different tests in patients with primary hyperparathyroidism. J Intern Med 1990;227:317-24.
15. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014;99:3561-9.
16. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int 2017;28:1-19.
17. Hedbäck G, Odén A, Tisell LE. Parathyroid adenoma weight and the risk of death after treatment for primary hyperparathyroidism. Surgery 1995; 117: 134-139.
18. Posen S, Clifton-Bligh P, Reeve TS, et al. Is parathyroidectomy of benefit in primary hyperparathyroidism QJM 1985;54:241-51.
19. Rowlands C, Zyada A, Zouwail S, et al. Recurrent urolithiasis following parathyroidectomy for primary hyperparathyroidism. Ann R Coll Surg Engl 2013;95:523-8.

20. Silverberg SJ, Shane E, Jacobs TP, et al. A 10 year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med 1999;341:1249-55.
21. Rao DS, Phillips ER, Divine GW, et al. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 2004;89:5415-22.
22. Bollerslev J, Jansson S, Mollerup CL, et al. Medical Observation, compared with parathroidectomy, for asymptomatic primary Hyperparathroidizm: a prospective, randomized trial. J Clin Endocrinol Metab 2007;92:1687-92.
23. Ambrogini E, Cetani F, Cianferotti L, et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. J Clin Endocrinol Metab 2007;92:3114-21.
24. Egan RJ, Dewi F, Arkell R, et al. Does elective parathyroidectomy for primary hyperparathyroidism affect renal function? A prospective cohort study. Int J Surg 2016;27:138-41.
25. Tassone F, Guarnieri A, Castellano E, et al. Parathyroidectomy halts the deterioration of renal function in primary hyperparathyroidism. J Clin Endocrinol Metab 2015;100:3069-73.
26. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Am J Kidney Dis 2017;70:737-51.
27. Clarke BL. Epidemiology of primary hyperparathyroidism. J Clin Densitom 2013;16:8-13.
28. Torres M, Gimeno E, Garcia R, et al. Results from a national survey on the management of primary hyperparathyroidism. J Endocrinol Invest 2012;35:957-63
29. Scholz DA, Purnell DC. Asymptomatic primary hyperparathyroidism. 10-year prospective study. Mayo Clin Proc 1981;56:473-8.
30. Bilezikian JP, Potts JT Jr, Fuleihan H, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Bone Miner Res 2002;17:2-11.
31. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg 2016:151; 959-68.
32. Yu N, Donnan PT, Flynn RW, et al. Increased mortality and morbidity in mild primary hyperparathyroid patients. The Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol (Oxf) 2010;73:30-4.
33. Yu N, Donnan PT, Leese JP. A record linkage study of outcomes in patients with mild primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol (Oxf) 2011;75:169-76.
34. Caliskan M, Kizilgul M, Beysel S, et al. Factors associated with glomerular filtration rate variation in primary hyperparathyroidism after paratridectomy. Turk J Med Sci 2019;49:295-300.
35. Ghose RR, Morgan WD. Improvement in renal function in primar hyperparathyroidism following parathyroidectomy. Postgrad Med J 1981;57:28-30.
36. Rowlands C, Zyada A, Zouwail S, et al. Recurrent urolithiasis following parathyroidectomy for primary hyperparathyroidism. Ann R Coll Surg Engl 2013;95:523-8.
37. Falkheden T, Ohlsson L, Sjögren B. Renal function in primary hyperparathyroidism. A follow-up study two to eleven years after surgery comprising 139 patients. Scand J Urol Nephrol 1980;14:167-75.