



ORIGINAL ARTICLE

Evolution of renal function in patients with primary hyperparathyroidism submitted to parathyroidectomy

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Abstract

Introduction: Primary hyperparathyroidism (PHPT) is a hypercalcemic disorder resulting from inappropriate parathyroid secretion (PTH). The surgical treatment is considered the mainstay of therapy. Several studies have observed the worsening of renal function in these patients after parathyroidectomy (PTX), however, the pathophysiology of this phenomenon is unknown. **Objective:** The purpose of this study is to describe the postoperative renal function in patients with PHPT operated at the Federal University of São Paulo - UNIFESP- between the years 2007 and 2016, evaluating the risk factors for renal function decline. **Materials and Methods:** This is a cohort study. A total of 142 patients were divided into two groups according to their renal function: Group I (> 60 mL / min / 1.73 m²) and Group II (<60 mL / min / 1.73 m²). **Results:** Increased serum creatinine was observed in both groups in the first 96 hours, with partial recovery over the first month. Creatinine values > 1.82 mg / dL in patients with renal disease are associated with worse prognosis for renal function after surgery and PTH values > 400 pg / dL are associated with a poor renal outcome, independent of previous renal function. **Conclusion:** Patients with elevated baseline PTH and creatinine had a worse outcome of renal function one year after surgery

Keywords: primary hyperparathyroidism; parathyroidectomy; renal insufficiency; postoperative period; glomerular filtration rate.

Introduction

Primary hyperparathyroidism (HPTP) is a hypercalcemic metabolic disorder resulting from high or inappropriately normal secretion of parathyroid hormone (PTH). The surgical treatment is safe, effective and it is considered the standard gold treatment¹⁻³.

However transient variations of renal function after parathyroidectomy (PTX) in patients with HPTP were described in different publications after Fuller-Albright's initial description². Montenegro et al.⁴ found a decrease in the estimated glomerular filtration rate (eGFR) in the postoperative period, independent of preoperative eGFR. Tassone et al.⁵ identified that patients with normal renal function were more subject to creatinine (Cr) elevations than those with previous renal dysfunction.

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The exact mechanisms of this alteration have not been identified, nor have the factors that allow identifying which patients are more likely to develop renal function decline. The goal of this study is to describe the historical series of patients with HPTP operated and followed in the Universidade Federal de São Paulo. Epidemiological, laboratorial and surgical data was collected and the incidence and distribution of change in renal function of these patients were analyzed with the objective of evaluating risk factors, duration and time required for normalization of renal function.

Method

This is a cohort study of patients that underwent PTX due to HPTP. The surgeries took place between January 2007 and June 2016 at the Unifesp hospital complex, a tertiary referral service for head and neck surgery formed by Hospital São Paulo, Hospital de Transplantes Euryclides de Jesus Zerbini and Hospital do Rim.

The work was submitted and approved by the Local Research Ethics Committee, prospectively from June 2000 to December 2016, according to technical documents CEP 886/00, CEP 0234/06, CEP 0354/09.

All patients underwent preoperative laboratory evaluation composed of PTH, total calcium (Ca), ionic calcium (iCa), vitamin D and Cr serum tests.

To determine the eGFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used, which takes into account age, gender and serum Cr. In Brazil, the use of correction of eGFR for blacks is not performed^{6,7}. Patients with $eGFR > 60 \text{ mL/min/1.73 m}^2$ were allocated to Group I and patients with $eGFR \leq 60 \text{ mL/min/1.73 m}^2$, to Group II. The patients were operated by the same surgical team. Intraoperative PTH (ioPTH) was routinely collected, If ioPTH decay (ioPTH) was more than 50%, the surgery was considered to be a success^{8,9}.

Laboratory tests were performed postoperatively, six different times, between the 1st and 2nd day, between the 3rd and 4th day, between the 5th and the 7th day, and one, six and twelve months after the surgery.

Acute Kidney Injury Network (AKIN) criteria was used to define acute kidney injury (AKI). The criterias used to define AKI are an increase in serum Cr of 1.5 times compared to baseline or an increase $\geq 0.3 \text{ mg/dL}$ ⁸. Patients were divided again according to the presentation of AKI after surgery into Subgroups Ia (non AKI), Ib (AKI) and Subgroups IIa (non AKI) and IIb (AKI).

All patients with a diagnosis of PTHP with ages between 15 and 85 years were included. However, subjects with loss to follow-up, patients with Class V renal insufficiency or renal replacement therapy, patients with surgical treatment failure or in need for reoperation and those with serious postoperative complications such as sepsis, cardiorespiratory arrest and death were excluded.

The Statistical Package for the Social Sciences program was used for statistical analysis. Student's t test, ANOVA, MANOVA (two or more independent variables), Pearson correlations (to verify the degree of relationship between two variables), and Logistic Regression for odds ratio calculation were used

for inferential evaluations. $P \leq 0.05$ was considered significant. The Bonferroni test was performed for evaluation of non-paired samples.

Results

During follow-up, six patients in Group II progressed to class V chronic kidney disease (CKD) and were excluded from the statistical evaluation, thus a total of 142 patients were included.

A total of 86 (60.5%) patients were allocated in Group I and 56 (39.4%) in Group II. Table 1 shows the distribution of age, gender, and preoperative exams for both groups.

There was a significant difference between the groups in PTH levels, however de ioPTH decay were similar (Table 2).

A gradual increase in serum Cr was observed up to 96 hours after surgery in both groups (Graphic 1). Cr elevations consistent with AKI was observed in 29.5% of patients, and this occurred more frequently in group II (58.9%) than in group I (16.3%). This increase was statistically significant between baseline Cr and postoperative Cr in both groups, except after one year in group I ($p > 0.05$). The eGFR presented a significant reduction in both groups, showing stabilization after the first month (Graphic 1).

In Group I, 72 patients showed no changes in Cr or eGFR during the study period (subgroup Ia), while 14 patients (16.3%) presented with AKI (subgroup Ib). Five patients from subgroup IIb developed class III CKD and one, class IV CKD. Thus, 6.9% of the patients developed CKD at the end of the first year of follow-up.

For patients in Group I, PTH values > 400 pg / dL and Cr > 0.75 mg / dL were associated with the development of AKI in 50% of the cases (Table 3).

In Group II, 23 patients did not present with changes in renal function (subgroup IIa), whereas 33 (58.92%) did develop AKI (subgroup IIb). It was observed, through logistic regression, that PTH values > 400 pg/dL and baseline Cr > 1.82 mg/dL were associated with AKI in about 85% of the cases with Odds ratio of 3.2 and 3.4 respectively. However, ioPTH decay and baseline calcium levels do not appear to be implicated in this renal function loss. Patients in subgroup IIb presented with persistent elevation of Cr at the end of the first year (Table 3).

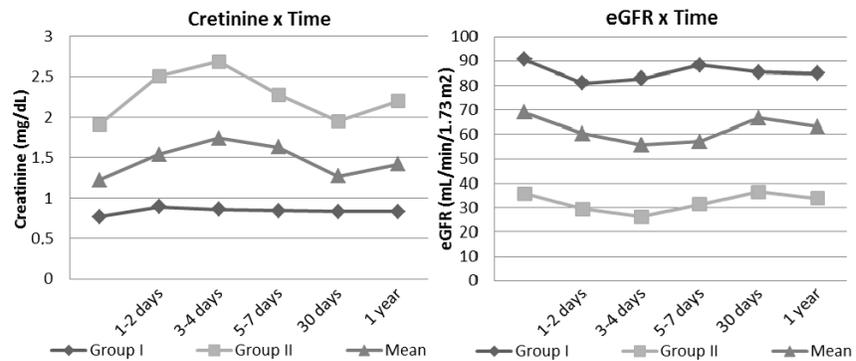
Table 1. Distribution of age, gender, and preoperative exams for group.

	Sex ¹	Age ²	Ca ³	iCa ⁴	PTH ⁵	Cr ⁶	eGFR ⁷
Group I	81.4%	56.2	12.05	1.60	303.04	0.77	90.58
Group II	80.4%	63.7	13.07	1.68	809.68	1.91	35.83
P	NS	NS	0.04	0.05	< 0.001	< 0.001	< 0.001

¹ Female; ² Years old; ³ Calcium (reference 8.6-10.2 mg/dL); ⁴ Ionized Calcium (reference 1.15-1.32 mmol/dL); ⁵ Parathyroid hormone (reference 15.0-65.0 pg/mL); ⁶ Creatinine (reference 0.5-1.2 mg/dL); ⁷ Estimated glomerular filtration rate mL/min/1.73 m².

Table 2. Intra-operative levels and follow-up of PTH (pg/mL) and ioPTH decay (%) for groups.

	ioPTH 0'	ioPTH 10'	ioPTH decay	1st month	6th month	1st year
Group I	335.5	65.21	76.96%	51.69	52.03	42.69
Group II	957.24	216.48	74.08%	155.83	124.86	163.40
P	< 0.001	< 0.001	0.23	< 0.001	< 0.001	< 0.001



Graphic 1. Distribution of creatinine and eGFR values over time (in mg/dL and mL/min/1.73 m²) by groups.

Table 3. Distribution of the Group's I and II laboratory tests subdivided by the presentation of acute postoperative renal injury.

	Group I			Group II		
	Non AKI	AKI	P	CKD non AKI	CKD + AKI	P
Number	72	14	-	23	33	-
Ca¹	12.24	11.55	0.28	12.92	13.11	0.83
iCa²	1.59	1.63	0.6	1.63	1.71	0.2
Cr³	0.75	0.85	0.035	1.4	2.26	<0.001
eGFR⁴	91.47	86.04	0.3	45.48	29.1	<0.001
PTH⁵	277.17	428.67	0.016	369.9	1128.14	0.001
ioPTH decay (%)	77.2%	75.5%	0.47	71.4%	75.6%	0.36
1st year Cr³	0.76	1.20	<0.001	1.44	2.71	<0.001
1st year eGFR⁴	89.21	62.77	<0.001	45.15	26.42	<0.001

¹ Calcium (reference 8.6-10.2 mg/dL); ² Ionized Calcium (reference 1.15-1.32 mmol/dL); ³ Creatinine (reference 0.5-1.2 mg/dL); ⁴ Estimated glomerular filtration rate mL/min/1.73 m²; ⁵ Parathyroid hormone (reference 15.0-65.0 pg/mL).

Discussion

In this cohort the global incidence of postoperative AKI after PTX was 29.5%. The incidence was 58.9% among patients from group II and 16.3% from Group I. This incidence surpasses large surgeries, such as cardiac (incidence of 18.7% to 25%), abdominal (13.2% - 15%), thoracic (12%) or major orthopedic

surgeries (14.7%)^{10,11}. It is also higher when compared to surgeries of similar size, such as otolaryngologic surgeries (4.1% of the total), hernioplasties (1.4%)¹² and rectal surgeries (3.8%)¹³.

When considering other studies with patients with previous CKD, the incidence of AKI was also greater than for elective surgeries of similar size, such as hernioplasties (6.9% in patients with GFR <30 mL/min/1.73 m²)¹⁰ or hip prosthesis placement (30.9% in patients with eGFR <60 mL/min/1.73 m²)¹¹.

This observation suggests that some factor that markedly affects renal function after PTX, as observed by Fuller-Albright, who described postoperative oliguria. This renal change was described as the Fuller-Albright effect².

In this study, an average increase of 0.52 mg / dL in the Cr in the first 4th postoperative days was found, with a mean maximum drop of 13.43 mL/min/1.73 m² in GFR. Montenegro et al observed a transient variation of renal function after PTX in patients with HPTP, from an estimated preoperative mean eGFR of 82.67 mL/min/1.73 m² to about 63 mL/min/1.73 m² in the first 48 hours after surgery⁴.

Parikh et al.¹⁴ observed a reduction of the eGFR during the first two months after PTX in transplanted patients, with partial recovery of the graft function in the first year of follow-up. The eGFR varied from 51.19 mL/min/1.73 m² to 44.78 mL/min/1.73 m², with an average recovery of up to 49.76 mL/min/1.73 m².

Tassone et al.⁵ observed a significant decrease in the eGFR six months after surgery in relation to the baseline eGFR in patients with previous normal renal function (86.8 to 81.6 mL/min/1.73 m²), but not on those with previous CKD (52.6 to 50.2 mL/min/1.73 m²). A protective effect of PTX in CKD patients in patients with eGFR <60 mL/min/1.73 m², is, therefore, suggested by this study.

Schwarz et al.¹⁵ found in transplanted patients a reduction of the eGFR greater than 20% after PTX in 47% of the patients, with partial recovery in the first month. In patients with Cr clearance <60 mL/min/1.73 m², both Cr and eGFR remained increased after the end of the first year.

In our study, it was identified that for Cr values > 1.82 mg / dL, there was an odds ratio of 3.2 in relation to the development of AKI in Group II patients, with AKI occurring in 85% of cases. For Group I patients it was not possible to establish a significant OR value, although 50% of patients with creatinine > 0.75mg/dL presented with worsening of renal function.

The evolution of CKD was observed in six patients (6.9%) in Group I. It should be noticed that, even though they did not enter into the statistics, six patients from Group II also progressed to class V CKD (10.7% of the total). This suggests that PTX may have a possible long-term effect on renal function.

These findings corroborate Schwarz's results¹⁵ and contrast with the results of Tassone et al.⁵ and Montenegro et al.⁴, because in patients with higher basal Cr and GFR there is association with a worse renal outcome in the first year.

Possible explanations to the effect of PTX on renal function in patients with previous CKD can be their lower functional reserve as well as their greater sensitivity to acute events¹⁶.

In the present study, baseline PTH was a risk factor for unfavorable renal outcomes. Patients with PTH > 400 pg/dL had about 3 times more chance of developing AKI, independent of previous renal function (OR 3.4). For patients in group II with baseline PTH levels > 400 pg / dL, there was a 85% incidence of AKI. Parikh et al.¹⁴ also observed that preoperative PTH levels in transplanted patients are associated with marked decreases in Cr clearance after PTX.

There was no statistical difference between the renal function and the intensity of the ioPTH decay. This contrasts Schwarz's¹⁵ findings that ioPTH variation is primarily responsible for the deterioration of renal PTX function. Similarly, for statistical purposes, when comparing patients with a PTH decay <80% and a fall > 80%, no difference was found in relation to the variation in renal function.

It is known, by experimental observation, that PTH is a potent vasodilator of renal arteries and arterioles by stimulating and releasing adenylate cyclase in the smooth muscle of the endothelium, leading to increased glomerular flow and increased GFR^{14,17,18}. Probably the abrupt drop in PTH levels rapidly increases preglomerular resistance leading to pre-renal AKF^{17,19}. This pathophysiology is highly suggested by the high association found between the higher baseline PTH values and the higher incidence of unfavorable renal outcomes.

As in other studies in the literature, gender, age and baseline levels of calcium did not appear to be associated with renal alterations after PTX^{5,14}.

Conclusion

Approximately 15% of patients with normal renal function and 50% of those with CKD presented significant elevation of Cr levels within the first 96 hours after surgery. Those with CKD have a greater tendency to reduce renal function. In patients with CKD class III or IV, Cr values > 1.82 mg / dL are associated with worse prognosis for renal function after surgery, as well as values > 0.75 mg / dL in patients without CKD. PTH values > 400 pg / dL are associated with a poor renal outcome, independent of eGFR.

Patients with HPT, irrespective of preoperative renal function and PTH levels, need to be intensively monitored for renal function during the postoperative period.

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