

# Secondary Hyperparathyroidism in Dialysis Patients: Short- and Long-Term Outcomes of Conservative Parathyroidectomy

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## Abstract

Secondary hyperparathyroidism (HPT) is frequent in dialysis patients. Parathyroidectomy (PTX) is indicated for patients who failed medical therapy. We reviewed the data from 184 dialysis patients who underwent PTX between January 2015 and January 2023. We aimed to evaluate the short and long term outcomes of PTX in dialysis patients, comparing the conservative 3/4 versus 7/8 techniques in this population. 166 dialysis patients with secondary HPT were included. A conservative subtotal PTX (sPTX) 7/8 was performed in 72% of patients and sPTX 3/4 in 28% of them. Severe postoperative hypocalcaemia occurred in 45 patients (27%). Hypocalcaemia was significantly more frequent in the sPTX 7/8 group ( $p = 0.012$ ). One case of persistent HPT (0.6%) and 20 cases of recurrence (12%) were diagnosed. Recurrence was more frequent in the sPTX 3/4 group (15%). No deaths were reported during the perioperative period.

## Keywords

Secondary Hyperparathyroidism, Dialysis, Chronic Kidney Disease, Conservative Subtotal Parathyroidectomy

## 1. Introduction

Secondary hyperparathyroidism (HPT) is a complex mineral and bone disorder that is common in patients with long-term chronic kidney disease (CKD). It involves an over activity of the parathyroid glands induced by hyperphosphatemia, hypocalcaemia, vitamin D deficiency and the fibroblast growth factor 23-klotho axis dysfunction [1]. This results in elevated levels of intact parathyroid hormone (iPTH) and histologically leads to hyperplasia of the parathyroid glands.

Symptoms often include bone pain, pruritus, pathological fractures, and brown tumors. Other complications such as vascular calcifications and calciphylaxis can threaten the patient's prognosis [2].

In dialysis patients, the therapeutic management of HPT relies on calcimimetics, calcitriol and vitamin D analogs [3]. Achieving phospho-calcium balance in dialysis patients can be challenging often due to poor therapeutic adherence and the high costs of treatments. Parathyroidectomy (PTX) is considered the best treatment option for patients who have failed medical therapy or those with advanced HPT [4].

Total PTX (tPTX) involves the removal of all parathyroid glands and can be associated with parathyroid tissue autotransplantation (tPTX-AT). Subtotal PTX (sPTX) allows the preservation of a certain parathyroid volume. However, while guidelines specify the iPTH level at which PTX is indicated, they do not specify the type of surgery to be performed. Numerous studies have sought to determine the optimal surgical method. The dilemma lies between total resection methods, which carry the risk of permanent hypoparathyroidism and the conservative subtotal methods, less aggressive but exposing to the risk of persistent or recurrent HPT. While most studies conclude the safety of sPTX and tPTX-AT, to our knowledge, none have provided clear guidance on management.

The aim of the study is to evaluate the short and long term, clinical and biological outcomes of PTX in dialysis patients, comparing the conservative 3/4 versus 7/8 techniques.

## 2. Subjects and Methods

We retrospectively reviewed the data from 184 dialysis patients with secondary HPT. All patients underwent PTX between January 2015 and January 2023 and were under the care of the nephrology team for their dialysis sessions. The patients' records were retrieved using the dialysis unit registry. We excluded all cases of reoperation for recurrent HPT, renal transplantation or incomplete medical records.

The surgery was performed according to the following criteria: iPTH level > 1000 pg/ml; clinical signs refractory to medical treatment: bone or joint pain, pruritus, radiological signs of renal osteodystrophy, brown tumors or calciphylaxis. All patients underwent sPTX without auto-transplantation. We defined two groups: sPTX 3/4: 3 of the 4 parathyroid glands were resected, leaving 1 parathyroid gland in place. sPTX 7/8: 3 and a half gland were resected, leaving half of a parathyroid gland in place.

Clinical and biological data were collected during the perioperative period from the patients' medical records. The one-year data were collected from the dialysis centers where patients received care.

Clinical signs monitored included persistent bone pain or pruritus. We recorded the levels of calcium, phosphorus, iPTH, alkaline reserves, and alkaline phosphatase (PAL).

The cases of severe postoperative hypocalcaemia (defined by serum calcium <

60 mg/L associated with clinical symptoms) and postoperative hypoparathyroidism (defined by iPTH levels < 40 pg/ml) were recorded and compared between the groups sPTX 3/4 and 7/8.

We defined persistent HPT as the persistence of biological HPT (iPTH > 1000 pg/ml) 6 months after the procedure and recurrent HPT as the elevation of iPTH levels beyond 6 months after surgery. The cases of persistence/recurrence were compared between the two groups, sPTX 3/4 and sPTX 7/8.

Data entry and analysis were performed using SPSS 23 (Statistical Package for the Social Sciences). Quantitative variables were expressed as either mean  $\pm$  standard deviation or median with interquartile range and analyzed using the Student's t-test. Qualitative variables were expressed as percentages and frequencies and analyzed using the chi-square test. The difference was considered significant from a P value less than 0.05.

### 3. Results

A total of 166 dialysis patients with secondary HPT were included in this study (Figure 1).

#### 3.1. Patients Characteristics

The mean age was  $46 \pm 14$  years, with extremes ranging from 12 to 81 years, and a sex ratio of 0.78. The majority of patients were on hemodialysis (93%). They received 3 weekly 4-hour sessions of conventional hemodialysis. The mean duration on hemodialysis was 7.5 years. Peritoneal dialysis patients represent 7% of the total, with an average duration of 3.5 years. In 68% of cases, the initial cause of CKD was unidentified. At the time of surgical intervention, 64% of patients reported clinical symptoms (Table 1). Bone pain was the most common symptom (121 patients), followed by pruritus (28 patients), and pathological fractures (19 patients).

#### 3.2. Biological Results

The preoperative biological results are reported in Table 2. The average iPTH level is  $1713 \pm 925.1$  pg/ml. Hypercalcemia was observed in 35% of patients, with an average calcium level of  $98 \pm 7.6$  mg/L (equivalent to  $2.4 \pm 0.1$  mmol/L). Hyperphosphatemia was found in 80% of patients, with an average phosphorus

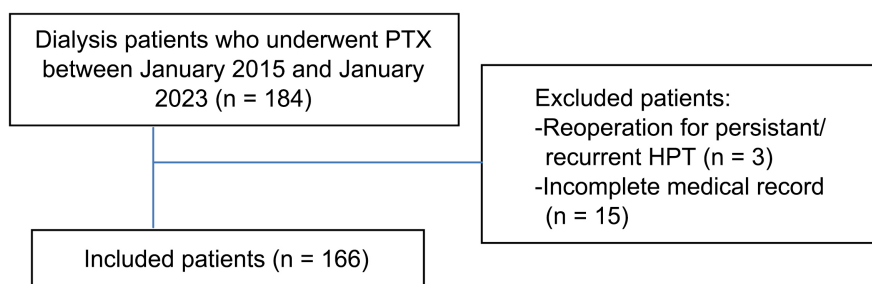


Figure 1. Flowchart of the included patients.

**Table 1.** Preoperative symptoms.

Clinical signs	Number of patients	Percentage
Bone/Joint pain	121	73%
Pruritus	28	17%
Pathological fractures	19	11%

**Table 2.** Preoperative biological results.

	n = 166
iPTH (pg/mL)*	1713 ± 925.1
Calcium (mg/L)* (mmol/L)	98 ± 7.6 2.4 ± 0.1
Phosphate (mg/L)*	58.4 ± 15.2
PAL (UI/L)**	449 [284 - 1034]
Vitamin D (ng/ml)*	30 ± 7.0
Alkaline reserves (meq/L)*	19 ± 5.1

\*Mean ± standard deviation; \*\*Median [interquartile].

level of  $58.4 \pm 15.2$  mg/L. The median PAL level is 449 [284 - 1034] IU/L. The mean levels of vitamin D and alkaline reserves are respectively  $30 \pm 7.0$  ng/ml and  $19 \pm 5.1$  meq/L.

### 3.3. Preoperative Imaging

All patients underwent skeletal radiographs (hands, pelvis, lateral skull) as well as cervical ultrasound. The ultrasound revealed hypertrophy of the parathyroid glands in 65% of cases. In 85 patients, a  $^{99m}\text{Tc}$ -SestaMIBI parathyroid scintigraphy was necessary to localize the pathological glands.

### 3.4. Surgical Outcomes

All patients underwent sPTX without auto-transplantation. A sPTX 7/8 was performed in 72% of patients and sPTX 3/4 in 28% of them. Thymectomy and thyroidectomy were performed in respectively 18% and 16% of cases. Histopathological examination concluded hyperplasia of the parathyroid glands in 96% of cases. During the perioperative period, no deaths were reported. Surgical complications are resumed in **Table 3**.

### 3.5. Postoperative Metabolic Complications

Severe postoperative hypocalcemia related to a hungry bone syndrome occurred in 45 patients (27%): 39 in group sPTX 7/8 and 6 in group sPTX 3/4. Hypocalcemia was significantly more frequent in the sPTX 7/8 group ( $p = 0.012$ ) (**Table 4**). Postoperative hypoparathyroidism was noted in 48 patients (28.9%): 38 in group sPTX 7/8 and 10 in group sPTX 3/4. Hypoparathyroidism was more common in the sPTX 7/8 group but no statistical association was proven.

**Table 3.** Surgical complications.

Surgical complications	N (%)
Dysphonia	2 (1.2%)
Cervical hematoma	2 (1.2%)
Ischemic stroke	1 (0.6%)

**Table 4.** Patients characteristics in the two groups sPTX 3/4 and 7/8.

	Group sPTX 3/4 (n = 46)	P value	Group sPTX 7/8 (n = 119)	P value
Demographic characteristics				
Age (years)*	44.4 ± 14.8		46.7 ± 14.1	
Male sex	20 (43.4%)		53 (44.5%)	
Duration of dialysis*	7.7 ± 4.6		7.1 ± 3.7	
Biological results				
Calcium (mg/L)*	97.0 ± 9.0		98.7 ± 7.0	
iPTH (pg/mL)*	826.1 ± 707.4		2053.2 ± 759.4	
Postoperative hypocalcaemia	6 (13.0%)	0.026	39 (32.7%)	0.012
Postoperative hypoparathyroidism	10 (21.7%)	0.325	38 (31.9%)	0.207
Persistent HPT	1 (2.1%)	0.110	0 (0%)	0.105
Recurrent HPT	7 (15.2%)	0.491	13 (10.9%)	0.449

\*Mean ± standard deviation.

### 3.6. Long-Term Follow-Up

During postoperative follow-up, 1 case of persistent HPT (0.6%) and 20 cases of recurrence (12%) were diagnosed. Recurrence was more frequent in the PTX 3/4 group (15%) compared to the 7/8 group (11%), but it was not statistically associated with the type of surgery.

## 4. Discussion

HPT is common in patients with chronic kidney disease (CKD). Treatment involves the use of phosphate binders, calcimimetics, calcitriol, and vitamin D analogs [3]. The majority of patients included in our study are receiving phosphate binder therapy. However, it is noted that 80% of them have an above-normal phosphatemia despite satisfactory therapeutic adherence. This highlights the limitations of medical treatment in this dialysis population.

According to the latest Kidney Disease Improving Global Outcomes (KDIGO) guidelines the target range for iPTH is 2 to 9 times the upper normal limit in dialysis patients. It equates to 130 to 600pg/mL. KDIGO recommends PTX for patients who failed medical treatment without specifying a threshold value for iPTH. According to the Japanese Society for Dialysis, the target range for PTH is

60 to 240 pg/mL, and PTX is recommended for an iPTH level above 500 pg/mL or a total PTH level above 300 pg/mL. In addition to these biological indications, radiological abnormalities and ectopic calcifications may also warrant PTX [5] [6].

An analysis of United States Renal Data System (USRDS) has demonstrated that PTX improves bone mineral density and reduces the frequency of fractures [7] [8]. A complementary analysis has shown a 41% reduction in all-cause mortality and cardiovascular mortality among dialysis patients with secondary hyperparathyroidism [9]. A recent study using data from the USRDS and the Japanese Society for Dialysis Registry has also demonstrated superior 5- and 6-year survival rates in the PTX-treated group compared to the cinacalcet-treated group [10] [11]. Additionally, PTX appears to be more cost-effective than cinacalcet treatment [12] [13].

While KDIGO offers guidelines for medical management and criteria for surgical indications, there is a lack of consensus regarding the surgical management of renal hyperparathyroidism [14], total PTX (tPTX) involves the removal of all parathyroid glands. The risk of postoperative recurrence is low, but the risk of chronic hypoparathyroidism is higher [15]. Hypoparathyroidism is linked to elevated cardiovascular mortality when levels drop below 47 pg/mL in individuals with stage V chronic kidney disease [16]. Hypoparathyroidism affects bone metabolism, and vascular calcifications can result from the administration of high doses of calcium and vitamin D. A prospective multicenter study involving 2164 patients treated with high calcium dialysate reported increased cardiovascular mortality [17]. Consequently, tPTX is not considered a first-line treatment. The 2009 KDIGO guidelines contraindicate tPTX in candidates for renal transplantation due to the risk of permanent hypoparathyroidism after transplantation [18]. Subtotal PTX (sPTX) allows for the preservation of a parathyroid volume ranging from 30 to 50 mg [19]. The incidence of postoperative hypocalcaemia and hypoparathyroidism is low. Therefore, sPTX is generally preferred over tPTX [20]. Hypocalcaemia is identified in 25% of dialysis patients who have undergone PTX [21]. Our data align with the literature as the total frequency of postoperative hypocalcaemia was estimated to be 27%. A French study corroborates that a more conservative approach by performing 3/4 PTX, is preferable to 7/8 PTX. sPTX 3/4 lowers PTH levels within target values, reduces the risk of recurrent hypoparathyroidism and results in a shorter hospital stay. In case of recurrent HPT, a secondary removal of part of the remnant parathyroid gland left is possible. In contrast, severe hypoparathyroidism that may be caused by sPTX 7/8 remains irreversible [2]. In our series, all patients underwent sPTX: 72% of type 7/8 and 28% of type 3/4. Postoperative hypocalcaemia and hypoparathyroidism were more frequent in the sPTX 7/8 group than in the sPTX 3/4 group. Total PTX with auto-transplantation (tPTX-AT) involves the removal of all parathyroid glands. Normal parathyroid tissue (30 - 50 mg) is cut into 1 - 2 mm<sup>3</sup> fragments and transplanted into the forearm muscle or sternocleidomastoid muscle and sometimes even into subcutaneous tissue. Some experts recom-

mend tPTX-AT because reoperation at the forearm autograft site is simpler than in the neck after sPTX [22]. Parathyroid auto-transplantation is not available in our facility, tPTX techniques are consequently not performed due to the significant risk of permanent hypoparathyroidism.

To monitor parathyroid function after PTX, KDOQI recommends quarterly PTH level monitoring [23]. According to the Japanese Society for Dialysis, the threshold for PTH at which surgical reintervention should be considered is 500 pg/ml [20].

A German series involving 304 patients who underwent PTX reports an overall persistence rate of 3% and a recurrence rate of 5.5%. Persistence/recurrence was more common in the sPTX group (10%) than in the tPTX-AT group (6%) [24]. Overall, the persistence/recurrence rates vary widely and depend on the surgical practices specific to each team. They can range from 2.5% to 12% [25]-[32]. In our series only one case of persistence (0.6%) and 20 cases of recurrence (12%) were diagnosed during postoperative follow-up. We also found that recurrence was more common in the 3/4 PTX group (15%) compared to the 7/8 PTX group (11%).

Based on our team's experience, sPTX appears to be a reasonable surgical method for treating hyperparathyroidism. In particular, the sPTX3/4 technique seems to result in less permanent hypoparathyroidism.

Currently, the selection of a surgical approach relies on the surgeon's discretion and the clinical characteristics of the patients [33].

## 5. Limitation

The limitations of our study include its retrospective nature which may introduce bias or missing data, the reliance on medical records, which could lead to incomplete or inaccurate information and the potential for selection bias as only patients who underwent subtotal parathyroidectomy were included. The generalizability of findings may be limited to the specific population or setting studied.

## 6. Conclusion

Secondary hyperparathyroidism (HPT) is an early and common mineral and bone disorder in dialysis patients. Its therapeutic management is complex. In cases of advanced or tertiary HPT, PTX should be recommended. sPTX is an effective surgery with relatively few surgical complications and a low rate of perioperative mortality. Its complications may include persistence/recurrence of HPT if the resected parathyroid volume is insufficient, or definitive hypoparathyroidism if the resection is too aggressive. sPTX3/4 method seems to be a reasonable surgical method. However, more studies are needed to determine the type of surgery required for each patient.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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