



# Surgery for Secondary Hyperparathyroidism. Total or Subtotal?

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## Abstract

**Objectives** Secondary hyperparathyroidism (sHPT) develops as a result of the chronic parathyroid stimulation associated with hypocalcemia, hyperphosphatemia, or vitamin D deficiency and leads to an increase in parathormone (PTH) synthesis and parathyroid cell proliferation in all of the four glands.

**Background** There are currently three surgical approaches to the treatment of renal hyperparathyroidism: subtotal parathyroidectomy, total parathyroidectomy without autotransplantation, and total parathyroidectomy with autotransplantation.

**Methods** Included in the study were 79 of which 35 underwent a total parathyroidectomy with autotransplantation (TPTX+AT), while 44 patients underwent a subtotal parathyroidectomy (SPTX).

**Results** A significant decrease was noted in PTH, calcium, and phosphate levels following both types of parathyroidectomy. It was observed that PTH and phosphate serum levels were controlled significantly better following a total parathyroidectomy with autotransplantation, and the recurrence rate was higher in the subtotal parathyroidectomy group (14.3% vs. 27.3%).

**Conclusion** Considering its significantly superior outcomes in the short- and long-term, total parathyroidectomy with autotransplantation should be the preferred treatment option in countries where access to kidney transplantation is difficult and where healthcare services are expensive.

**Keywords** Secondary hyperparathyroidism · Parathyroidectomy · End-stage renal disease · Renal transplantation

## Introduction

Secondary hyperparathyroidism (sHPT) develops as a result of chronic parathyroid stimulation. It is caused by hypocalcemia, hyperphosphatemia, or vitamin D deficiency and leads to

an increase in parathormone (PTH) synthesis and parathyroid cell proliferation in all of the four glands [1]. It most commonly develops secondary to chronic renal failure requiring hemodialysis, and it is observed in 90% of such patients. It is a significant complication in patients with end-stage renal

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failure (ESRD) and contributes greatly to complications in this patient group, increasing the risk of fracture and cardiovascular mortality [2]. The parathyroidectomy (PTX) rate in sHPT has been reported to be approximately 5.4/1000 patients per year in the USA and 8.8 in 1000 per year in Sweden [3, 4]. While it is known that the optimum renal replacement therapy in end-stage renal failure is renal transplantation, the problems sourcing organs for transplantation are among the most significant in these patients group. When evaluating patients with renal failure, physicians take into account the possibility of hyperparathyroidism (Table 1).

Symptoms may include renal osteodystrophy, hyperphosphatemia, and bone pain caused by hypercalcemia, while more severe hyperparathyroidism-related symptoms may develop at higher parathormone levels, above 1000 pg/mL. Surgery is the only viable option for the treatment of renal parathyroid disease which cannot be managed with medical treatment and persists for longer than 6 months according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[5]. There are currently three surgical options for the treatment of renal hyperparathyroidism: subtotal parathyroidectomy, total parathyroidectomy without autotransplantation, and total parathyroidectomy with autotransplantation.

The present study compares the results of parathyroidectomy, using both techniques, including biochemical marker levels, recurrence, morbidity, or mortality, in a sample of patients with renal hyperparathyroidism who have no access to renal transplantation or calcimimetic therapy or who are resistant to medical therapy.

## Patients and Methods

The data for the present study were obtained from a retrospective review of the files of patients who presented to General Surgery Clinic of the Faculty of Medicine, Pamukkale University due to renal hyperparathyroidism and who underwent parathyroid surgery between January 2008 and

June 2020. A total of 79 patients were included in the study, all of which were aged >18 years, and in whom enlarged glands were identified through imaging methods. Of the sample, 35 patients underwent a total parathyroidectomy with autotransplantation, while 44 patients underwent a subtotal parathyroidectomy. All of the patients were on the waiting list for renal transplantation and had been treated long term with hemodialysis or peritoneal dialysis as a renal replacement therapy. In the absence of a definitive lower PTH threshold, parathyroidectomy was considered appropriate in patients on dialysis when the levels were in the 600–800 pg/ml range, in the presence of persistent hypercalcemia or hyperphosphatemia (corrected serum calcium 10.2 mg/dl [2.5 mmol/L] or phosphorus 5.5 mg/dl [1.8 mmol/L]) despite patient diet compliance and optimized vitamin D analog/calcimimetic doses, and in the presence of elevated risk or presence of calciphylaxis, or erythropoietin-resistant anemia when other modifiable factors, such as iron deficiency or gastrointestinal bleeding, were ruled out [6–8].

The patients underwent either total parathyroidectomy with autotransplantation (TPTX+ATx) or subtotal parathyroidectomy (SPTX), guided by the results of a pre-intervention parathyroid scintigraphy (<sup>99m</sup>Tec sestamibi) and neck ultrasound, taking into account also the experience of the surgeon in the assessment of parathyroid glands during the surgical procedure (increased uptake and adenomatous like seem) (Fig. 1). We considered subtotal parathyroidectomy as a favored approach for patients with moderate SHPT and a chance of short-term kidney transplantation. This is due to two reasons: first, a less aggressive parathyroid resection should lead to a less severe decline in PTH along with its sometimes problematic consequences; and second, resection the more abnormal parathyroid glands is often sufficient to obtain one of the main clinical objectives of normalizing the Ca level. The fact that in recurrent disease a reoperation at the autograft in the forearm is simpler than a reoperation in the neck, lead to our recommendation that TPTX+AT should be considered. Patients with primary hyperparathyroidism or tertiary hyperparathyroidism were excluded from the study.

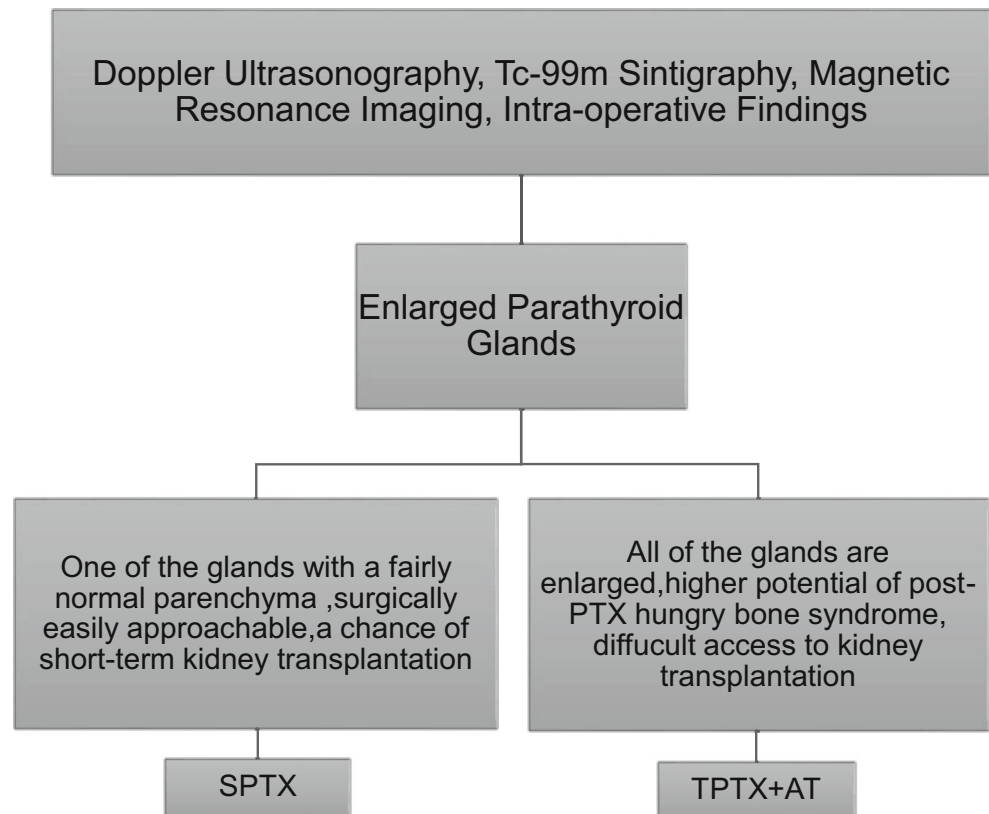
**Table 1** Symptoms of hyperparathyroidism

• Fatigue / mental state change
• Kidney stones
• Proximal muscle pain
• Bone pain due to osteitis fibrosa cystica, especially in the weight-bearing joints, including the hip, knee, ankle, and lower back
• Joint pain, inflammation of the joints due to periarticular calcium deposit
• Bone fracture, non-traumatic fractures, or fractures not healing
• Itching
• Calciylaxis, which causes enlarged, painful, cutaneous, purpuric lesions that cause tissue calcification and ischemic necrosis, if left untreated, leading to dry gangrene

## Surgical Technique

All surgical procedures were performed by the same experienced surgical team, and all surgeons involved in the study were experienced in performing these types of operations. For autotransplantation procedures, the parathyroid gland, that appeared the most normal and free of nodular enlargement, as determined during an examination, was implanted into the brachioradialis muscle, either as a 1 mm-sized section or as fine-cut parathyroid tissue. All four glands were located, and the smallest parathyroid gland, preferably non-nodular, was partially excised and left in situ, marking it with a hemostatic

**Fig. 1** Patient selection criteria according to the surgical method



clip to maintain its nutrition in patients undergoing a subtotal PTX (SPTX). Parathormone, calcium, phosphate, and alkaline phosphatase levels were analyzed preoperatively.

### Postoperative Follow-up

The patients were supported with oral calcium, calcitriol, and magnesium treatment following the surgery. Intravenous calcium treatment was administered in the event of a decrease in the serum calcium level to  $<7$  mg/dl. PTH, calcium, and phosphate levels were analyzed at 6 and 24 h postoperatively. Alkaline phosphatase levels and other parameters were analyzed at the postoperative third month. The long-term follow-up of patients for renal hyperparathyroidism recurrence following surgery was carried out in cooperation with a nephrology team who followed-up the patients during dialysis. Serum parathormone and calcium levels were tested regularly. If the parathormone level was noted to have increased to three times the upper limit of 6 months following the parathyroidectomy, a biochemical recurrence was assumed. The initial treatment of recurrent hyperparathyroidism was planned medically, followed by a resection of the autograft or the residual parathyroid gland in refractory cases.

### Statistical Analysis

The data were analyzed using the SPSS (Version 16.0, Chicago, SPSS Inc) software package. All results were

expressed in median values SD median standard error and percentages. A Fisher's test was used to determine any statistically significant differences between the groups. A  $p$  value of  $<0.05$  was considered statistically significant.

### Results

The demographical data of the patients, including gender, age, and comorbidities, are presented in Table 2. While 35 of the 79 patients underwent total parathyroidectomy and autotransplantation, 44 patients underwent a subtotal parathyroidectomy. A pathological examination of the patients who underwent a total parathyroidectomy revealed that not all glands were completely excised in four patients. Among those who underwent subtotal parathyroidectomy, three glands were excised in 38 patients (86.3%) and two glands were excised in 6 patients (13.6%). The patients underwent hemodialysis treatment for a mean 74.6 months in the total parathyroidectomy group and a mean 53.8 months in the subtotal parathyroidectomy group. There was no statistical difference between the two groups in this regard. A total of 45.7% and 59.1% of the patients were male in the total parathyroidectomy and subtotal parathyroidectomy groups, respectively. Preoperative and postoperative PTH, calcium, phosphate, and ALP levels, as well as any and alterations, are presented in Table 3. A significant decrease in PTH, calcium, and

**Table 2** Demographic data

	TPTX+AT( <i>n</i> :35 )	SPTX ( <i>n</i> :44 )	Overall ( <i>n</i> :79)	<i>p</i> value
Age	49.4(21-71)	53.6(33-76)	51.5(21-76)	NS
Gender(%)				
Male	16(45.7)	26(59.1)	42(53.1)	
Female	19(54.3)	18(40.9)	37(46.8)	
Co-morbidities (%)				
HT	29(82.8)	33(75)	62(78.4)	
CAD	8(22.8)	15(34.1)	23(29.1)	
CVD	2(5.7)	1(2.2)	3(3.7)	
Dialysis time(month)	74.6(39-115)	53.8(28-92)	64.2(28-115)	NS
Recurrence	5(14.3%)	12(27.3%)	17(21.5%)	NS

HT hypertension, CAD coronary artery disease, CVD cerebrovascular disease, NS not significant

phosphate levels was noted following both types of parathyroidectomy, although PTH and phosphate serum levels were significantly better controlled in the TPTX+AT group. After a 23.2-month follow-up of the total parathyroidectomy group, an increase in parathormone levels and biochemical recurrence were identified in five patients and in whom the parathyroid glands transplanted into the forearm were then excised. The incidence of recurrence was higher in the subtotal parathyroidectomy group (14.3% vs. 27.3%), although the difference between the two groups was not considered statistically insignificant. The mean serum PTH level of the patients experiencing recurrence was 195.7 pmol/L in the total parathyroidectomy group, and 289.9 pmol/L in the subtotal parathyroidectomy group. Age, time to surgery following first dialysis, serum PTH, calcium, ALP, and phosphate levels had no significant effect on the recurrence of hyperparathyroidism. The patients were also followed-up postoperatively for early complications and long-term mortality, during which symptomatic hypocalcemia was the most common postoperative complication, and was observed in both groups. No perioperative or postoperative mortality was experienced in either groups. Of the total, 11 of the patients in the subtotal

parathyroidectomy group and three in the total parathyroidectomy underwent a kidney transplantation.

## Discussion

Secondary hyperparathyroidism affects 15% of patients with chronic renal failure, undergoing hemodialysis, especially as renal replacement therapy, throughout their lives. In 2007, Joy et al. [9] reported parathormone levels to increase in between 2.0 and 4.7 million patients with chronic renal disease and there are candidates for treatment.

Unlike in the USA and in other Western populations, patients undergoing dialysis in our country have unique characteristics; a high prevalence of the chronic renal disease, lack of kidney donors, and inconvenience of cinacalcet treatment are among distinguishing characteristics. Only around 10% of patients with renal failure on the waiting list can undergo transplantation each year. The mean holding period for kidney transplantation is approximately 8–10 years. Although the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest both subtotal and total parathyroidectomy as

**Table 3** Biochemical parameters before and after parathyroidectomy

Variables		Pre-op levels	Post-op levels	<i>p</i> value
Serum PTH pmol/L	TPTX+AT	1446.8 SD 289	39.6 SD 17	0.001
	SPTX	1358.7 SD 315	146.9 SD 45	0.001
Serum Calcium, (mmol/L)	TPTX+AT	9.3 SD 1.2	6.9 SD 1.3	0.001
	SPTX	9.1 SD 0.8	6.8 SD 1.1	0.001
Serum Phosphate, (mmol/L)	TPTX+AT	2.4 SD 0.6	1.2 SD 0.4	0.001
	SPTX	2.1 SD 0.9	1.3 SD 0.6	0.001
Serum ALP (U/L)	TPTX+AT	421 SD 157	163 SD 114	NS
	SPTX	397 SD 215	187 SD 89	NS

PTH parathormone, TPTX total parathyroidectomy with autotransplantation, SPTX subtotal parathyroidectomy, ALP alkaline phosphatase

preferred treatments, considering abovementioned causes, a total parathyroidectomy and autotransplantation should be considered in most patients [10].

In the present study, it was found that serum PTH, calcium, and phosphate levels decreased significantly after both TPTX+AT and SPTX, although serum PTH and phosphate levels were significantly better controlled with TPTX+AT than with SPTX. We had been applying the subtotal parathyroidectomy method in our clinic for about 12 years, but for the last 10 years, we have opted where possible for the total parathyroidectomy with autotransplantation approach to reduce the risk of recurrence. We also identified a significant decrease in bone alkaline phosphatase levels 3 months after both operations. We are aware of the fact the levels may remain the same or may increase as a result of permanent osteoblastic activity. It is difficult to predict ALP levels during the early postoperative period. Rothmund et al. [11] reported encountering significantly lower ALP levels ( $p < 0.03$ ) 19–25 months after surgery, and so, it can be concluded that the long-term follow-up of ALP levels will lead more sensitive results.

A meta-analysis revealed no differences in recurrence, reoperation rates, or clinical symptoms were noted between the SPTX and TPTX+AT groups [12]. In the present study, the recurrence rate of the disease was lower in the total parathyroidectomy group. In the total parathyroidectomy group, recurrences were not symptomatic, which excluded from the five patients who required resection of autotransplanted tissue. Perioperative morbidity and long-term mortality were similar between the groups with deaths occurring secondary to cardiovascular events.

The subtotal parathyroidectomy approach has been reported to cause less reduction in graft perfusion in kidney transplant patients than total parathyroidectomy [13, 14]. This led us to prefer subtotal parathyroidectomies for patients undergoing dialysis treatment who were on the kidney transplant waiting list.

Preoperative high PTH, high alkaline phosphatase, and longer duration of renal replacement therapy were associated with an increased risk of hungry bone syndrome (HBS) [15]. Since hypocalcemia will develop in the long term after hungry bone syndrome, we preferred TPTX+AT in high risk patients.

This study has some limitations; primarily, case series analysis of patients was included in the study. Despite these limitations, this study highlights the importance of performing total parathyroidectomy with autotransplantation in parts of the world where access to kidney transplantation is difficult. This procedure may play an important role as an early intervention in the prevention of metabolic and bone-related complications in patients with chronic renal failure, although this is controversial and a longer follow-up period will be beneficial to determine the efficacy of surgery, as well as long-term management hyperparathyroidism.

In conclusion, medical therapy is the first-line treatment for renal hyperparathyroidism. Calcimimetics have proven their efficacy in the control of the disease, thereby decreasing the need for parathyroidectomy. Considering its significantly superior outcomes in the short- and long-term, however, total parathyroidectomy with autotransplantation should be the approach of choice in countries where access to kidney transplantations is difficult and where healthcare is expensive.

## Declarations

**Competing Interests** The authors declare no competing interests.

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