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# Surgical outcomes of secondary and tertiary hyperparathyroidism in King Salman Armed Forces Hospital, Tabuk

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## ABSTRACT

**Objective:** To investigate surgical outcomes of tertiary and secondary hyperparathyroidism in King Salman Armed Forces hospital, Tabuk, Saudi Arabia. **Methods:** A record-based research that was retrospective in nature was carried out between January 1, 2015 and August 1, 2022. The King Salman Armed Forces hospitals' documents were gathered, including all valid surgical records. A predesigned data collection pro forma was used to capture the data, which was then revised, coded and entered into the statistical programme IBM SPSS version 22. **Results:** 17 patients who had undergone hyper parathyroidectomy surgery and had a clinical diagnosis of hyperparathyroidism were included in the research. Among the patients, 11.8% had CKD and 88.2% also had hypertension. Following surgery, mean (SD) calcium levels substantially decreased from 2.31 (0.36) to 2.10 (0.29) ( $P=0.029$ ). Additionally, there was a substantial decrease in phosphate mean levels from 2.06 (0.90) to 1.38 (0.63) ( $P=0.047$ ). Additionally, there was a substantial decrease in creatinine levels from 752.52 (305.91) to 544.41 (301.33) ( $P=0.024$ ). A substantial decrease in PTH mean levels was also observed, going from 1888.76 (77.38) pre-operative to 494.42 (577.74) post-operative ( $P=0.013$ ). 35.7% of patients had hypocalcaemia and 11.8% had hematomas as post-operative complications. **Conclusion:** In individuals with chronic renal disease, complete parathyroidectomy with auto-transplantation is a safe and efficient method of treating tertiary and secondary hyper parathyroid disorders. The study sample did not have any recurrence, and the incidence of complications was quite low.

**Keywords:** CKD, hyperparathyroidism, hyper parathyroidectomy

## 1. INTRODUCTION

Hypocalcemia and hyperphosphatemia are significant inducers of PTH secretion, which is triggered by the parathyroid hormone PTH, which is

released by the parathyroid glands and involved in the metabolism of calcium and skeletal tissue. Likewise, 1, 25 (OH) vitamin D reduces PTH secretion (Muppidi et al., 2020). In most cases, parathyroid gland hyperplasia that produces excess parathyroid hormone causes tertiary and secondary hyperparathyroidism (HPT) (PTH). Combined, tertiary and secondary HPT patients make up a small portion of those receiving an HPT diagnosis (Gasparri et al., 2001).

Secondary hyperparathyroidism (S-HPTH) in humans is primarily caused by chronic kidney disease (CKD), which leads to an unbalanced phosphor-calcium metabolism that acts as a systemic stimulus on the parathyroid glands. According to estimates, up to 90% of chronic kidney disease patients CRF have this condition by the time hemodialysis is started (Amza et al., 2017). Chronically elevated levels of parathyroid hormone (PTH) in the bloodstream exacerbate biochemical and morphological changes, particularly promoting the emergence of CKD-related mineral and bone disorders (CKD-MBD). The ideal therapeutic option for CKD patients is still a functional kidney transplant before the parathyroid glands undergo structural changes, but this is challenging to accomplish (Pitt et al., 2009). When patients with secondary HPT have high PTH levels after receiving a renal allograft, tertiary HPT most frequently develops. Almost 30% of kidney transplant recipients have this disease (Chou et al., 2002).

The surgical approach is a turning point in the management of tertiary and secondary hyperparathyroidism. One year after starting hemodialysis, at least 1% of patients and 15% after ten years will need a parathyroidectomy. However, the choice of surgical therapy is debatable because there is no agreement on the kind of parathyroidectomy that must be done to prevent recurrence and concurrent permanent hypoparathyroidism, which forces the surgeon to make a choice based on personal experience (Khan et al., 2022; Li et al., 2011). The main objective of this study is to investigate surgical outcomes of tertiary and secondary hyperparathyroidism in King Salman Armed Forces hospital, Tabuk, Saudi Arabia.

## Literature Review

According to a prospective randomized trial outlined by the crew of Rothmund et al., (1991) patients with secondary hyperparathyroidism who underwent total parathyroidectomy and auto-transplantation had remarkably better clinical outcomes than those who underwent subtotal parathyroidectomy. Comparing the parathyroidectomy group to the subtotal parathyroidectomy group, a parathyroidectomy followed by autotransplantation resulted in a lower percentage of patients who required surgical reintervention as well as lower serum calcium levels (Rothmund et al., 1991).

Isaksson et al., (2019) study on 824 patients, 436 subtotal and 388 totals, who underwent parathyroidectomy to assess the results of parathyroid surgery in patients with S-HPTH, reported no variance in death or risk of hip fracture in both groups. Patients who underwent total parathyroidectomy had elevated risk of cardiovascular events than those who underwent subtotal parathyroidectomy, but they also had a lower risk of having another parathyroidectomy (Isaksson et al., 2019).

A retrospective investigation on 446 patients had parathyroid surgery after partial parathyroidectomy, total parathyroidectomy with autotransplantation and total parathyroidectomy, the recurrence rate ranged from 5% to 8%; it was only after incomplete parathyroidectomy that the rate increased to 34.7 percent. The proliferative percentage found by Ki-67 in the recurrence group was 1.9 percent compared to 0.81 percent in the control group. The nodular type was prevalent in this group (Gasparri et al., 2001).

Another study on twelve patients with mean age 50.6 years and the main etiology was tertiary hyperparathyroidism (83%). At some point after surgery, all patients had abnormal calcium levels; nevertheless, 90% of them were normocalcemic at the time of the last follow-up. One recurrent laryngeal nerve damage and one wound infection were additional side effects (one). No perioperative deaths occurred. The typical length of stay in the hospital was 7.75 days (range 3-17 days). The average follow-up time was 11 months. The results of the parathyroidectomy at UMMC are satisfactory with few significant side effects. The outcomes still need to be improved significantly in order to match those from specialized endocrine centers (Roslani and Chang, 2016).

## 2. METHODOLOGY

A retrospective record-based study was conducted in Tabuk, KSA, during the period from 1st of Jan 2015 to August 2022. Using convenience sampling, the study included all the valid complete records of surgery in the current year and the previous 7 years in our study. The complete valid surgical records from King Salman Armed Forces hospitals' records were collected. Although convenience sampling included all valid and complete surgical records of the target hospital, sample size calculation turned to be 380 (Sullivan and Soe, 2016).

Data was collected using a predesigned data collection proforma. In cases of uncertainty due to recorded vague/incomplete information particularly for records with the target anomaly, authors personally communicated with patient or their relatives through the data collection period to confirm specific information considering surgery and its outcome. The collected data included socio-demographic characteristics of participants (gender, age, marital status, educational and working status) as well as data

regarding surgery (type of surgery, surgery outcome, intra-operative or post-operative complications and recurrence of hyperparathyroidism).

#### **Inclusion criteria**

2ry hyperparathyroidism & Terity hyperparathyroidism underwent surgery in KSAFH Adult age (14 years and above).

#### **Exclusion criteria**

Primary hyperparathyroidism

#### **Ethical considerations**

Approval to conduct the study was obtained by the Research Ethics committee in King Salman armed forces hospital. Although special groups are involved, the study is record-base and no need for direct interaction with patients. There are no biological samples in this study and data collected was totally de-identified since names and specific address of the participants are not required and collected. Data was safeguarded till group statistical analysis and publication. No access was allowed for anyone but authors of the study. There is no conflict of interest.

#### **Data analysis**

After data was collected, it was revised, coded and fed to statistical software IBM SPSS version 22 (SPSS, Inc. Chicago, IL). All statistical analysis was done using two tailed tests. P value less than 0.05 is statistically significant. Descriptive analysis based on frequency and percent distribution was done for all variables including demographic data, co-morbidities and surgical outcomes. Significance of relations in cross tabulation was tested using exact probability test (due to small frequencies).

### **3. RESULTS**

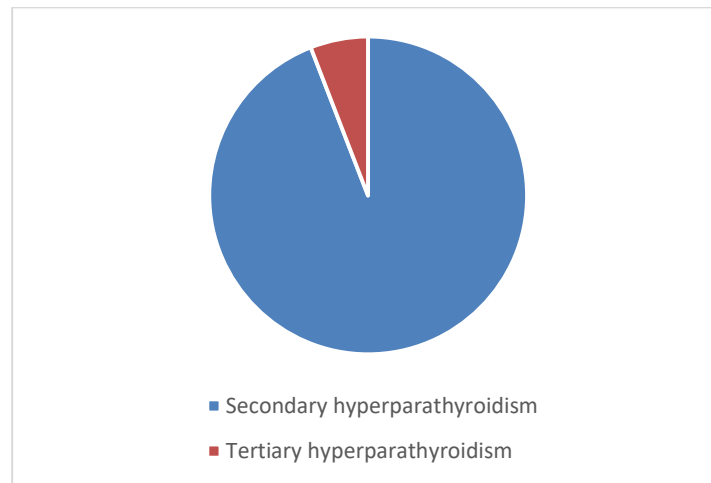
The study included 17 patients clinically diagnosed with hyperparathyroidism and underwent hyper parathyroidectomy surgery. 64.7% of patients were females. 58.8% aged between 30- 44 years old, 23.5% aged between 45- 59 years old and 17.6% age between 14- 29 years old. 70.6% were married and 64.7% work as illustrated (Table 1). Figure 1 shows that 94.1% of participants had secondary hyperparathyroidism while 5.9% had tertiary hyperparathyroidism.

**Table 1** Socio-demographic characteristics of participants (n=17)

Parameter		No.	%
Gender	Male	6	35.3
	Female	11	64.7
Age	14-29	3	17.6
	30-44	10	58.8
	45-59	4	23.5
Marital status	Married	12	70.6
	Single/ Divorced/ Widowed	5	29.4
Working Status	Work	11	64.7
	No work	6	35.3

Table 2 shows that 11.8% of participants had CKD and 88.2% had CKD with hypertension. Follow-up period was more than 6 months in all patients. All patients underwent complete parathyroidectomy with auto-transplant. Also, all patients had preoperative treatment of hypercalcemia. 35.3% of participants had active nodules (adenoma/ hyperplasia) in MIBI scan finding.

Table 3 illustrate laboratory findings pre- and post-operative. Mean ( $\pm$ SD) calcium levels significantly dropped post-operative from 2.31 ( $\pm$ 0.36) to 2.10 ( $\pm$ 0.29) ( $P=0.029$ ). Phosphate means levels also dropped significantly from 2.06 ( $\pm$ 0.90) to 1.38 ( $\pm$ 0.63) ( $P=0.047$ ). Creatinine levels also dropped significantly from 752.52 ( $\pm$ 305.91) to 544.41 ( $\pm$ 301.33) ( $P=0.024$ ) as well as albumin dropped from 37.41 ( $\pm$ 12.55) to 31.93 ( $\pm$ 8.75) ( $P=0.074$ ). PTH mean levels also significantly dropped from 1888.76 ( $\pm$ 77.38) pre-operative to 494.42 ( $\pm$ 577.74) post-operative ( $P=0.013$ ). Post-operative complications were reported as 11.8% had hematoma and 35.7% had hypocalcaemia. No patients reported wound infection or recurrence of disease as shown (Table 4).



**Figure 1** Type of hyperparathyroidism among study participants

**Table 2** Co-morbid diseases, type of hyperparathyroidism and type of surgery (n=17)

Parameter		No.	%
Co-morbid diseases	Chronic kidney disease	2	11.8
	Chronic kidney disease + Hypertension	15	88.2
Follow up period (months)	> 6 months	17	100.0
Type of surgery	Complete parathyroidectomy with auto-transplant	17	100.0
Preoperative treatment of hypercalcemia	Yes	17	100.0
Presence of nodules (adenoma/hyperplasia) in radiological finding	Yes	9	52.9
	No	8	47.1
Presence of active nodules (adenoma/hyperplasia) in MIBI scan finding	Yes	6	35.3
	No	11	64.7

**Table 3** Laboratory findings pre- and post-operative among study participants (n=17)

Parameter	Pre-operative	Post-operative	P value
Calcium mmol/L	2.31 ( $\pm 0.36$ )	2.10 ( $\pm 0.29$ )	0.029
Creatinine ( $\mu\text{mol/L}$ )	752.52 ( $\pm 305.91$ )	544.41 ( $\pm 301.33$ )	0.024
Phosphate mmol/L	2.06 ( $\pm 0.90$ )	1.38 ( $\pm 0.63$ )	0.047
Albumin g/L	37.41 ( $\pm 12.55$ )	31.93 ( $\pm 8.75$ )	0.074
PTH. Pg/mL	1888.76 ( $\pm 77.38$ )	494.42 ( $\pm 577.74$ )	0.013

**Table 4** Post-operative complications among participants (n=17)

Complication	Yes	No
Wound infection	0 0%	17 100.0%
Hematoma	2 11.8%	15 88.2%
Skin Tethering	0 0%	17 100.0%
Keloid formation	0 0%	17 100.0%
Recurrent nerve injury	0 0%	17 100.0%
Persistent/recurrent disease	0 0%	17 100.0%

Bone hunger symptoms	0 0%	17 100.0%
Hypocalcaemia	6 35.3%	11 64.7%
Cardiovascular complication	0 0%	0 0%
Bone fracture	0 0%	0 0%
Calciophylaxis	0 0%	0 0%
Death	0 0%	0 0%

#### 4. DISCUSSION

This is a retrospective cohort study of patients with renal hyperparathyroidism aiming to investigate surgical outcomes of tertiary and secondary hyperparathyroidism in King Salman Armed Forces hospital, Tabuk, Saudi Arabia. Parathyroidectomy for rHPT must be taken into account when severe rHPT is vulnerable to medical and pharmacological therapy, though the precise indications for this procedure are unclear. The US Kidney Foundation's K/DOQI guidelines recommend parathyroidectomy for patients with severe secondary hyperparathyroidism (persistent serum iPTH levels >800 pg/mL), which is linked to hypercalcemia or hyperphosphatemia and is resistant to medical treatment (Yuen et al., 2016). Given that secondary hyperparathyroidism progresses are known to affect mortality, the Japanese Society for Dialysis Therapy guidelines advice surgical treatment at an early stage (Tentori et al., 2015). An adequate balance between the extent of parathyroid resection, prevention of persistent/recurrent disease and avoidance of postoperative permanent hypoparathyroidism should be the goal of surgical treatment for rHPT (Lim et al., 2018).

In our study, all of studied patients underwent total parathyroidectomy with autotransplant. A previous study reported that (59%) patients had subtotal parathyroidectomy (STP) and (37%) had total parathyroidectomy (TP) and (3%) were treated with TP with autotransplant (Low et al., 2009). The scope of surgery may be decided based on the surgeon's preferences and the patient's clinical condition, considering things like the patient's age, eligibility for kidney transplantation, likelihood of surviving after parathyroidectomy and capacity for obtaining and adhering to medication (Okada et al., 2021).

According to our study results, there was a significant drop in calcium, phosphate, creatinine and PTH levels post-operatively; however, there was non-significant drop in albumin levels. This was comparable to results of previous literature as a previous study reported a significant drop in the levels of calcium, alkaline phosphatase (ALP) and PTH after parathyroidectomy (Low et al., 2009) which was in accordance with a study reported that mean preoperative serum calcium, iPTH and inorganic phosphorus were 1,199.0±571.3 pg/mL, 10.5± 1.0 mg/dL and 6.0±2.3 mg/dL, respectively, as mean serum iPTH and calcium levels dropped significantly to 49.2±47.6 pg/mL ( $P<0.01$ ) and 8.0±1.0 mg/dL ( $P<0.01$ ), respectively 6 months after operation (Kim et al., 2020). Another study reported decrease in all values as post-operative mean serum calcium was 2.1±0.32mmol/L (mean±SD), serum phosphorus was 1.26±0.35mmol/L (mean±SD) and serum alkaline phosphatase was 158±75U/L (mean±SD). Serum PTH decreased in all patients (Gourgoutis et al., 2006) which was on the line with a study reported long-term follow up during 2-years period, significant reductions in parathyroid hormone, alkaline phosphatase blood levels, skeletal changes and soft tissue calcifications were observed (Rashed et al., 2004).

According to a study, the average patient's preoperative PTH level was 866 pg/mL. After three months, the median PTH level for all patients decreased by 93%, from 866 (407-1447) pg/mL to 61 (23-148) pg/mL. Patients with secondary HPT compared to tertiary HPT patients did not have significantly different postoperative PTH levels. After PTx, median-adjusted calcium levels significantly decreased from 2.6 (2.4-2.8) mmol/L to 2.3 (2.1-2.5) mmol/L ( $p=0.001$ ) and did not significantly differ between patients with secondary HPT and those with tertiary HPT. Additionally, preoperative phosphate levels were elevated in those with secondary HPT and low but within the normal range (0.81-1.45 mmol/L) in those with tertiary HPT patients (Plas et al., 2018).

According to Salem, (1997) research on chronic hemodialysis patients, 50% of the patients had serum PTH levels that were three times above normal despite receiving conventional medical treatment to treat hyperparathyroidism. In SHPT patients, hypercalcemia also increases the need for surgery (Llach, 1995; Llach, 1990). Bone pain, joint pain, muscle weakness and pruritus the progression of soft tissue calcification and spontaneous bone fractures were among the clinical symptoms of SHPT that were resistant to conventional medical treatment in a previous study (Maxwell and Fabian, 2003).

Regarding post-operative complications, our study results show that 11.8% of participants had hematoma and 35.7% had hypocalcemia. No patients reported wound infection or recurrence of disease. This was on the line with a study reported low rate of post-operative complications, mild although asymptomatic postoperative hypocalcemia was noticed in 4 patients (Gourgiotis et al., 2006). According to a different study, cases with high preoperative alkaline phosphatase levels experienced transient postoperative hypocalcemia that necessitated intensifying calcium and vitamin D therapy and recurrence was noted in two cases (Rashed et al., 2004). According to a study, complications were relatively more common: 0.9% of patients had wound infections, 0.9% experienced temporary vocal cord paralysis, 0.9% experienced seizures brought on by severe hypocalcemia, 0.9% had neck haemorrhages that needed to be evacuated and 9.6% of patients experienced recurrent hyperparathyroidism (Low et al., 2009).

In a retrospective review of complete parathyroidectomy with and without autotransplantation, a group of patients with forearm tissue autografts demonstrated a considerably greater rate of recurrence than those without autografts (45% vs. 0%) (Ockert et al., 2002). Additionally, Lorenz et al., (2006) found that after total parathyroidectomy without autotransplantation, the recurrence rate was 0%. Another study found that the varied types of surgeries did not affect the recurrence rate, which ranged from 5% to 8%. After total parathyroidectomy, 17.3% of patients experienced permanent hypocalcemia. In a different study, the rate of hypocalcemia was higher; during hospital admission, hypocalcemia was noted in 48.5% of the patients. In 2.4% of the patients, admission to an intensive care unit was necessary to treat hypocalcaemia. 37.4% of patients continued taking calcium supplements three months after their last dose of PTx (Plas et al., 2018).

For calcium to remain stable, activated vitamin D levels must be adequate. KDOQI advises up to 2 g/day of calcitriol postoperatively (Mc-Cann, 2005), despite the fact that preoperative loading may also help maintain postoperative calcium levels. One retrospective study found that taking 0.5 mg of calcitriol twice day for five days greatly reduced the likelihood that the patient would require intravenous calcium (given for symptoms, calcium below 7.0 mg/dl or as chosen by the surgeon). In addition, hospital stays for individuals receiving calcitriol were 2.0 days shorter. Postoperative calcitriol therapy of up to 4 g/day considerably decreased the fall in calcium levels in a short, placebo-controlled experiment (Clair et al., 1987). It is unknown if intravenous and oral calcitriol have different levels of effectiveness. High-calcium dialysate may also be used to treat postoperative hypocalcemia in dialysis patients (Florescu et al., 2014).

## 5. CONCLUSION

Complete parathyroidectomy with auto-transplant is a safe and effective way in management of tertiary and secondary hyperparathyroid diseases in chronic kidney disease patients. No recurrence was reported among study sample and complication rate was very low. Depending on the surgeon's preference and the patient's clinical condition, the extent of the surgery may be decided.

### Abbreviations

Hyperparathyroidism (HPT)

Secondary hyperparathyroidism (S-HPTH)

Chronic kidney disease (CKD)

Parathyroid hormone (PTH)

CKD-related mineral and bone disorders (CKD-MBD)

Total parathyroidectomy (TP)

Alkaline phosphatase (ALP)

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### Author Contributions

YSA, KF and SAS regarded and designed the study, conducted research, provided research materials and collected and organized data. YSA, KF and SAS analyzed and interpreted data. YSA, KF and SAS wrote initial and final draft of article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript



### Ethical approval

The study was approved by the Medical Ethics Committee of King Salman armed forces hospital (Ethical approval code: KSAF-REC-2022-464).

### Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

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This study has not received any external funding.

### Conflict of interest

The authors declare that there is no conflict of interests.

### Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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