



A Comparison of Surgical Treatments for Tertiary Hyperparathyroidism. A Systematic Review

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Abstract

Introduction: Tertiary hyperparathyroidism develops in patients who have secondary hyperparathyroidism that persists despite successful kidney transplantation or in patients who are on chronic dialysis.

Aim: This study aims to present a comparison of surgical treatments of tertiary hyperparathyroidism.

Materials and methods: A systematic review of studies published in English that reported on the surgical management of tertiary hyperparathyroidism was conducted using PubMed databases in accordance with the PRISMA guidelines. Two authors independently reviewed the full text of potentially selectable articles and selected appropriate studies. Surgical treatment options were evaluated.

Results: This review contains thirteen relevant studies. The treatments recommended by the studies included limited parathyroidectomy, subtotal parathyroidectomy, total parathyroidectomy with autotransplantation, and total parathyroidectomy without autotransplantation. The choice of the appropriate surgical technique demands individualization of the treatment and depends mainly on the experience of the surgeon.

Conclusion: The predominant treatment options appear to be subtotal parathyroidectomy and total parathyroidectomy with autotransplantation.

Keywords

autotransplantation, chronic kidney disease, parathyroid hormone, parathyroidectomy, tertiary hyperthyroidism

INTRODUCTION

Patients with long-standing chronic kidney disease (CKD) develop elevated serum parathyroid hormone (PTH) concentrations, which are frequently accompanied by hypercalcemia and cannot be explained by calcium carbonate or calcitriol supplements.^[1,2] This condition is defined as tertiary hyperparathyroidism and occurs in patients with sec-

ondary hyperparathyroidism that persists even after a successful kidney transplant or in patients who are on chronic dialysis.^[1,2] The chronic kidney disease is associated with hyperphosphatemia, calcitriol deficiency, and hypocalcemia. These metabolic disturbances lead to prolonged parathyroid cell stimulation and nodular hyperplasia of the parathyroid gland. Hyperplastic parathyroid glands become autonomous, resulting in PTH hypersecretion. In

this stage, even elevated serum calcium levels cannot prevent the secretion of parathyroid hormone. Indications for treatment are persistent hypercalcemia and/or increased parathyroid hormone levels.^[2] As treatments with vitamin D or calcitriol offer low cure rates, usually fail, and are not indicated, the primary treatment is surgery.^[2-4] Four are the surgical procedures that are usually performed: total parathyroidectomy (PTX) with autotransplantation, total parathyroidectomy without autotransplantation, subtotal parathyroidectomy, and limited parathyroidectomy.

The benefits of surgery may include improving survival and bone mineral density and alleviating the unpleasant and painful symptoms of tertiary hyperparathyroidism.^[5] Because of the diversity of tertiary hyperparathyroidism and the specificities of chronic kidney disease patients, the indications for surgical treatment, the selection of appropriate surgical treatment, and the potential complications that may arise are all subjects of investigation.

AIM

This study aims to present a comparison of the surgical treatments of tertiary hyperparathyroidism.

MATERIALS AND METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Review & Meta-Analyses (PRISMA) guidelines. The search was performed using PubMed databases up to 1988. The following Medical Subject Headings terms and keywords were used: “tertiary parathyroidism” and “surgery”. The following MeSH terms were used: parathyroidism, chronic kidney diseases, and surgery. After the search, titles and abstracts were screened. Two authors reviewed the full text of potentially selectable articles independently and appropriate studies were selected. The first selection was performed based on the title and abstract. Afterwards, the whole text was reviewed. A study was included when it was a retrospective cohort study that suggested a surgical approach for tertiary hyperparathyroidism. The following criteria were used to exclude studies from consideration: 1) whether it was a letter, review, case report, conference abstract, remark, or discussion; 2) whether surgical treatment was not recommended; 3) studies that were not published in English; 4) studies for which it was not possible to obtain the complete study text online or through a request to the authors. The data extracted from each included publication were first author, publication year, study design, and operations performed.

RESULTS

The literature search yielded over 828 articles. 718 articles were removed before screening by automation tools. After

screening the titles and abstracts, 13 articles remained for full-text review. After the review, 13 articles were suitable for qualitative synthesis.

Fig. 1 shows the PRISMA flowchart of the search and selection process and **Table 1** summarizes the final list of included studies. In total, 1705 patients were included in 13 studies.

Subtotal parathyroidectomy was suggested by six studies. In total, it concerned 380 patients. Total parathyroidectomy with autotransplantation was proposed by four studies which included 1112 patients. Total parathyroidectomy without autotransplantation appeared in two studies in which 130 patients participated. Finally, limited parathyroidectomy was supported only by one study with 83 patients.

DISCUSSION

The ideal surgical intervention for the treatment of tertiary hyperparathyroidism has not been established. The adequate surgical treatment of tertiary hyperthyroidism should aim for an appropriate balance between the method of resection, control of recurrences, and prevention of persistent postoperative hypoparathyroidism.^[11] Surgical complications are rare, and parathyroidectomy appears to be a safe and feasible treatment option for tertiary hyperparathyroidism. Parathyroidectomy increases bone mineral density and leads to a reduced risk of major cardiovascular events and death compared with conservative treatment.^[19]

Confined published studies compare surgical techniques. In their majority, they suggest that a limited or focused PTX should be avoided as it continues to be unclear and controversial. Although, limited resections are recommended because of their high success rates and minimum complications compared to more extensive surgeries, in patients with chronic kidney disease^[14] and kidney transplantation, renal graft function deteriorates.^[2] Moreover, in limited resections, hypocalcemia, although transient in the postoperative period, could also be detected.^[2]

Some authors recommend subtotal PTX with simultaneous thymectomy, and others subtotal PTX without thymectomy. Subtotal parathyroidectomy with the identification of all parathyroids (even supernumerary or ectopic ones) is recognized as a safe and effective method for tertiary hyperparathyroidism. This operation is associated with an acceptably low recurrence rate, long-term correction of hypercalcemia, and rehabilitation of bone disease over extremely long follow-up periods. Furthermore, studies show that the risk of permanent hypoparathyroidism is less likely with subtotal parathyroidectomy. Additionally, subtotal parathyroidectomy does not impair renal graft function and provides long-term correction of hypercalcemia and tertiary hyperparathyroidism. For all these reasons, subtotal parathyroidectomy seems to be preferred in most studies (**Table 1**).^[7,10,11,13,17,18]

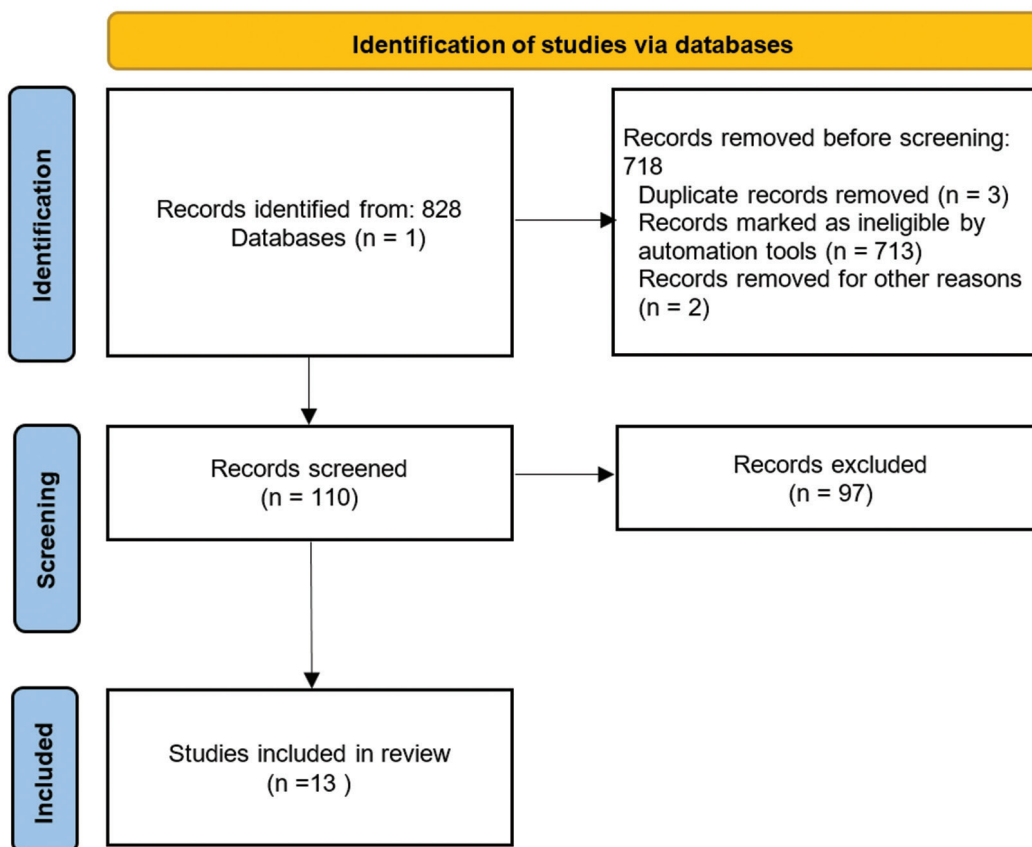


Figure 1. PRISMA 2020 flow diagram of the search and selection process.

Table 1. The results of the search for ideal surgical treatment of tertiary hyperparathyroidism. The names of the first author, the year of publication, the number of patients who participated in each study and underwent parathyroidectomy, and the recommended procedure by each article are listed.^[6-18]

Study	Year	Number of patients with tHPT included in the respective study	Subtotal PTX	Total PTX with autotransplantation	Total PTX without autotransplantation	Limited PTX
Alexander PT et al. ^[6]	1988	20		+		
Punch JD et al. ^[7]	1995	91	+			
Wheatley TJ et al. ^[8]	1997	15			+	
Tominaga Y et al. ^[9]	2001	1053		+		
Triponez F et al. ^[10]	2005	70	+			
Schlosser K et al. ^[11]	2007	69	+			
Coulston JE et al. ^[12]	2010	115			+	
Park JH et al. ^[13]	2011	15	+			
Jäger MD et al. ^[14]	2011	83				+
Robin-Lersundi A et al. ^[15]	2012	13		+		
Sadideen HM et al. ^[16]	2012	26		+		
Gawrychowski J et al. ^[17]	2015	30	+			
Choi HR et al. ^[18]	2021	105	+			
Total number of studies: 13		Total number of patients: 1705				

Total parathyroidectomy appears to be a safe and effective method for the treatment of hyperparathyroidism in CKD patients who have been transplanted or who are awaiting renal transplantation.^[8,12] In renal failure patients who have been transplanted or who are awaiting renal transplantation, a total parathyroidectomy frequently leaves functioning parathyroid tissue behind.^[8] Rates of persistent hypoparathyroidism after total parathyroidectomy without autotransplantation have been reported to be low and it appears to be protective against disease recurrence.^[8,12] Subsequently, if it is performed early in the course of the disease, total parathyroidectomy is associated with long-term patient survival, based on long-term follow-up of patients population with chronic kidney disease.^[8,12] Nevertheless, this surgical procedure is suggested by fewer studies compared to the other surgical methods.

Total parathyroidectomy with autograft has proven to be a satisfactory and commonly performed procedure. PTX should be combined with forearm autotransplantation for easier management of possible recurrence and immediate normalization of serum calcium, phosphorus, and parathormone.^[6,9,15,16] It has been proved that this access provides pleasant bone disease rehabilitation. The choice of gland to be transplanted into the forearm, as well as the transplantation procedure used, are critical factors in determining the outcome of the operation.^[6,9,15,16] The morphology of the gland to be autotransplanted must be assessed both macroscopically and microscopically. The nodular appearance of the glands on histological examination should be taken into account as nodular hyperplasia is associated with increased rates of postoperative hypertrophy.^[6,9,15,16] Thus, total parathyroidectomy with autotransplantation is an effective treatment for tertiary hyperparathyroidism but carries an increased risk of impaired renal graft function as decreased graft perfusion, particularly for patients who already have poor renal function at the time of surgery. Moreover, the chance of complications and reoperation rates are generally increased.^[9,20-22] The high rate of recurrence could be attributed to the method's widespread use.

Renal function after parathyroidectomy for tertiary hyperparathyroidism appears to decline transiently or permanently.^[2,5,11] The existing literature shows either, no effect of parathyroidectomy on overall renal graft survival. In contrast, others show that subtotal or total parathyroidectomy, based on long-term follow-up of this population of patients with chronic kidney disease, is associated with long-term patient survival if performed early.^[2,5,11] The renal function decrease could happen either due to parathyroidectomy or the graft's chronic rejection. This fact can only be determined by controlled, prospective studies investigating the long-term consequences of parathyroidectomies on renal function in patients with tertiary hyperparathyroidism. Currently, there are no such studies.

An accurate and careful parathyroidectomy guided by intraoperative parathyroid hormone measurement should be considered the best surgical option for the definitive

treatment of tertiary hyperparathyroidism, avoiding recurrences and ruling out the presence of supernumerary glands. Rapid biopsy could be performed as an adjuvant treatment. The choice of appropriate surgical management strongly depends on the endocrine surgeon's experience which plays a decisive role in the outcome of the operation. Due to the specificity of nephrological patients, the individualization of treatment seems imperative.

CONCLUSION

In conclusion, it appears that subtotal parathyroidectomy and total parathyroidectomy with autotransplantation are safe and efficient methods for the surgical treatment of tertiary hyperparathyroidism. Although a total parathyroidectomy with autotransplantation is the most common method, subtotal parathyroidectomy seems to be a method without complications, without an extremely high occurrence of hypoparathyroidism and it is characterized by good prognosis and survival in transplant patients.

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Competing Interests

The authors have declared that no competing interests exist.

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Сравнение хирургических методов лечения третичного гиперпаратиреоза. Систематический обзор

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Резюме

Введение: Третичный гиперпаратиреоз развивается у пациентов со вторичным гиперпаратиреозом, который сохраняется, несмотря на успешную трансплантацию почки, или у пациентов, находящихся на хроническом диализе.

Цель: Целью данного исследования является представление сравнения хирургического лечения третичного гиперпаратиреоза.

Материалы и методы: Систематический обзор опубликованных на английском языке исследований, в которых сообщалось о хирургическом лечении третичного гиперпаратиреоза, был проведен с использованием баз данных PubMed в соответствии с рекомендациями PRISMA. Два автора независимо друг от друга рассмотрели полный текст статей, которые потенциально можно было бы выбрать, и выбрали соответствующие исследования. Были оценены варианты хирургического лечения.

Результаты: Этот обзор содержит тринадцать соответствующих исследований. Лечение, рекомендованное в исследованиях, включало ограниченную паратиреоидэктомию, субтотальную паратиреоидэктомию, тотальную паратиреоидэктомию с аутооттрансплантацией и тотальную паратиреоидэктомию без аутооттрансплантации. Выбор подходящей хирургической техники требует индивидуализации лечения и зависит главным образом от опыта хирурга.

Заключение: Преобладающими вариантами лечения являются субтотальная паратиреоидэктомия и тотальная паратиреоидэктомия с аутооттрансплантацией.

Ключевые слова

аутооттрансплантация, хроническая болезнь почек, паратиреоидный гормон, паратиреоидэктомия, третичный гиперпаратиреоз