Tertiary hyperparathyroidism: a review

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Abstract

Tertiary hyperparathyroidism (HPT III) occurs when an excess of parathyroid hormone (PTH) is secreted by parathyroid glands, usually after longstanding secondary hyperparathyroidism. Some authorities reserve the term for secondary hyperparathyroidism that persists after successful renal transplantation. Long-standing chronic kidney disease (CKD) is associated with several metabolic disturbances that lead to increased secretion of PTH, including hyperphosphatemia, calcitriol deficiency, and hypocalcemia. Hyperphosphatemia has a direct stimulatory effect on the parathyroid gland cell resulting in nodular hyperplasia and increased PTH secretion. Prolonged hypocalcemia also causes parathyroid chief cell hyperplasia and excess PTH. After correction of the primary disorder CKD by renal transplant, the hypertrophied parathyroid tissue fails to resolve, enlarge over and continues to oversecrete PTH, despite serum calcium levels that are within the reference range or even elevated. They also may become resistant to calcimimetic treatment. The main indication for treatment is persistent hypercalcemia and/or an increased PTH, and the primary treatment is surgery. Three procedures are commonly performed: total parathyroidectomy with or without autotransplantation, subtotal parathyroidectomy, and limited parathyroidectomy. It is important to remove superior parts of thymus as well. The most appropriate surgical procedure, whether it be total, subtotal, or anything less than subtotal including “limited” or “focused” parathyroidectomies, continues to be unclear and controversial. Surgical complications are rare, and parathyroidectomy appears to be a safe and feasible treatment option for HPT III. Clin Ter 2021; 172 (3):241-246. doi: 10.7417/CT.2021.2322

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Introduction

Some patients with End Stage Renal Disease (ESRD) develop markedly elevated serum PTH concentrations, often associated with hypercalcemia, which cannot be explained by the administration of calcium carbonate or calcitriol supplements. This condition is defined as tertiary hyperparathyroidism (3HPT) and it is usually subsequent to a longstanding secondary HPT that persists even after successful renal transplantation, or in those patients who have been on dialysis therapy for years. The state of prolonged stimulation of parathyroid cell growth in chronic kidney disease (CKD) patients due to high phosphate, low calcitriol, and hypocalcemia, results in nodular hyperplasia. Nodular parathyroid glands do not undergo involution, despite of the resolution of some triggering mechanisms, resulting in an oversecretion of PTH. In this case, even elevated serum calcium levels cannot avoid PTH secretion. Treatments with active vitamin D or calcimimetic usually become uneffective and fail to work (1,2). Hyperplasia of all four glands is a distinguishing feature of this condition; literature reports patients with single or double adenomas (over 20%) (3,4). Monoclonal parathyroid adenoma is another important pathogenetic factor in many cases of tertiary hyperparathyroidism. The mechanisms responsible for the switch to monoclonal proliferation are not well understood. One factor may be vitamin D receptor density, which appears to be markedly reduced in areas of nodular transformation. This change could further reduce the normal inhibitory effect of calcitriol on PTH secretion and, perhaps, favour parathyroid growth. The aetiology of 3HPT in this subset of patients may also result from asymmetric hyperplasia (3). Furthermore, high serum concentration of phosphate and calcium could result in diffuse calcinosis (5,6). In this article, etiopathogenesis, indications for surgical treatment and surgical options were reviewed to put an order in the management of 3HPT.

Etiopathogenesis

Phosphate retention is one of the most important concern of CKD patients. In addition, high Fibroblast Growth Factor (FGF)-23 levels are frequently detectable in these patients. Following a successful kidney transplantation, there is a strict correlation between urinary phosphate excretion and high FGF-23 serum levels; in these cases, renal phosphate excretion is increased, resulting in progressively decreasing serum phosphate concentrations. Despite FGF-23 reduces
rapidly in the first 3 days up until 3 months after transplantation, the average FGF-23 values maintain serum concentrations higher than normal; the detection rate could reach up to 90% of patients who experience hypophosphatemia (7,8). The degree of hypophosphatemia is mild-to-moderate (1.5-2.3 mg/dL) in 20% of patients and severe (< 1.5 mg/dL) in 60% of them. FGF-23 normally returns to baseline approximately 1 year after transplantation (9,10).

Unfortunately, normal values of FGF-23 detected at 1 year following transplantation, could not be followed by normal serum phosphate level, with concentrations lower than those in CKD patients (9). Literature reports hypophosphatemia in up to 5-6% of transplanted patients, with serum calcium levels higher than those in CKD patients with equivalent eGFR (11,12). In such cases, FGF-23 cannot explain high phosphate excretion, because its serum levels are lower than the levels observed in CKD patients (12,13). The presence of decreased serum phosphate and increased serum calcium seems to suggest a prominent role of PTH in renal phosphate loss.

PTH levels in kidney transplant recipients are higher than those in CKD patients, independently of eGFR, and only increased PTH levels display an independent association with fractional excretion of phosphate (FEP) during this later period, after kidney transplantation (11).

Following a functional renal transplant, PTH levels decline during the first 3 months. Different authors report long-term kidney transplant recipients showing high PTH levels, even in presence of a well-functioning graft (9,11,14-16). Elevated PTH level in this later period is responsible for an increase in serum calcium, a decrease in serum phosphate and an increase in FEP, suggesting that the secretion of PTH is not entirely under the normal feedback control (11,17). Risk factors for persistent high PTH level after transplantation are: high PTH values before transplant, long dialysis vintage, nodular hyperplasia of parathyroid glands. The latter results in an upward increase in the set point of calcium that triggers PTH release and a resistance to active vitamin D and FGF-23 (12,14,18-21). Pre-transplant PTH and calcium levels can also predict the severity of persistent hyperparathyroidism and the need for parathyroid surgery after transplantation (22, 23). Patients with high PTH level prior to transplantation are likely to experience long-term persistent HPT. Calcimimetic administration contributes to influence the response of hyperplastic parathyroid glands to a functional graft. Some authors reported a higher incidence of post-transplant nephrocalcinosis and parathyroidectomy in patients who had been for long time on cinacalcet for high PTH levels and for whom parathyroidectomy was delayed (24).

25-hydroxyvitamin D (25-OH-D) deficiency is another factor involved in post-transplantation 3HPT. Possible causes of 25-OH-D deficiency could be resumed as follow: a reduced sunlight exposure; the use of sun protectors; renal function failure; the use of immunosuppressive drugs, especially steroids; the presence of metabolic syndrome and obesity (25,26). In renal transplant recipients, lower 1,25-dihydroxyvitamin D (1,25-OH₂-D) could be also related to the reduced production of the substrate 25-OH-D (27). In the early post-transplant period, a severe 1,25-OH₂-D deficiency has been observed in up to 80% patients (28). After 3-12 months the concentration of 1,25-OH₂-D increases and becomes comparable to CKD patients with equivalent kidney function (9).

In the early post-transplantation period, 1,25-OH₂-D is negatively related to FGF-23: it could be likely due to the suppression of 1,25-OH₂-D production by an excess of FGF-23. Twelve months after transplantation, only functioning allograft displays an association with higher 1,25-OH₂-D levels, indicating an alignment of vitamin D physiology to that expressed in CKD patients (9). Serum calcium decreases immediately after successful kidney transplantation due to the discontinuation of calcium and active vitamin D therapy. The rapid decline in PTH induces the shift of calcium back into the bone and the loss of calcium into the urine (29). After 3-6 months serum calcium become normal. Hypercalcemia develops in 10%-15% of kidney transplant recipients due to the high prevalence of persistent hyperparathyroidism, as mentioned before (11,16). Hypercalcemia after transplantation is linked to pre-transplant PTH and calcium levels (10,19). High serum calcium may also be linked with low PTH levels. In this case, other causes such as malignancy and opportunistic infection, should be considered. Currently, after kidney transplantation, abnormal bone and mineral metabolism continues to present in most patients despite the improvement in mineral metabolites and mineral regulating hormones. The most important factors are the persistent hyperparathyroidism and high dose corticosteroids. Steroid therapy suspension is beneficial in long term preservation of bone mass. Active vitamin D with or without bisphosphonate is useful in preventing bone loss in the first period after transplant. An alternative therapy to parathyroidectomy (PTX) in kidney transplants recipients with persistent HPT, is represented by calcimimetics. Whenever PTX is required, subtotal to near total PTX seems to be more favourable, in terms of long-term outcomes, compared to total PTX with autotransplantation.

**Treatment indications**

In patients with severe HPT and hypercalcemia, PTX is preferred during the waiting period, prior to transplantation. The surgical treatment is necessary because it reduces the parathyroid mass and cell number, normalizing serum calcium concentration. The most obvious indication for surgery is long-term sustained hypercalcemia (>11.0 mg/dL), as already indicated by the American National Institutes of Health for intervention in asymptomatic primary HPT. Sustained PTH levels (a trend rather than a single measurement), 2 - 9 times above the upper limit of normal, even with normocalcemia, should lead to consideration of PTX. Mild hypercalcemia and/or hyperparathyroidism are common during the first 12 months after renal transplantation, and decisions regarding management should be delayed for 12 months following the return of phosphorus, calcium, and vitamin D homeostasis to normality. In addition, because severe hypophosphatemia can be observed early after renal transplantation, careful replacement and monitoring of the serum phosphorus may be indicated in early hypercalcemia after transplantation.

Indications for PTX in patients with 3HPT are ill-defined as there are currently no evidence-based guidelines; they
can be easily summarized as follows: severe or persistent hypercalcemia (serum calcium >11.5 mg/dL or >10.2 mg/dL more than three months to one year after surgery); severe osteopenia, bone pain or pathologic bone fractures; HPT-related symptoms; fatigue; peptic ulcer; mental status changes; history of renal calculi / nephrocalcinosis.

For sure, persistent hypercalcemia after renal transplant as well as achievement of normocalcemia postoperatively is the most important value to take into account in order to plan the right treatment (30). Due to the high morbidity and mortality rates related to high serum calcium concentrations, the main objective of the treatment is the achievement of post-operative normocalcemia. Subsequently, elevated PTH levels can no longer be considered an indication for PTX in 3HPT, without other findings. On the contrary, persistent hypercalcemia after 12 months of observation could be considered the main indication (31). A decrease in intraoperative PTH >50%, measured at least 10 min after resection, could be considered the operative endpoint. The total excision of macroscopically abnormal parathyroid glands, could be considered a secondary operative endpoint.

**Surgical strategies**

Cinacalcet, a calcimimetic, inhibits PTH secretion by modulating the CASR into the parathyroid gland and has been considered a potential treatment option. Unfortunately, its effectiveness has not been proven, and only few small, open-label trials of short duration have been performed.

From a systematic review of studies reporting surgical and medical therapy with cinacalcet for 3HPT, the surgical treatment has higher cure rates with low complications (32).

With regard to surgical treatment, to date, four different approaches have been reported: subtotal parathyroidectomy with bilateral cervical thymectomy (resection of 3 glands and half of the fourth gland), total parathyroidectomy with autotransplantation of parathyroid tissue and bilateral cervical thymectomy; total parathyroidectomy without autotransplantation and without thymectomy; total parathyroidectomy without autotransplant and with cervical bilateral thymectomy (33). The first three operations aim to maintain a residual production of PTH, while the goal of total parathyroidectomy plus bilateral cervical thymectomy is the complete elimination of PTH production (34). The subtotal parathyroidectomy provides for the removal of three glands and the preservation of half of the fourth gland (leaving from 40 to 80 mg of gland) (33,35-37). The exploration of the cervical thymic tissue must be performed in an attempt to remove any supernumerary ectopic parathyroid glands (33). Total parathyroidectomy with or without autotransplantation involves a careful identification of all four parathyroids and any ectopic and / or supernumerary glands. In order to perform autotransplantation, the macroscopically normal gland is broken up into 1-2 mm pieces and then re-implanted; possible re-implantation sites are: the sternocleidomastoid muscle, the brachioradial muscle or the subcutaneous fat of the forearm. In all cases, the site of replanting must be marked with a metal clip.(38,39) The reimplantation into the forearm is more advantageous in the event of any surgical re-examination during a relapse of HPT (33). The only randomized prospective study performed on 40 patients who compared subtotal with total parathyroidectomy with autotransplantation, showed lower rates of relapse in total parathyroidectomy + autotransplantation, with a more precocious normalization of serum calcium and phosphorus levels.(40) In a meta-analysis performed on 53 publications, with a total of 501 patients with 2HPT, which aimed to assess the rate of relapse and reoperation after a PTX, it is inferred that the rate of reoperation in patients treated with subtotal parathyroidectomy was 42%, compared to 34% of patients undergoing total parathyroidectomy + autotransplantation (41).

The subtotal parathyroidectomy is usually the intervention of choice in patients with 3HPT after renal transplantation, although there are no randomized controlled trials that show better results than the total parathyroidectomy + autotransplantation; retrospective studies also show that the results are similar for the two approaches (42-44). In a retrospective analysis conducted by Triponez et al., on 74 cases of 3HPT, patients submitted to subtotal parathyroidectomy showed an incidence of persistent or recurrent HPT 5.2 times higher than those submitted to total parathyroidectomy (45). Cervical thymectomy is considered by many authors an important component of any surgical treatment for 2HPT and 3HPT. Autopsy studies suggest that the prevalence of supernumerary parathyroids is 13% in the general population.(46) Other authors report a 30% of cases with a prevalent localization into the thymus (44-46). Therefore, in patients with HPT undergoing PTX, the supernumerary parathyroids located into the thymic context may be a cause of recurrence (47,48). While for some authors thymectomy is indicated in all patients submitted to PTX, for others it is necessary only when the four parathyroids are not identified into the canonical site (49).

Limited resections are recommended due to their high success rate with fewer complications in comparison with more extensive surgeries. In such cases, for example, patient usually experience a reduced renal function and graft deterioration. Hypocalcaemia, while transient in the postoperative period, could be detected, too (50).

To date, notwithstanding the great amount of scientific evidences, the most appropriate surgical procedure to treat 3HPT, has not been already established. The primary objective of the surgical operation is the resolution of HPT. The type of surgical treatment to be taken in the HPT should aim at an appropriate balance between extension of resection, control of relapses and prevention of persistent postoperative hypoparathyroidism. The selection of the type of surgery will also depend on the patient’s ability to undergo kidney transplantation (34).

Although there are no studies directly comparing these procedures, persisting and recurrent disease rates shown in the present review indicate that limited parathyroidectomy should be avoided: 4, 8.9 and 91 per cent for total, subtotal and limited resection respectively. Renal function after parathyroidectomy for 3HPT seems to decline transiently or permanently. Whether this decline in function is due to the parathyroidectomy or to chronic rejection can be determined only from studies...
with a control group. At present, no such studies are available. Studies show that there is no effect of parathyroidectomy on overall graft survival (32). Surgical complications are rare, and parathyroidectomy appears to be a safe and feasible treatment option for 3HPT. Parathyroidectomy increases bone mineral density and leads to a decreased risk of major cardiovascular events and death in comparison with conservative treatment, in contrast to cinacalcet (50,51). Finally, cost-effectiveness remains an important consideration in the choice of treatment. Compared with cinacalcet treatment, parathyroidectomy is more cost-effective in these patients (52), mainly due to the significant additional cost and chronic use of cinacalcet. Although high-quality evidence is lacking, this review shows that surgical treatment for HPT appears to be more effective than medical treatment. Furthermore, complication rates with surgical treatment are low and graft survival is comparable to that obtained with cinacalcet.

**Conclusions**

Currently, indication for parathyroidectomy in HPT is limited to those patients with hypercalcemia and sign and symptoms of calciphylaxis. Obviously, all patients suffering from 3HPT should be submitted to medical treatment before surgery; only a failure of therapy should indicate parathyroidectomy. The primary endpoint of surgery should be the normalization of serum calcium levels at least six months postoperatively; a drop over 50% in PTH serum levels should be the secondary goal. An accurate and cautious PTX, guided by IOPTH, should be considered the best surgical option to treat 3HPT definitively, avoiding recurrences and excluding the presence of supernumerary glands. Certainly, studies on metabolomics and proteomics will increase test sensitivity in order to achieve increasingly better results. Further prospective studies that investigate the long-term consequences of parathyroidectomies on renal function in patients with HPT III are needed, however.

**References**