Review article

Tertiary Hyperparathyroidism: A Narrative Mini-Review

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Abstract

Tertiary hyperparathyroidism (THPT) is characterized by persistent secondary hyperparathyroidism following successful kidney transplantation. In this case, there is an autonomous proliferation of the parathyroid glands and an over secretion of the parathyroid hormone, which is less likely to recover spontaneously. If untreated, this disease will affect patient survival and renal allograft. Classically in THPT; there is hyperplasia of all parathyroid glands; single or double adenomas are seen in 20% of patients.

Aim:
review the features of THPT, its pathophysiology, the risk factors, complications and treatment options.

Keywords:
Parathyroid gland; Parathyroid hormone; Tertiary hyperparathyroidism; Kidney transplantation.

الملخص

خلفية:
يتميز فرط نشاط جارات الدرق الثالثي (THPT) باستمرارية فرط نشاط جارات الدرق الثانوي بعد زرع الكلية الناجح. في هذه الحالة يوجد نمو مستقل لغدد جارات الدرق مع فرط إفراز لهرمون جارات الدرق، والذي من النادر أن يتحسن تلقائيا. في حالة عدم معالجة المرض سيؤثر ذلك على الكلية المزروعة وحياة المريض. عادة ما يكون السبب في فرط نشاط جارات الدرق الثالثي هو فرط تصنع لجارات الدرق الاربعة (hyperplasia)، وفي حوالي ٢٠٪ من الحالات يوجد ورم غدي(adenoma) مفرد أو مزدوج.

الهدف :
التعرف على الملامح السريرية لهذا المرض، علاماته المرضية، عوامل الخطورة ومعرفة المضاعفات المحتملة له وكذلك مناقشة طرق العلاج المتاح له.

Introduction

In chronic kidney disease, 90% of patients will develop secondary hyperparathyroidism (SHPT). This is due to hyperphosphatemia and diminished production of calcitriol (the active form of Vitamin D) which will eventually lead to hypocalcemia and high parathyroid hormone (PTH). Prolonged hyperphosphatemia, hypocalcemia and low Vitamin D will end up with parathyroid chief cell hyperplasia and excessive PTH production. Thus, successful renal transplantation reverses and corrects the metabolic, physiologic and mineral abnormalities observed in SHPT (e.g., uremia, acidosis, hyperphosphatemia, hypocalcemia, reestablishment of calcitriol production and reversal of skeletal resistance to PTH and vitamin D). During the first three months post renal transplantation, there is a significant decline in serum PTH, and then followed by a progressive reduction in the next nine months. Also, there is a decrease in the parathyroid function mass [1, 2]. In most post kidney transplantation patients, a spontaneous improvement occurs as the glomerular filtration rate (GFR) normalizes. The degree of parathyroid hyperplasia is highly considered in defining the ability for this resolution. In nodular hyperplasia or adenomatous transformation, this regression is difficult to happen [2, 3]. There are about 17–50% of transplanted patients will re-

main to have hyperparathyroidism at one year post successful kidney transplantation; this condition is known as tertiary or autonomous hyperparathyroidism. Autonomous HPT refers to the unresponsiveness of the parathyroid gland to negative feedback mechanisms. THPT is not only developed in patients with renal failure; it can also occur with any condition which leads to long-standing hypocalcemia such as gastric malabsorption or chronic dialysis use [4-7].

Clinical Presentations

The clinical features of THPT are listed in Table 1 [4, 8, 9]. Body systems involved are many and include gastrointestinal tract, central nervous system, cardiovascular system, renal system, as well as skin and soft tissues. Overall, the signs and symptoms are mostly attributable to the organ dysfunction caused by the high PTH and resultant high calcium levels. Thus, hypercalcemia can result in nausea, vomiting, constipation, abdominal pain, pruritus, calcification of soft tissues/cardiac valves/vascular structures, kidney stones, altered mental status and various metabolic derangements of carbohydrate and lipid metabolism. Moreover, the low level of calcium in bones, particularly, contributes to the undesired osteoporosis, pathological fractures, bone pain and muscle weakness.

Table 1. Clinical Presentation of Tertiary Hyperparaythyroidism

Bone and muscles	Bone pain and Muscle weakness - Pathological fractures - Osteopenia
Skin and soft tissue	Pruritus - Soft tissue calcifications
Renal	Nephrolithiasis
Gastrointestinal Tract	Peptic ulcer disease - Pancreatitis
Central Nervous System	Mental status changes
Cardiovascular system	Hypertension and cardiomyopathy - Vascular calcifications Calcifications of cardiac valves
Others	Impaired graft function Metabolic abnormalities of carbohydrate and lipid metabolism Organ calcifications

Problems After Kidney Transplantation

Persistent hyperparathyrodism and hypercalcemia

There are many factors that attribute to the persistent hyperparathyroidism such as duration of dialysis, the size of the parathyroid gland and formation of nodular and/or monoclonal hyperplasia of parathyroid glands. On the other hand, the possible causes of the hypercalcemia are resorption of extra-skeletal calcifications, phosphorus depletion or the gradual recovery of the normal calcemic activity of PTH after transplantation.

In most patients, the hypercalcemia resolves in a few months post kidney transplantation. It can persist after the first year but resolves gradually within 2 to 5 years in 5–10% of patients. This persistent mild hypercalcemia is usually well endured and not associated with graft dysfunction. On the other hand, a small percentage of unfortunate patients who still maintain persistent hypercalcemia will require parathyroidectomy (PTx) (1–5%). The surgery will reduce the risk of renal dysfunction, nephrocalcinosis, pancreatitis and vascular calcifications [8, 10].

Hypophyospheatemia

Hypophosphatemia after kidney transplantation is due to the reduction of phosphorus re-

absorption. THPT as well as some concurrent medications (e.g. immunosuppressives and diuretics) can cause urinary phosphorus wasting. Patients can experience muscle weakness and osteomalacia if plasma phosphate level drops below 1.4 mg/dl, and if it is less than 0.9 mg/dL, this can result in hemolytic anemia, rhabdomyolysis, decreased myocardial contractility and respiratory failure. One of the major sequelae of persistent phosphorus wasting after kidney transplantation is bone mineral density reduction, which in turn increases the risk of pathological bone fractures [4, 8, 10].

Bone diseases

In the first six months post renal transplantation, there is a quick rate of bone loss (i.e., 1.5% per month at the lumber spine). Immunosuppressive medications, renal phosphorus wasting and hypophosphatemia and calcitriol deficiency collectively increase the probability of pathological bone fractures [4].

The Risk Factors

There are several risk factors that contribute to the development of persistent hyperparathyroidism such as long duration of dialysis as well as high serum levels of intact parathyroid hormone, calcium, phosphorus and/or alkaline phosphatase at the time of transplantation. Furthermore, parathyroid gland size (by ultrasound), renal insufficiency, calcitriol deficiency, immunosuppressive medications (including steroids), high body mass index and female gender are also reported [4, 8, 9, 11].

Complications

The consequences of the autonomous proliferation of the parathyroid glands and high secretion of parathyroid hormone are hypercalcemia and hypercalciuria, both of which lead to dysfunction and loss of the renal allograft [8, 9, 12-15]. Furthermore, acute tubular necrosis, osteoporosis, cardiovascular diseases and bone fractures (particularly in the first five years post transplantation) have been reported [9, 16-18].

Preoperative Imaging

The most common preoperative imaging modalities used are neck ultrasound and 99mTc sestamibi scintigraphy. Both provide the site and size of the biggest parathyroid glands. In contrast to primary hyperparathyroidism in which the preoperative imaging studies localize the abnormal gland (i.e., adenoma), these radiological investigations are not routinely done in patients with SHPT or THPT, except in ectopic or re-operative cases [4, 13, 14]. It is published that bilateral neck exploration is needed in SHPT and THPT; thus, the utility of preoperative imaging is technically unnecessary [15]. In the case of re-operative PTx for THPT, Triponez and colleagues suggest starting with neck ultrasound and 99mTc sestamibi scintigraphy. If both preoperative imaging studies are inconclusive, then magnetic resonance imaging (MRI) and fine needle aspiration of the suspicious lesion—with measurement of parathyroid hormone in the aspirated fluid—are advised. Additionally, in the case of persistent or recurrent hyperparathyroidism, if neck ultrasound, 99mTc sestamibi scan and MRI are negative or equivocal, then selective venous sampling is indicated [4]. On the other hand, Karipineni et al. support the routine utilization of preoperative localization images [16].

Management

In THPT, the most favorable management remains unclear. Overall, in comparison to medical treatment, surgical intervention has higher cure rates. In a systemic review in 2017, the vast majority of studies on cinaclet in THPT

were limited to 22 small-sized observational studies and only two randomized controlled trials. Medically, cinacalcet is the most frequently used drug. Mechanistically, cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor and thus, decreases the circulating parathyroid hormone level. It can achieve normocalcemia in around 80.8% of patients with THPT. Cinacalcet is a fairly safe and successful drug which is an alternative option to PTx in post-transplant hyperparathyroidism patients, especially if there are contraindications for surgical intervention or potenteial complications following PTx [17, 18, 23, 24]. Accumulating evidence suggest that PTx is superior than cinacalcet in normalizing parathyroid hormone and calcium levels [23, 25] with low complication rates [5, 18]. Furthermore, PTx improves bone density, symptomatic relief, patient survival and renal allograft function [14, 18, 26, 27].

In a review by Dulfer et al., it was concluded that no study reported data regarding the efficacy of surgical or medical treatment on cardiovascular complications in patients with THPT. However, in patients with SHPT, several published studies confirmed the reduction in cardiovascular events and mortality after PTx when compared to conservative management. Additionally, PTx far improves bone density compared to cinacalcet [18].

There are no evidence-based guidelines for indications of surgery in THPT; however, there were several proposed indications. Persistent hypercalcemia (more than 3–12 months after renal transplantation) is the only major criterion. Other reported indications include persistent hypercalciuria, renal phosphorus wasting (including hypophosphatemia), low bone marrow density, nephrocalcinosis, pruritus, parathyroid glands weighing more than 500 mg (as evaluated by ultrasound), severe renal osteopathy, calcification of tendons and soft tissue, calciphylaxis, progressive extra skeletal calcifications, severe bone pain or fractures and formation of renal stones in grafted kidney [4, 7, 28-31].

Total parathyroidectomy (TP) with or without auto transplantation and subtotal parathyroidectomy (SP) plus/minus thymectomy are satisfactory and well-accepted surgical options in patients with THPT [13, 18]. Both procedures have persisted and recurrence rates (4% and 8.9%, respectively) [18] with a lower incidence of hypocalcemia in the latter [12]. Furthermore, it was reported that TP with forearm autograft was a proper surgical technique for patients with THPT [32]. On the other hand, Triponez et al. recommended SP in patients with THPT and concluded that limited parathyroidectomy has a higher risk of persistent/recurrent HPT [33]. This conclusion was also supported by another study by Abouchacra et al. in which the authors concluded that SP had excellent outcomes with favorable metabolic control and preservation of allograft function, without an increase in the rate of acute rejection [3]. Another study by Dulfer et al. recommended the SP surgical approach as it had low incidences of postoperative hypocalcemia and persistent hyperparathyroidism [23]. Moreover, it was observed that the impairment of kidney graft function was less with SP [29]. The gamma probe was used as an adjunct to PTx with high cure rates [34]. A limited parathyroidectomy (i.e., removal of enlarged parathyroid glands only) is rarely used. However, the rate of persistence and recurrence reaches up to 90% [18, 33, 35].

Thymectomy is routinely done by some surgeons, while others recommend it in certain situations (Table 2) [4]. Unlike primary hyperparathyroidism (PHPT), the role of intraoperative PTH monitoring in SHPT and THPT remains uncertain. Its accuracy rate reaches up to 95% in PHPT [4,13].

Table 2. Indications for thymectomy (Triponez et al.)

1	If the inferior gland is not found in its location.
2	If the intrathymic gland has been found by preoperative localizing techniques
3	In patients with higher risk of recurrent HPT (in patients with decreased renal function and in young patients with a long life expectancy).

Kidney transplantation is the most suitable treatment option for patients with end stage renal disease (ESRD)-related THPT, as kidney transplantation is projected to eliminate the underlying force of HPT [36]. However, spontaneous regression of hyperparathyroidism following kidney transplantation does not take place in all patients. In a study of roughly 1700 patients with hyperparathyroidism undergoing kidney transplantation, Lou et al. showed 70% and 43% of patients had persistent THPT at one- and two-years post kidney transplantation [37]. The most appropriate time for THPT patients to undergo kidney transplantation continues to be a topic of controversy [36].

The time of surgery is different from center to another. As published before, most centers recommend the delay of parathyroidectomy till after renal transplantation up to one year, in order to give a chance for the glands to regress [4]. Conversely, institutes suggest the surgery to be done at three months [8].

Data showed that PTx (either TP or SP) itself could impair kidney graft function [29, 32] and unfavorably decrease the glomerular filtration rate [26]. In patients with THPT, several studies demonstrated a stable renal graft function along with a concurrent cinacalcet use [20, 38, 39]. On the other hand, a reduction in the glomerular filtration rate [40] and an increase in the serum creatinine level [41] were reported, too. The effect of percutaneous ethanol injection therapy (PEIT) after SP was studied in patients with recurrent SHPT. However, this technique is useful and effective, especially if the cinacalcet and cryopreservation are not attainable [42]. On the contrary, it has side effects such as nerve paralysis and adhesions, which could complicate parathyroidectomy [43].

Conclusion

The management of THPT is challenging. The hyperparathyroidism alone is not an indication for PTx; thus, other associated factors should be thought of (i.e., hypercalcemia and its symptoms). Although cinacalcet is helpful and safe, PTx is indicated for refractory cases. Prospective multicenter studies should be considered as this will help to resolve the controversies concerning the best surgical approach and the indications of parathyroidectomy in patients with THPT.

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