REVIEW ARTICLE

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Surgical and Medical Management of Tertiary Hyperparathyroidism

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ABSTRACT

Persistent hyperparathyroidism (HPT) after successful kidney transplantation (RTx) (tertiary HPT; THPT) is a common complication in patients with RTx and may affect bone disease, deterioration of graft function and cardiovascular events. Parathyroidectomy (PTx) is the most successful treatment for resolving advanced HPT in patients with THPT. However, the surgical indications for THPT and timing of the operation are problematic because hypercalcemia can be resolved spontaneously. Subtotal and total PTx with autotransplantaion are widely accepted for THPT. The evidence to know which procedure is more appropriated could not be found. Recently the deterioration of kidney graft function after PTx for THPT has been reported and hypoparathyroidism after PTx may be avoided. Recently cinacalcet has been applied for patients with THPT and the medicine can dramaticaly control HPT and hypercalcemia. Possible risks of cinacalcet are hypocalcemia and increased calciuria and the approval for THPT remains highly controversial. A large number of prospective controlled clinical trial should be required.

Keywords: Tertiary hyperparathyroidism, Parathyroidectomy, Parathyroid gland.

DEFINITION

Secondary hyperparathyroidism (SHPT) refers to the situation in which a derangement in calcium homeostasis leads to a compensatory increase in parathyroid hormone (PTH) secretion.[1,2] SHPT requiring parathyroidectomy (PTx) virtually only relates to progressive chronic kidney disease (CKD)[3] and less commonly to long-term lithium therapy.[4] Altogether this condition also arise from disorder of gastrointestinal absorption, deficiency of vitamin D, liver disease and pseudohypoparathyroidism, etc.

Tertiary hyperparathyroidism (THPT) is a confusing term, which originally denoted the occurrence of an adenoma and hyperplasia in different gland in the same patient and the patient acquired autonomous secretion of PTH.[5] The value of classifying one gland as an adenoma in a patient with 4 enlarged parathyroid glands is questionable. The term autonomous HPT refers to a specific functional state of parathyroid glands being nonresponsive to negative feedback mechanism. Actually, the term of THPT has been used to define SHPT accompanied by spontaneous hypercalcemia, clinically persistent SHPT after successful renal transplantation (RTx) (1).[6]

PATHOPHYSIOLOGY AND PREVALENCE OF THPT

Successful RTx reintroduces the ability to produce 1, 25 dihydroxy vitamin D and functionally respond to phosphate homeostatic signals correcting the balance of key stimuli responsible for SHPT.

Immediately after successful RTx, serum PTH level gradually decline during the first three months. However, in approximately about one-third of patients high PTH level (>100 pg/mL) persists during Six months and in 20% of patients, high PTH concentration continues for five years after RTx.

The main factors contributing to the persistent HPT are longer dialysis duration prior to transplantation and severity of pretransplant HPT, degree of parathyroid hyperplasia and function of transplanted kidney.[7]

The persistent high level of PTH could be attributed to existing parathyroid hyperplasia, nodular type hyperplasia at RTx. Decreased expression of calcium sensing receptor (CaSR) and vitamin D receptor (VDR) in nodular hyperplasia increases resistance to PTH control mechanism.[8] Another factor which influences HPT after RTx is impaired kidney graft function. Post RTx patients have estimated glomerular filtration rates averaging 30 to 60 mL/min and the impaired renal function induces excess PTH secretion and parathyroid hyperplasia.[7]

Presence of hypercalcemia after RTx mainly is induced by elevated PTH level.

Spontaneous resolution of post-transplant hypercalcemia occurs within one year in up to 50% of these patients.[7]

Hypophoshatemia is a common phenomenon in post-transplant patients and the prevalence is 93% in 5 weeks after RTx. Hypophosphatemia occurs mainly due to inappropriate urinary phosphate wasting. High PTH level mainly contributes to phosphate wasting by decreasing the activity of sodium phosphate cotransporter in tubules.[7] Recently, the role of fibroblast growth factor 23 (FGF 23), which is one of the

phosphatonins has been clarified. FGF 23 regulates renal phosphate excretion by inducing expression of the sodium dependent cotransporters i.e. GNaPi2a and NaPi2c.[9] In hemodialysis patients, the serum level of FGF 23 is remarkably high and falls gradually following kidney transplantation suggesting efficient clearance by the kidney.[7] However, high FGF 23 level persists in post-RTx patients and may contribute to phosphorus wasting and hypophosphatemia. Usually hypophosphatemia and phosphorus wasting regress by one year after successful RTx and less than 5% of patients hypophosphatemia persists[10] (Fig. 1).

CLINICAL MANIFESTATIONS

Laboratory investigation reveals hypercalcemia, hypophosphatemia, moderately elevated PTH level and usually increased alkaline phosphates (Al-p) level.[10]

Disturbance in bone metabolism, i.e. bone loss, high-risk of fracture and cardiovascular events are common complications that affect patients after successful RTx and represent important cause of morbidity and mortality.

Three major components contribute to bone metabolism disturbances in patients after RTx: pre-existing renal osteodystrophy at time of RTx, immunosuppressive agents and reduced renal function after transplantation.[11]

Patients with THPT may suffer from bone pain, joint pain, fractures, bone loss, nephrolithiasis, soft tissue calcification including nephorocalcinosis, and sometimes may influence graft function.

MEDICAL TREATMENTS

In the early phase after RTx, immunosuppressive agents, especially steroid may contribute to bone loss and risk of fracture. KDIGO guideline proposed that calcitriol, alphacalcidol therapy and bisphosphonates may prevent loss of bone mineral density in the first year after kidney transplantation. However, there are no data that this prevents fracture and there may be adverse events.[12,13] Some reports proposed the efficacy of bisphosphonate to prevent bone loss and fracture after RTx.[14,15]

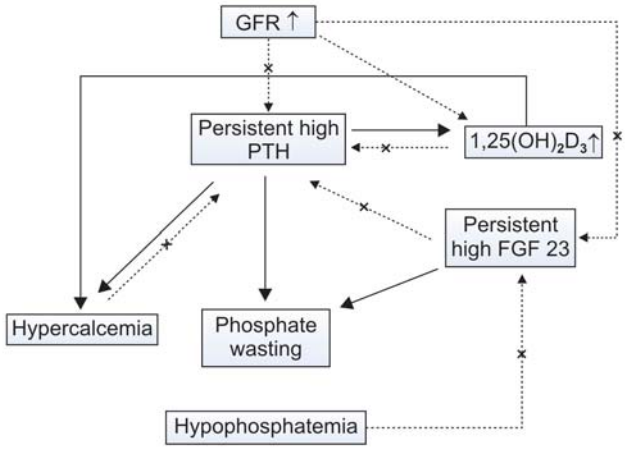

Fig. 1: Pathophysiology of tertiary hyperparathyroidism, GFR: Glomerular filtration rate, FGF: Fibroblast growth factor, PTH: Parathyroid hormone

Cinacalcet HCl (cinacalcet) directly reduces PTH by allosterically modulating the CaSR in parathyroid cells resulting in increased sensitivity to effects of extracellular calcium. Cinacalcet is widely approved for patients with severe SHPT and with hypercalcemia due to inoperative parathyroid carcinoma.[16-19] Recently cinacalcet has been applied for patients with THPT and it has been reported that the treatment with cinacalcet can control HPT and hypercalcemia among patients with THPT with a low incidence of side effects.[20-26] Possible risks are hypocalcemia and increased calciuria that induce nephrolithiasis and nephrocalcinosis are pointed out. It is important to recognize that some patients cannot tolerate cinacalcet because of gastrointestinal symptoms and drug interaction. At present, there are no data of prospective controlled clinical trials with larger numbers and the use of cinacalcet in patients with CKD stage 3or 4 and THPT has yet to be approved and remains highly controversial.[27]

SURGICAL INDICATIONS

It is well-known that advanced HPT is persistent after successful RTx and PTx and sometimes is required in these patients.[28,29] Requiring surgical intervention occurs in 1 to 5% of patients with THPT. Long-term dialysis before renal transplantation and detection of enlarged parathyroid gland, nodular hyperplastic parathyroid gland are predictive factors for requirement of PTx for THPT.[8,30]

As same as dialysis patients with advanced SHPT, PTx is the most successful treatment for resolving advanced HPT in patients with THPT. However, the surgical indications for THPT and timing of the operation are problematic because hypercalcemia can be resolved spontaneously within one year after RTx. Generally, the indications include persistent asymptomatic hypercalcemia (more than 3-12 months after RTx), symptomatic THPT (neprolithiasia or nephrocalcinosis, severe or rapid bone loss and bone fracture, soft tissue calcification, including tumoral calcinosis, calciphylaxis, vessel and valvular calcification, symptoms associated with HPT, i.e. bone and joint pain, muscular weakness, purities, etc.) or deterioration of kidney function associated with HPT at anytime after RTx.

It has been reported when parathyroid hyperplasia progresses to nodular hyperplasia, HPT cannot be relieved by successful RTx. Then to evaluate size of glands estimated by ultrasonography before or after, RTx is recommended to recognize whether HPT is persisting or not after RTx[1,8,31] (Table 1).

SURGICAL PROCEDURES

Subtotal PTx and total PTx with autograft are widely accepted for THPT.[1,2,31] Total PTx without autograft cannot be accepted for patients with THPT because of persistent uncontrollable hypocalcemia after PTx. The evidence, which procedure is more

Table 1: Indications for parathyroidectomy in patients with tertiary hyperparathyroidism

1. Severe hypercalcemia (serum Ca > 11.5 or 12 mg/dL).
2. Persistent hypercalcemia (serum Ca >10.3 mg/dL more than 3 months to 1 year after renal transplant).
3. Severe osteopenia (low bone mineral density) and bone fracture.
4. Renal stone and nephrocalcinosis
5. Soft tissue calcification (tumoral calcinosis, calciphylaxis, vessel and valvular calcification).
6. Symptomatic hyperparathyroidism (purities, fatigue, bone and joint pain, muscular weakness, mental disturbance, peptic ulcer, etc.)
7. Deterioration of kidney function associated with hyperparathyroidism at any time after kidney transplant.
8. Volume of gland estimated by ultrasonography > 500 mm^3 or diameter of gland > 1 cm.

appropriate for THPT could not be found. However, majority of endocrine surgeons prefer subtotal PTx for patients with THPT and recommend volume equivalent to four normal parathyroid gland that should be remained with successful kidney graft to prevent hypoparathyroidism and hypocalcemia.[1,2]

Recently, the deterioration of kidney graft function after PTx for THPT has been pointed out. It has been hypothesized that transient hypoparathyrodism may be a possible explanation for impairment of kidney graft function: PTH has vasodilatory effect on preglomerular vessels,while efferent arteriole suffer from constriction that is supposed to be induced by renin release. The deterioration occurred already during the first week following the PTx, however usually renal function showed a slow but steady improvement over years toward baseline. It has been reported the risk for impairing graft function demonstrated in these patients with poor kidney function at PTx. It has been recommended subtotal PTx instead of total PTx with autograft is preferable for patients with THPT to prevent kidney function.[31-33]

Our preferable operative procedure for THPT is total PTx with forearm autograft. Simultaneous thymectomy, resection of thymic tongues from neck incision is performed routinely. Patients with transplanted kidney have the risk of deterioration of graft function and reinduction of hemodialysis treatment. Reoperation for persistent HPT or recurrent HPT cannot be avoided in these patients. Because it is easier and safer to remove residual parathyroid tissue from the forearm at recurrence compared with a neck re-exploration, total PTx with forearm autograft is according to our opinion recommended in a patient with THPT,[3] and to avoid persistent and recurrent HPT, it is very important to remove all parathyroid glands at the initial operation. Thymectomy should be performed even in patients with THPT because supernumerary gland, most frequently, is located in thymus.[34,35]

Intraoperative PTH monitoring (ioPTH) also has been performed in patients with THPT in the limited institutes. The ioPTH is beneficial to recognize all parathyroid glands and are resected.[36]

Our procedure of parathyroid autograft is based on Well's report.[37] The procedure for THPT fundamentally is same as that for SHPT. Resected parathyroid glands are preserved in cold saline just after the removal. After pathological confirmation, we make 1 × 1 × 3 mm slices from diffuse hyperplastic tissue for autograft. We make a pocket in the brachioradial is muscle of forearm without A-V fistula and put a piece in each pocket and tie muscle using non-absorbable thread. We perform same procedure 30 times and totally about 90 mg parathyroid tissues is autografted.[38] Cryopreservation of parathyroid tissue for retransplantation is not performed routinely except for special cases.

Usually as maintaining sufficient kidney graft function, recurrent HPT can be avoided after PTx except for the patients, who underwent total PTx with autograft of nodular hyperplastic parathyroid tissue before RTx.[39]

SURGICAL OUTCOMES

After PTx, serum PTH and calcium levels drop rapidly because autografted parathyroid tissue begins functioning after two to three weeks after PTx, and usually patients have severe hungry bone syndrome, and calcium and phosphorus move to bone from blood and bone formation becomes prominent.[40] Hypophosphatemia usually rapidly relieves after the operation. Each institute has each protocol to supplement calcium agent. We initiate calcium replacement therapy in patients with THPT when the serum calcium level decreases under 8.0 mg/dL or when patients complain on hypocalcemic symptoms. If the Al-p level before PTx is more than 500IU/L, that means the patient has severe hungry bone syndrome, sometimes intravenous calcium supplementation should be required. Usually oral supplementation (alphacalcidol, and calcium carbonate or calcium lactate) are sufficient to control hypocalcemia. We adjust dose of calcium agent and vitamin D within serum calcium level 8 to 9 mg/dL.[41]

Function of grafted parathyroid tissue can be recognized by measuring PTH levels sampling from both antecubital veins. PTH gradient is defined as PTH level of grafted arm per PTH level from non-grafted arm. If the gradient is over 1.5, it can be recognized that autograft is functioning.[41] In almost all patients grafted parathyroid tissue functioned by our procedure.

Symptoms of HPT, i.e. bone pain, depression, itching, easy fatigue, etc., have been efficiently relieved by successful PTx. Bone metabolism has been clearly improved by PTx. The bone mineral content in trabecular bone measured by X-ray absorptiometry has increased about 10% after PTx, and fracture risk has been lower.[42-44]

It is well-known that calciphylaxis and tumoral calcinosis are generally remarkably improved by PTx. Unfortunately, vascular and valvular calcifications are usually not affected, even by successful PTx.[45] Therefore, it is important that PTx should be performed at an early stage before the calcification has become progressive. Beneficial effects by PTx on anemia, muscle strength, nutritional state, cognition, immune system, and on blood pressure have been reported.[3]

PTx is expected to improve survival in hemodialysis patients with advanced SHPT. Some papers presenting that PTx and mortality can be found.[46] However, the report about improvement of mortality or prolonged graft function after PTx for patients with THPT cannot be found.

Comparing the patients with SHPT, the risks of death and bleeding after the operation in patients with THPT are usually low. Husky voice due to palsy of recurrent laryngeal nerve is usually less than 1%, and nerve monitoring during operation is beneficial to avoid injury of recurrent laryngeal nerves even in patients with both SHPT and THPT. Incidentally thyroid tumor is complicated. When thyroid carcinoma is speculated by US before the operation, thyroidectomy should be performed concomitantly.[47]

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