Review

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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 hypocalcaemia. Hyperphosphatemia has a direct stimulatory effect on the parathyroid gland cell resulting in nodular hyperplasia and increased PTH secretion. Prolonged hypocalcaemia 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 resolute, 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***

Key words: *calcimimetics, metabolic disturbances, parathyroidectomy, tertiary hyperparathyroidism*

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). Furtermore, 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

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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-OH_2-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-OH_2-D deficiency has been observed in up to 80% patients (28). After 3-12 months the concentration of 1,25-OH_2-D increases and becomes comparable to CKD patients with equivalent kidney function (9).

In the early post-transplantation period, 1,25-OH_2-D is negatively related to FGF-23: it could be likely due to the suppression of 1,25-OH_2-D production by an excess of FGF-23. Twelve months after transplantation, only functioning allograft displays an association with higher 1,25-OH_2-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 fallowing 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 follow: 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; itching; 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 + autotransplanation (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 after surgery are low and graft survival is comparable to that obtained with cinacalcet.

Intraoperative PTH monitoring for 3HPT: does it work?

Intraoperative PTH (IOPTH) monitoring has been standardized and optimized for primitive hyperparathyroidism, while its use in cases of secondary and 3HPT remains controversial though. The IOPTH monitoring for 3HPT is less simple, compared to the primitive one:

3HPT results from a hyperplasia of the four parathyroid glands and, before PTH achieves optimal values, all the glands should be removed (53-55);

pathophysiological changes related to renal failure can be related to a variability of the clearance of PTH after the removal of the hyperfunctioning tissue (47).

PTH dosage can overestimate PTH levels (1-84 PTH fragment) due to the reduced renal function that allows the accumulation of PTH fragments, as PTH 7-84 (54,56,57).

According to Haustein et al., in patients with secondary HPT and excised hyperfunctional parathyroid tissue, IOPTH avoided further operations in the 16% of cases. The accuracy of IOPTH during surgery depends on renal function and from the specificity of the test performed.

Furthermore, there are no substantial differences in the measurement of IOPTH with the PTH measured at the reference laboratory (55).

In patients with secondary HPT surgically treated, an increase in false positives can be recognized. This is probably due to an increase in concentrations of PTH 7-84 fragments in patients with poor renal clearance, compared to PTH 1-84 (60-62).

According to some authors, IOPTH during PTX for 2HPT in patients on waiting list for renal transplantation, has allowed to verify the correct exeresis of the glands hyperplastic and to exclude the presence of supernumerary glands and avoid re-operation (63).

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

1. Hirai T, Nakashima A, Takasugi N, et al. Association of nodular hyperplasia with resistance to cinacalcet therapy for secondary hyperparathyroidism in hemodialysis patients. Ther Apher Dial 2010; 14:577-582
2. Okada M, Tominaga Y, Izumi K, et al. Tertiary hyperparathyroidism resistant to cinacalcet treatment. Ther Apher Dial 2011; 15:33-37
3. Kerby J, Rue L, Blair H, et al. Operative treatment of tertiary hyperparathyroidism: a single-center experience. Ann Surg 1998; 227:878
4. Kilgo M, Pirsch J, Warner T, et al. Tertiary hyperparathyroidism after renal transplantation: surgical strategy. Surgery 1998; 124:677
5. Lo Monte AI, Bellavia M, Damiano G, et al. A complex case of fatal calciphylaxis in a female patient with hyperparathyroidism secondary to end stage renal disease of graft and coexistence of haemolytic uremic syndrome. Biomed Pap Med Fac Univ Palacky Olomuc Czech Repub 2012; 156:262-265
6. Lo Monte AI, Bellavia M, Maione C, et al. Sistemic calciphylaxis and thrombotic microangiopathy in a kidney transplant patient: two mixing fatal syndromes? Med Hypotheses 2012; 79:74-75
7. Bhan I, Shah A, Holmes J, et al. Post-transplant hypophosphatemia: Tertiary 'Hyper-Phosphatoninism'? Kidney Int 2006; 70:1486-1494
8. Evenepoel P, Naesens M, Claes K, et al. Tertiary 'hyperphosphatoninism' accentuates hypophosphatemia and suppresses calcitriol levels in renal transplant recipients. Am J Transplant 2007; 7:1193-1200
9. Evenepoel P, Meijers BK, de Jonge H, et al. Recovery of hyperphosphatoninism and renal phosphorus wasting one year after successful renal transplantation. Clin J Am Soc Nephrol 2008; 3:1829-1836
10. Kawarazaki H, Shibagaki Y, Fukumoto S, et al. The relative role of fibroblast growth factor 23 and parathyroid hormone in predicting future hypophosphatemia and hypercalcemia after living donor kidney transplantation: a 1-year prospective observational study. Nephrol Dial Transplant 2011; 26:2691-2695
11. Sirilak S, Chatsrisak K, Ingsathit A, et al. Renal phosphate loss in long-term kidney transplantation. Clin J Am Soc Nephrol 2012; 7:323-331

12. Tomida K, Hamano T, Ichimaru N, et al. Dialysis vintage and parathyroid hormone level, not fibroblast growth factor-23, determines chronic-phase phosphate wasting after renal transplantation. Bone 2012; 51:729-736
13. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol 2005; 16:2205-2215
14. Messa P, Sindici C, Cannella G, et al. Persistent secondary hyperparathyroidism after renal transplantation. Kidney Int 1998; 54:1704-1713
15. Bleskestad IH, Thorsen IS, Jonsson G, et al. Soluble Klotho and intact fibroblast growth factor 23 in long-term kidney transplant patients. Eur J Endocrinol 2015; 172:343-350
16. Muirhead N, Zaltman JS, Gill JS, et al. Hypercalcemia in renal transplant patients: prevalence and management in Canadian transplant practice. Clin Transplant 2014; 28:161-165
17. Kawarazaki H, Shibagaki Y, Fukumoto S, et al. Natural history of mineral and bone disorders after living-donor kidney transplantation: a one-year prospective observational study. Ther Apher Dial 2011; 15:481-487
18. Torres A, Rodríguez AP, Concepción MT, et al. Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations. Nephrol Dial Transplant 1998; 13:94-97
19. Nakamura M, Tanaka K, Marui Y, et al. Clinicopathological analysis of persistent hypercalcemia and hyperparathyroidism after kidney transplantation in long-term dialysis patients. Ther Apher Dial 2013; 17:551-556
20. Torregrosa JV, Fuster D, Duran CE, et al. Set point of calcium in severe secondary hyperparathyroidism is altered and does not change after successful kidney transplantation. Endocrine 2015; 48:709-711
21. Komaba H, Goto S, Fujii H, et al. Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. Kidney Int 2010; 77:232-238
22. Dewberry LC, Tata S, Graves S,et al. Predictors of tertiary hyperparathyroidism: Who will benefit from parathyroidectomy? Surgery 2014; 156:1631-1637
23. Taniguchi M, Tokumoto M, Matsuo D, et al. Persistent hyperparathyroidism in renal allograft recipients: vitamin D receptor, calcium-sensing receptor, and apoptosis. Kidney Int 2006; 70:363-370
24. Evenepoel P, Sprangers B, Lerut E, et al. Mineral metabolism in renal transplant recipients discontinuing cinacalcet at the time of transplantation: a prospective observational study. Clin Transplant 2012; 26:393-402
25. Eyal O, Aharon M, Safadi R, et al. Serum vitamin D levels in kidney transplant recipients: the importance of an immunosuppression regimen and sun exposure. Isr Med Assoc J 2013;15:628-633.
26. Kulshrestha S, Ojo AO, Luan FL. Metabolic syndrome, vitamin D deficiency and hypoadiponectinemia among nondiabetic patients early after kidney transplantation. Am J Nephrol 2013; 37:399-404
27. Penny H, Frame S, Dickinson F, et al. Determinants of vitamin D status in long-term renal transplant patients. Clin Transplant 2012; 26:E617-E623
28. Falkiewicz K, Boratynska M, Speichert-Bidzińska B, et al. 1,25-dihydroxyvitamin D deficiency predicts poorer outcome after renal transplantation. Transplant Proc 2009; 41:3002-3005
29. Nobata H, Tominaga Y, Imai H, et al. Hypocalcemia immediately after renal transplantation. Clin Transplant 2013; 27:E644-E648
30. Tang JA, Friedman J, Hwang MS, et al. Parathyroidectomy for tertiary hyperparathyroidism: A systematic review. Am J Otolaryngol 2017; 38:630-635.
31. Inabnet WB, Lee JA, Palmer BJA. Parathyroid disease. In: Garden OJ, Paterson-Brown S, editors. Endocrine surgery. London, UK: Elsevier; 2014; 1-40
32. Dulfer RR, Franssen GJH, Hesselink DA, et al. Systematic review of surgical and medical treatment for tertiary hyperparathyroidism. Br J Surg 2017; 104:804-813
33. Madorin C, Owen RP, Fraser WD, et al. The surgical management of renal hyperparathyroidism. Eur Arch Otorhinolaryngol 2012; 269:1565-1576
34. Lorenz K, Bartsch DK, Sancho JJ, et al. Surgical management of secondary hyperparathyroidism in chronic kidney disease – a consensus report of the European Society of Endocrine Surgeons. Langenbeck Arch Surg 2015; 400:907-927
35. Cocchiara G, Fazzotta S, Palumbo VD, et al. The medical and surgical treatment in secondary and tertiary hyperparathyroidism. Review. Clin Ter 2017; 168:e158-e167
36. Pulvirenti D, Campagna A, Ignaccolo L, et al. Medical-surgical integrated approach in the treatment of non-paraneoplasic hyperparathyroidism: our experience. Clin Ter 2009;160:21-24
37. Pulvirenti D, Aikaterini T, Campagna A, et al. Medical-surgical integrated approach in the treatment of non-paraneoplasic hyperparathyroidism: our experience. Clin Ter 2008; 159:307-310
38. Chou FF, Chan HM, Huang TJ, et al. Autotransplantation of parathyroid glands into subcutaneous forearm tissue for renal hyperparathyroidism. Surgery 1998; 124:1-5
39. Monchik JM, Bendinelli C, Passero MA, et al. Subcutaneous forearm transplantation of autologous parathyroid tissue in patients with renal hyperparathyroidism. Surgery 1999; 126:1152-1158
40. Rothmund M, Wagner PK, Schark C. Subtotal parathyroidectomy versus total parathyroidectomy and autotransplantation in secondary hyperparathyroidism: a randomized trial. World J Surg 1991; 15:745-750
41. Richards ML, Wormuth J, Bingener J, et al. Parathyroidectomy in secondary hyperparathyroidism: is there an optimal operative management? Surgery 2006; 139:174-180
42. Gasparri G, Camandona M, Abbona GC, et al. Secondary and tertiary hyperparathyroidism: causes of recurrent disease after 446 parathyroidectomies. Ann Surg 2001; 233:65-69
43. Tominaga Y, Uchida K, Haba T, et al. More than 1,000 cases of total parathyroidectomy with forearm autograft for renal hyperparathyroidism. Am J Kidney Dis 2001; 38:168-171
44. Triponez F, Dosseh D, Hazzan M, et al. Subtotal parathyroidectomy with thymectomy for autonomous hyperparathyroidism after renal transplantation. Br J Surg 2005; 92:1282-1287
45. Triponez F, Kebebew E, Dosseh D, et al. Less-than-subtotal parathyroidectomy increases the risk of persistent/recurrent hyperparathyroidism after parathyroidectomy in tertiary hyperparathyroidism after renal transplantation. Surgery 2006; 140:990-997
46. Pattou FN, Pellissier LC, Noel C, et al. Supernumerary parathyroid glands: frequency and surgical significance in treatment of renal hyperparathyroidism. World J Surg 2000; 24:1330-1334
47. Numano M, Tominaga Y, Uchida K, et al. Surgical significance of supernumerary parathyroid glands in renal hyperparathyroidism. World J Surg 1998; 22:1098-1102

48. Aly A, Douglas M. Embryonic parathyroid rests occur commonly and have implications in the management of secondary hyperparathyroidism. ANZ J Surg 2003; 73:284–288
49. Triponez F, Clark OH, Vanrenthergem Y, et al. Surgical treatment of persistent hyperparathyroidism after renal transplantation. Ann Surg 2008; 248:18-30
50. Costa-Hong V, Jorgetti V, Gowdak LH, et al. Parathyroidectomy reduces cardiovascular events and mortality in renal hyperparathyroidism. Surgery 2007; 142:699-703
51. Trombetti A, Stoermann C, Robert JH, et al. Survival after parathyroidectomy in patients with end-stage renal disease and severe hyperparathyroidism. World J Surg 2007; 31:1014-1021.
52. Narayan R, Perkins RM, Berbano EP, et al. Parathyroidectomy versus cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. Am J Kidney Dis 2007; 49:801-813
53. Gioviale MC, Damiano G, Altomare R, et al. Intraoperative measurement of parathyroid hormone: A Copernican revolution in the surgical treatment of hyperparathyroidism. Int J Surg 2016; 28:99-102
54. Gioviale MC, Gambino G, Maione C, et al. Intraoperative parathyroid hormone monitoring during parathyroidectomy for hyperparathyroidism in waiting list and kidney transplant patients. Transplant Proc 2006; 38:1003-1005
55. Damiano G, Gioviale MC, Maione C, et al. Comparison between rapid intraoperative and central laboratory parathormone dosage in 12 kidney transplant candidates. Transplant Proc 2016; 48:311-314
56. Yao DX, Hoda SA, Yin DY et al. Interpretative problems and preparative technique influence reliability of intraoperative parathyroid touch imprints. Arch Pathol Lab Med 2003; 127:64–67
57. Rohaizak M, Munchar MJ, Meah FA, et al. Prospective study comparing scrape cytology with frozen section in the intraoperative identification of parathyroid tissue. Asian J Surg 2005; 28:82-85
58. Haustein SV, Mack E, Starling JR, et al. The role of intraoperative parathyroid hormone testing in patients with tertiary hyperparathyroidism after renal transplantation. Surgery 2005; 138:1066-1071
59. Bieglmayer C, Kaczirek K, Prager G, et al. Parathyroid hormone monitoring during total parathyroidectomy for renal hyperparathyroidism: pilot study of the impact of renal function and assay specificity. Clin Chem 2006; 52:1112–1119
60. Chou FF, Lee CH, Chen JB, et al. Intraoperative parathyroid hormone measurement in patients with secondary hyperparathyroidism. Arch Surg 2002; 137:341-344
61. Kaczirek K, Riss P, Wunderer G, et al. Quick PTH assay cannot predict incomplete parathyroidectomy in patients with renal hyperparathyroidism. Surgery 2005; 137:431-435
62. Abruzzo A, Gioviale MC, Damiano G, et al. Reoperation for persistent or recurrent secondary hyperparathyroidism. Acta Biomed 2017; 88:325-328
63. Gioviale MC, Gambino G, Maione C, et al. Use of monitoring intraoperative parathyroid hormone during parathyroidectomy in patients on waiting list for renal transplantation. Transplant Proc 2007; 39:1775-1778