



# Management of Post-transplant Hyperparathyroidism and Bone Disease

Rowena Delos Santos<sup>1</sup> · Ana Rossi<sup>3</sup> · Daniel Coyne<sup>1</sup> · Thin Thin Maw<sup>2</sup>

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## Abstract

Significant advances in immunosuppressive therapies have been made in renal transplantation, leading to increased allograft and patient survival. Despite improvement in overall patient survival, patients continue to require management of persistent post-transplant hyperparathyroidism. Medications that treat persistent hyperparathyroidism include vitamin D, vitamin D analogues, and calcimimetics. Medication side effects such as hypocalcemia or hypercalcemia, and adynamic bone disease, may lead to a decrease in the drugs. When medical management fails to control persistent post-transplant hyperparathyroidism, treatment is a parathyroidectomy. Surgical techniques are not uniform between centers and surgeons. Undergoing the surgery may include a subtotal technique or a technique including total parathyroid gland resection with partial heterotopic gland reimplantation. In addition, there are possible post-surgical complications. The ideal treatment for persistent post-transplant hyperparathyroidism is the treatment and prevention of the condition while patients are being managed for their late-stage chronic kidney disease and end-stage renal disease.

## Key Points

Persistent post-transplant hyperparathyroidism is common after kidney transplantation, affects metabolic parameters, and is accompanied by morbidity.

Treatments for persistent post-transplant hyperparathyroidism include vitamin D, its analogues, and calcimimetics; regular monitoring is required to avoid adverse effects from treatment.

If medical management fails, parathyroidectomy should be considered.

## 1 Introduction

For most patients with end-stage renal disease (ESRD), kidney transplantation is the treatment of choice as it will improve patient survival while increasing quality of life compared to remaining on dialysis. Allograft survival has improved over the decades, where the one-year allograft survival has now reached over 93% for first-time transplant recipients, and over 72% for five-year allograft survival [1]. While patients benefit from improved allograft survival, they are burdened with the lasting effects of their chronic kidney disease (CKD). One of the accompanying conditions from CKD that can remain problematic post-transplantation is secondary hyperparathyroidism (SHPT), which occurs in virtually all patients who have CKD and requires ongoing management during dialysis. Even after kidney transplantation, recipients can continue to have elevated parathyroid hormone (PTH) levels [2–6]. Several studies have evaluated the levels of PTH post-kidney transplantation showing an initial decrease in the PTH levels within the first 12 months post-transplant [2–6]. However, in up to 50% of patients there is evidence of a persistent elevation in the PTH years after a successful transplantation [2, 3, 7, 8].

It is worth noting that there are different assays available to measure PTH. PTH is secreted from the parathyroid glands in several fragments and as an intact whole protein

✉ Rowena Delos Santos  
delossantos@wustl.edu

<sup>1</sup> Division of Nephrology, Washington University in St. Louis, 660 S. Euclid Ave, Campus Box 8126, St. Louis, MO 63110, USA

<sup>2</sup> Division of Nephrology and Hypertension, Keck School of Medicine of USC, 2020 Zonal Ave, IRD 806, Los Angeles, CA 90033, USA

<sup>3</sup> Division of Nephrology and Transplantation, Maine Medical Center, Maine Transplant Program, 19 West St., Portland, ME 04102, USA

84 amino acids in length. Different immunoassays detect the carboxyl terminal of the intact and partial proteins, making some testing assays non-specific because it would detect both whole and partial proteins. Improvements in immunoassays allow simultaneous detection of both the carboxyl and the amino terminals of the protein, and hence detects the biologically active whole PTH (wPTH) [9]. There is no consensus on a PTH level that clearly defines the presence of persistent post-transplant hyperparathyroidism. Most transplant physicians will allow up to 12 months post-transplant for normalization of PTH. Past this point, a PTH level greater than two times normal ( $> 130$  pg/mL) is consistent with persistent post-transplant hyperparathyroidism (PT-HPT). Other lab abnormalities such as hypercalcemia, hypophosphatemia, and an elevated alkaline phosphatase, can be associated with persistent PT-HPT.

## 2 Pathophysiology

Our understanding of the pathophysiology of SHPT and PT-HPT and its natural history has expanded over the last decade. In normally functioning kidneys, the parathyroid glands maintain homeostasis of calcium and phosphate balance through the kidneys, bones, and gastrointestinal tract. A fall in the ionized calcium below its normal set point stimulates increased PTH production from the parathyroid glands leading to increased renal tubular reabsorption of calcium. PTH stimulates renal proximal tubular conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ).  $1,25(\text{OH})_2\text{D}$  then stimulates increased intestinal calcium as well as phosphorus absorption and modulates the function of osteoblasts in bone. PTH and  $1,25(\text{OH})_2\text{D}$  help stimulate production of fibroblast growth factor 23 (FGF23) production from osteocytes. PTH also leads to increased skeletal release of calcium through the stimulation of osteoclasts in bone. Once the ionized calcium is returned to the individual's set point, negative feedback through the calcium-sensing receptors (CaSR) on the parathyroid glands decreases production of PTH. Higher  $1,25(\text{OH})_2\text{D}$  level also provides negative feedback on the parathyroid glands, reducing PTH production.

Phosphate balance is maintained through the combined actions of FGF23,  $1,25(\text{OH})_2\text{D}$ , and PTH. Increasing blood levels of phosphate early in CKD increases bone production of FGF23, which downregulates reabsorption of phosphate and  $1-\alpha$ -25-(OH)-vitamin D hydroxylase in the proximal tubule, leading to enhanced phosphaturia and decreased production of  $1,25(\text{OH})_2\text{D}$ . Lower levels of  $1,25(\text{OH})_2\text{D}$  lead to decreased intestinal phosphate absorption, and increased PTH production and parathyroid (PT) hyperplasia, resulting in SHPT and enlarging PT glands. These responses to declining renal function are usually able to maintain serum

phosphate within the normal range until CKD stage 4–5 [10].

With the onset of severe CKD, overt hyperphosphatemia, low levels of  $1,25(\text{OH})_2\text{D}$  lead to progressive SHPT and PT hyperplasia. FGF23 levels continue to increase due to hyperphosphatemia [10]. Thus, at the time of kidney transplant, patients commonly have SHPT and enlarged PT glands, hyperphosphatemia, low  $1,25(\text{OH})_2\text{D}$  levels, and elevated FGF23.

Once a new kidney allograft is functional, the typical response is the reversal or improvement of these abnormalities, though persistent abnormalities in PTH and FGF23 can lead to alterations in bone and mineral homeostasis. Several groups have studied the changes in levels of PTH, FGF23, phosphate, calcium, and  $1,25(\text{OH})_2\text{D}$  after receiving a renal allograft. Within the first 3 months post-transplant, mild to profound hypophosphatemia may develop, and appears due to the combined phosphaturic actions of PTH and FGF23. Evenepoel et al. performed a single center observational study in 1165 kidney transplant recipients and found that hypophosphatemia affects approximately 40% of patients post-transplant, and is an early finding within the first three months of transplant [2]. The study concluded that the hypophosphatemia was due to the phosphaturic effect of PTH; however, this is before the discovery of FGF23 [2]. Wolf et al. did a similar multicenter study to monitor changes in biochemical parameters of mineral metabolism that included FGF23 [11]. They found that the FGF23 level decreases precipitously in the first 3 months then reaches a steady state [11]. Serum phosphate also drops significantly in the first 3 months post-transplant, with hypophosphatemia (defined as a serum phosphate  $< 2.5$  mg/dL) seen in 35–55% of patients [11]. Hypophosphatemia is a short-lived event in most patients and improves over the course of the first-year post-transplant.

The same group also evaluated the PTH levels in post-transplant patients, separating those with a low PTH (defined as  $\text{PTH} > 65$  and  $< 300$  pg/mL) from those with a high PTH (defined as  $\text{PTH} > 300$  pg/mL) at the time of transplant. Within 1 week of transplant, hypercalcemia (serum calcium  $> 10.2$  mg/dL) developed in 21% of patients with low PTH and 30% with high PTH. The proportion of patients with hypercalcemia peaked at 29% for low PTH patients and 48% for high PTH patients by 8 weeks post-transplant, and then steadily decreased. However, the improvement in hypercalcemia is incremental; by 12 months post-transplant there were 11% of patients in the low PTH group and 25% of patients in the high PTH who continued to have hypercalcemia [11]. Both groups had a significant decline in PTH from baseline levels in the first 3 months, and a slower improvement over the succeeding months. At 12 months, the PTH was still elevated above normal values (high PTH group 146 pg/mL, low PTH group 118 pg/mL) [11]. Levels of

1,25(OH)<sub>2</sub>D increased in both groups through to 12 months post-transplant. Muirhead et al. describe their long-term experience with 1000 consecutive transplant recipients over several years of follow-up. They reported that nearly 17% of patients were hypercalcemic at 12 months post-transplant, and 10% were hypercalcemic at 48 months post-transplant [8]. In addition, while nearly 48% of patients had an elevated PTH at Month 12 post-transplant, approximately 39% continued to have an elevated PTH at Month 48 post-transplant [8].

Most transplant professionals will allow patients with SHPT up to the first-year post-transplant to improve, as some patients will experience normalization of biochemical parameters over time. Despite the improvement in FGF23, phosphate and vitamin D levels after a kidney transplant, there is a subset of patients that maintain a persistently high PTH level as well as hypercalcemia in some cases. One of the main drivers of persistent SHPT is the enlarged PT glands due to hyperplasia that can occur during long-standing SHPT. As a result of the ongoing stimulation of parathyroid tissue by the dysregulation in metabolic bone mineral parameters, the parathyroid tissue first undergoes diffuse hyperplasia, and in some patients develops into nodular hyperplasia. These nodules exhibit characteristics of autonomous adenomas seen in patients with primary hyperparathyroidism, with a marked reduction in expression of CaSR and Vitamin D receptors, rendering them less responsive to elevation in serum calcium and 1,25(OH)<sub>2</sub>D levels. If control of these metabolic parameters is accomplished at the hyperplastic stage and maintained until the patient is transplanted, then the hyperplasia may be more likely to regress [12].

Unfortunately, there are no overt physical findings of PT-HPT. Persistent PT-HPT will primarily be discovered through laboratory testing. As previously described, patients will have a persistently elevated PTH. Some affected patients will have evidence of hypercalcemia on lab testing. There may be evidence of increased bone turnover through an elevated bone-specific alkaline phosphatase or osteocalcin [13].

Persistent PT-HPT has been associated with increased risk of bone fractures, increased mortality and decreased allograft survival [14, 15]. Perrin et al. evaluated the association between persistent PT-HPT and fracture risk in a cohort of 143 patients who were transplanted between 2004 and 2006 [14]. In a multivariable analysis, they found that HPT at 3 months, defined as a PTH > 130 ng/L, and pre-transplant osteopenia were associated with post-transplant fractures within 5 years post-transplant [14]. In addition to the risk of fractures, Pihlstrom et al. sought to evaluate the association of persistent HPT with mortality, cardiovascular disease, and renal allograft survival in patients who participated in the ALERT trial [15]. In this long-term study of 1840 renal transplant recipients, an elevated PTH was

associated with an increased risk of all-cause mortality (4%) and allograft loss (5%), but not with major adverse cardiovascular events [15]. Given the significant morbidity and mortality associated with persistent PT-HPT, the main clinical goal for patients with PT-HPT after renal transplantation is to obtain a level of PTH appropriate to the graft function and to normalize levels of calcium, phosphate and vitamin D. It is a common practice to follow a conservative approach with regard to serum PTH levels until adequate renal allograft function ensues, allowing the normalization of calcium and phosphate levels, and increasing the production of calcitriol to control HPT.

### 3 Pre-transplant Management of Secondary Hyperparathyroidism

Proper management of SHPT prior to transplantation can minimize PT-HPT and its complications of hypercalcemia and hypophosphatemia. In general, hypercalcemia post-transplantation is unusual if PTH is maintained in the advanced CKD and ESRD population at less than 600 pg/mL through use of active vitamin D and control of serum phosphate to < 6.0 mg/dL. While calcimimetics are effective at lowering PTH, they also lower serum calcium, and therefore may mask tertiary HPT. Consequently, we prefer to measure the PTH in transplant candidates 2–4 weeks after stopping the calcimimetic as part of the evaluation for transplant. If the PTH is < 800 pg/mL, the patient's risk of hypercalcemia post-transplant appears to be low [16]. If the PTH is > 1000 pg/mL, this is indicative of severe HPT-related bone disease. We generally prefer a pre-transplant parathyroidectomy (PTX) with 3½ glands removed as this will lead to marked bone healing and increased bone mineral density (BMD) and obviates the need for cinacalcet post-transplant. PTX during the pre-transplant period increases BMD much more than surgery after transplantation [16]. We generally wait about 6 months after PTX to allow maximal bone healing and stable serum calcium and phosphate [16].

### 4 Medical Management and Treatment Options of Persistent Post-transplant Hyperparathyroidism

Once the kidney transplant takes place, there is little consensus about how to manage persistent PT-HPT. Treatment for persistent PT-HPT is challenging because there are no large randomized controlled trials to guide treatment decisions. Current Kidney Disease Improving Global Outcomes (KDIGO) guidelines from 2017 provide recommendations on testing calcium, phosphate, PTH and alkaline phosphatase, and 25-hydroxyvitamin D levels in intervals

according to the post-kidney transplant recipients' level of renal function [17]. KDIGO also suggests treatment using vitamin D, calcitriol/alfacalcidol and/or antiresorptive agents within the first 12 months of transplant to correct abnormal biochemical testing and prevent BMD loss. KDIGO guidelines only recommend bone biopsy if it will help guide treatment, while dual-energy X-ray absorptiometry (DEXA) testing can be used to evaluate fracture risk, especially in those where the results may alter treatment [17]. Other societies and countries, such as the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), Renal Association of the United Kingdom, National Institute for Health and Care Excellence, Caring for Australians with Renal Impairment (CARI) and the Japan Society for Dialysis Therapy, have commented on current or previous KDIGO guidelines, and provide specific additions or recommendations for their members [18–22].

The management of persistent PT-HPT and related mineral bone abnormalities post-transplant vary between transplant centers; therefore, treatment should be individualized and be causal whenever possible. Here we provide a summary of different therapeutic measures for PT-HPT. A summary of the various medication classes and their safety, tolerability, effect on renal function, contraindications and special considerations is in Table 1. Table 2 describes the changes in calcium, phosphate and PTH with use of these medications.

#### 4.1 Use of Vitamin D and its Analogues

The liver converts vitamin D<sub>2</sub> and D<sub>3</sub> to 25-OH-vitamin D (calcidiol), which is measured to assess vitamin D status. Calcidiol levels > 30 ng/mL are considered normal. Calcidiol deficiency is common in kidney transplant recipients. Torres et al. showed that treatment with calcium supplements (0.5 g/day) during 1 year plus intermittent calcitriol (0.5 µg/every 2 days) for the first 3 months post-transplant, prevented bone loss and decreased PTH levels more rapidly than calcium supplementation alone [23]. Studies using vitamin D metabolites (calcidiol) or calcitriol, have shown a reduction in immediate bone loss by decreasing the effect of glucocorticoid on intestinal absorption or by suppressing PTH secretion [24, 25]. However, calcium and vitamin D use is limited by its capacity to produce hypercalcemia similar to the pre-transplant period. A study by Wissing et al. showed that kidney transplant recipients who received low doses of corticosteroid and cholecalciferol supplementation (25,000 IU/month) experienced normalization of PTH levels, but treatment did not prevent post-transplantation bone loss [26].

Paricalcitol, a synthetic metabolically active vitamin D analog of calcitriol, has been shown to suppress PTH post-transplantation [27]. However, it was also associated with a

higher risk of hypercalcemia, with 20% developing hypercalcemia in the paricalcitol group, but only 6% of patients in the control group [27]. The same study showed that moderate renal allograft fibrosis was reduced in the paricalcitol group compared with the control group. Trillini et al. conducted a crossover study showing that paricalcitol also reduced bone remodeling as reflected by reduction of bone alkaline phosphatase and osteocalcin together with improvements in lumbar spine BMD [28]. There was a reduction in estimated glomerular filtration rate (eGFR) associated with paricalcitol therapy [28]. In a placebo-controlled trial of paricalcitol in patients with type 2 diabetes and proteinuria, paricalcitol decreased proteinuria and eGFR in a dose-dependent fashion. The reduction in eGFR was small (2–4 mL/min/1.73 m<sup>2</sup>) and resolved after stopping the drug, and therefore appeared to reflect hemodynamic changes [29]. A randomized open-label trial comparing the use of paricalcitol and calcifediol found that more participants had a higher end of study PTH (defined as PTH > 110 pg/mL) in the calcifediol group compared to the paricalcitol group, although it did not reach statistical significance [30]. The proportion of patients who had a PTH < 70 pg/mL was greater in the paricalcitol group compared to the calcifediol group. Bone turnover markers including C-telopeptide, bone-specific alkaline phosphatase and osteocalcin were not different between groups, as were serum calcium and phosphate levels [30]. The paricalcitol group had a higher proportion of participants with a lower GFR and more fibrosis on protocol biopsy [30]. One of the limitations of this study was the short 6-month duration follow-up, thus limiting its application.

Many transplant physicians are often reluctant to use vitamin D and calcium supplementation in kidney transplant recipients for fear of inducing or aggravating hypercalcemia, and vascular calcifications. Hypercalcemia, a common complication in the early post-transplant period, is mostly caused by calcium release from the bone through PT-HPT [31]. In spite of the several studies of vitamin D or its analogues, the presence of autonomous parathyroid adenomas with decreased calcitriol, FGF23 or CaSR expression makes it difficult to achieve a successful outcome, and many cases of post-transplant persistent HPT become refractory to treatment with calcium and vitamin D analogues.

#### 4.2 Calcimimetics

Cinacalcet is a calcimimetic drug that allosterically activates the CaSR expressed on the surface of the chief cells of the parathyroid glands among other cells. Calcium-sensing receptor activation inhibits PTH secretion and leads to a decrease in serum calcium [32]. The mechanism of calcium reduction is two-fold: first through a decrease in PTH-mediated calcium release from the bone, and second, through an increased renal calcium loss owing to a

**Table 1** Medications, efficacy, safety, tolerability, complications and special considerations

Description	Medication					
	Vitamin D	Vitamin D analogues	Calcimimetics	Bisphosphonate	Anti-RANKL	Anabolic rPTH
Efficacy	Can be useful in high doses	Effective	Effective in controlling calcium and PTH	Effective for stabilization of BMD	Effective for stabilization or improvement of BMD	No improvement in BMD in kidney transplant patients
Safety in kidney transplant recipients	Safe to use without effect on kidney function	Safe to use without effect on kidney function	Differing results on its effects on kidney function	Unclear utility as there is little evidence that this medication decreases fracture risk	No effect on renal allograft function	No effect on kidney function
Major side effects	Hypercalcemia	Hypercalcemia	Hypocalcemia PTH can have significant decrease	Possible osteonecrosis of jaw Transient hypocalcemia	Cystitis Hypocalcemia	Hypercalcemia Hypercalciuria
Tolerability	Well tolerated	Well tolerated	GI side effects	Esophagitis/ulcers	Well tolerated	Tolerated
Contraindications	Significant pre-existing hypercalcemia	Significant pre-existing hypercalcemia	Avoid in adynamic bone disease	Use not recommended in CrCl < 35 ml/min	Avoid in adynamic bone disease	Conditions causing hypercalcemia Hyperparathyroidism
Special considerations	Limited use in preventing bone loss post-transplant	Possible decrease in eGFR Use has improved bone mineral density Possible relationship to allograft fibrosis	No effect on BMD Close monitoring and adjustments to medication is imperative to avoid adynamic bone disease	Does not affect PTH or course of persistent PT-HPT Consider bone biopsy to rule out adynamic bone disease before start use	Does not affect PTH or course of persistent PT-HPT Consider bone biopsy to rule out adynamic bone disease before start use	Vitamin D and calcium levels should be normalized prior to use

*BMD* Bone mineral density, *CrCl* creatinine clearance, *eGFR* estimated glomerular filtration rate, *PTH* parathyroid hormone level, *PT-HPT* post-transplant hyperparathyroidism, *RANKL* receptor activator of nuclear factor- $\kappa$ B ligand, *rPTH* recombinant parathyroid hormone

**Table 2** Medications and their effect on serum calcium, phosphate, PTH and BMD

Medication class	Change in biochemical parameter			
	Calcium	Phosphate	Parathyroid level	Bone mineral density
Vitamin D	Increase	Increase	Decrease	Increase
Calcimimetic	Decrease	Increase	Decrease	No effect
Bisphosphonate	Decrease	Decrease	No effect	Increase
Anti-RANKL	Decrease	No effect	No effect	Increase

BMD bone mineral density, PTH parathyroid hormone level, RANKL receptor activator of nuclear factor- $\kappa$ B ligand

direct activation of the CaSR on the basolateral membrane of the thick ascending limb of Henle's loop [33]. Calcimimetics have been used to reduce PTH levels in patients with persistent HPT on dialysis [34]. Cinacalcet has not been U.S. Food and Drug Administration (FDA) approved for use in kidney transplant recipients with persistent PT-HPT, although it has been used off-label in an effort to improve PTH and hypercalcemia and avoid parathyroidectomy (PTX).

Cinacalcet has been effective in reducing up to 50% PTH levels in moderate-to-severe PT-HPT [35, 36]. In addition to the effective decrease of PTH levels, cinacalcet could control two of the major problems of PT-HPT such as, hypercalcemia and hypophosphatemia. Observations regarding the effects of calcimimetic on kidney allograft function are contradictory. Some groups observed that cinacalcet use was associated with a decrease in GFR; however, others indicate no difference in kidney function, and no histologic effects on protocol-driven kidney transplant biopsies [37–40].

With the expectation that some transplant recipients will experience a regression of their parathyroid hyperplasia, with improvement in their biochemical parameters, some studies have looked at discontinuing cinacalcet at various times after a successful kidney transplantation [41]. Evenepoel et al. found that patients who discontinued cinacalcet at the time of transplant experienced a higher proportion of nephrocalcinosis and a higher rate of post-transplant parathyroidectomies (147.5 PTX/100 person-years at risk for the cinacalcet group and 22.2 PTX/100 person-years at risk for the cinacalcet-naïve group) [41]. Parathyroidectomy was more likely for patients who were on higher doses of cinacalcet at the time of kidney transplantation. While this study looked at the immediate discontinuation of cinacalcet post-kidney transplantation, another study discontinued the cinacalcet after 12 months post-transplant. Though this study had 10 participants, it found that after discontinuation of cinacalcet, there was an initial rise in both PTH and serum calcium ( $0.68 \pm 0.16$  mg/dL) and stabilized afterward. Serum phosphate remained largely unchanged while the

serum creatinine decreased after discontinuing cinacalcet [42].

In a randomized placebo-controlled 52-week trial of 114 hypercalcemic ( $> 10.5$  mg/dL) kidney transplant recipients with persistent PT-HPT, Evenepoel et al. showed that cinacalcet normalized serum calcium in 79% and lowered PTH from a mean of 328 pg/mL to 169 pg/mL, while changes in the placebo group were negligible. At 56 weeks, 4 weeks following withdrawal of cinacalcet, PTH rebounded to a mean of 234 pg/mL versus 277 pg/mL in the placebo group, suggesting limited or no regression of parathyroid hyperplasia while on cinacalcet. There was also no improvement in BMD at the femoral neck, lumbar spine, or distal 1/3 radius between cinacalcet and the placebo group. Both groups had comparable and stable eGFR [38].

Zavvos et al. recently conducted a prospective single-center study to assess the long-term treatment effects of cinacalcet for a period of up to 5 years in a cohort of kidney transplant recipients. Treatment with cinacalcet decreased serum calcium by 0.21 mmol/L during the first 6 months, and this reduction was sustained during follow-up. The intact PTH level decreased by 7.68 pmol/L at 6 months (P not significant); however, intact PTH level decreased further by 20.07 pmol/L at the end of follow up ( $p < 0.01$ ). Serum phosphate level increased significantly and eGFR remained stable throughout follow-up [39].

The new synthetic peptide calcimimetic, etelcalcetide, has been approved by the FDA for the treatment of SHPT in hemodialysis patients [43]. Although effective in this population, its applicability to the post-transplant population is limited by the fact that it is administered intravenously. No studies have investigated the use of this medication in kidney transplant recipients but could possibly be used in severely hypercalcemic post-transplant recipients who are awaiting PTX in a hospital.

Cessation of calcimimetic treatment leads to the return of serum calcium and PTH to pre-treatment levels, especially in patients with persistent SHPT [44]. Given the high prevalence of low bone turnover in renal transplant recipients with hypercalcemia and persistent HPT, the use of cinacalcet may

exacerbate bone disease, although serum calcium normalizes. A prospective study performed by Borchhardt et al. demonstrated that bone biopsies in 10 patients with hypercalcemia and HPT had low bone turnover in 4 of 10 renal transplant recipients prior to cinacalcet. After 18–24 months of cinacalcet therapy, 8 of 10 participants had low bone turnover, including 5 with undetectable bone formation rates [45]. This change over to a majority of patients having low bone turnover or adynamic bone disease is concerning, given that another study using cinacalcet in hemodialysis patients only showed 3 patients out of 19 developed adynamic bone disease [46]. Close monitoring of patients' biochemical parameters is imperative, and appropriate dose adjustments or discontinuation of the medication should be done while on cinacalcet.

### 4.3 Antiresorptive Agents Related to Osteopenia and Osteoporosis Post-transplant

The persistent HPT after kidney transplantation can also be associated with bone disease, especially bone loss and osteopenia/osteoporosis after transplant. Here we will discuss caveats related to the use of anti-resorptive agents, post-kidney transplant, as these agents are sometimes used for treatment of osteopenia and osteoporosis in this population. Many immunosuppressive regimens post-transplantation include corticosteroids and tacrolimus, which have been associated with the development of osteoporosis. Bisphosphonates induce osteoclastic apoptosis, reducing osteoclastic activity resulting in decreased bone resorption. There are several studies that used oral (risedronate, alendronate and ibandronate) and intravenous (pamidronate, zoledronic acid and ibandronate) bisphosphonates during the early post-transplant period. All of these studies showed the use of bisphosphonates preserves BMD in the short period after transplantation [47–52]. In this regard, bisphosphonates have shown efficacy in controlling bone loss, but there is no effect on PTH levels or the course of PT-HPT [53]. Additionally, there is no proven evidence that bisphosphonates decrease fracture risk in this population [54–56]. The levels of PTH and bone turnover biomarkers are not reflective of bone histology. Moreover, since bone biopsies are not routinely performed pre- and post-transplantation, it is practically challenging to avoid bisphosphonate use in patients with pre-existing adynamic bone disease. This group is one subset of transplant patients where bisphosphonates should be avoided. If there is suspicion of this condition, performing a bone biopsy to guide therapy is reasonable.

Denosumab is a fully humanized monoclonal antibody to receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclast. The use of denosumab causes a reduction in osteoclast formation and thus decreased bone

resorption and an increase in BMD [57]. In a study of postmenopausal women with osteoporosis, subcutaneous denosumab 60 mg every 6 months was found to be safe, and significantly reduced fracture risk [58]. Denosumab was also effective at reducing fracture risk and was not associated with increased adverse events among those with impaired kidney function [59]. Bonani et al. conducted an open-label, prospective, randomized trial to assess the efficacy and safety of denosumab to prevent the loss of BMD in the first year post-kidney transplantation [60]. In this study, total lumbar spine area BMD increased by 4.6% [95% confidence interval (CI) 3.3%–5.9%] in 46 patients in the denosumab group and decreased by –0.5% (CI –1.8% to +0.9%) in 44 patients in the control group [60]. The authors concluded that denosumab use increased BMD in the first year after kidney transplantation but found patients in the denosumab group to have more episodes of cystitis and asymptomatic hypocalcemia, while having no effect on PTH or serum creatinine levels post-transplant [60–62]. Others have found that while PTH levels remain stable before and after administration of denosumab, hypocalcemia can develop [63]. Hypocalcemia and an elevated PTH have been reported in a kidney transplant recipient [64]. Severe hypocalcemia after denosumab has been reported in patients with CKD, and therefore caution is advised. Denosumab should not be combined with cinacalcet therapy [65–67]. Similar to the bisphosphonates, it is not clear that denosumab has any effect on improvement of PT-HPT, and since its mechanism of action is to decrease bone resorption by decreasing osteoclast function, there is concern for use of this medication in patients who may have adynamic bone disease. Bone biopsy in patients suspected of having adynamic bone disease is reasonable prior to starting this medication.

Teriparatide, a recombinant human parathyroid hormone 1–34, is also used for the treatment of osteoporosis. A double-blind randomized study evaluated the use of this medication in 24 kidney transplant recipients. Over a 6-month period, there was no improvement in BMD, bone histology or bone turnover markers in the group receiving teriparatide compared to placebo [68]. Little evidence exists to support the use of this medication in the post-kidney transplant population [69].

When persistent PT-HPT does not respond to medical treatment, invasive management by percutaneous ethanol injection therapy (PEIT) of parathyroid glands or PTX should be considered.

## 5 Parathyroidectomy as a Treatment for Persistent Post-transplant Hyperparathyroidism

Approximately 80% of cases of SHPT resolve with a successful kidney transplant. As mentioned above, spontaneous regression of glandular hyperplasia may take 6–12 months; thus, it is prudent to wait 12 months post-transplantation before considering PTX. The prevalence of post-transplant PTX varies between 1 and 5.6% [70]. The most common indications for PTX are persistent hypercalcemia despite medical management, increase alkaline phosphatase indicating high bone turnover, and long-term complications of persistent PT-HPT and hypercalcemia such as osteoporosis, kidney stones, nephrocalcinosis and bone pain [71, 72].

Cruzado et al. performed the only randomized controlled trial to date comparing subtotal PTX to cinacalcet for the treatment of hypercalcemia caused by persistent HPT in kidney transplant recipients [73]. All patients with subtotal PTX and 67% with cinacalcet achieved normocalcemia. Moreover, the subtotal PTX group had a greater reduction of iPTH and was associated with improved BMD in the femoral neck. Vascular calcifications remained unchanged in both groups. A limitation of this study is the small sample size (only 15 participants per arm) and short-term follow up (12 months). Many observational studies examining outcomes after PTX in dialysis patients have demonstrated a significant reduction in mortality after PTX [74–76]. These positive findings are likely confounded by some degree of selection bias, as healthier patients tend to undergo surgery. This survival benefit has not been proven to be the case in kidney transplant recipients where graft function alone provides improvement in mineral bone metabolism; the possibility of selection bias is also likely reduced as all patients were deemed healthy enough to undergo kidney transplantation thus excluding the sickest patients [70, 74].

Given the lack of best practice guidelines, the specific surgical technique used depends more on surgeons' preferences rather than patients' characteristics [77]. Surgical techniques include subtotal PTX, or total PTX with or without auto-transplantation. In the rare event of a parathyroid adenoma, targeted PTX is also an option. Subtotal PTX involves the creation of a parathyroid remnant from the gland that has the best blood supply and accessibility. This technique has the benefit of fewer hypocalcemia complications but a higher incidence of treatment failure (5–30%) requiring repeated neck surgery [78, 79]. Total PTX with auto-transplantation involves creating a parathyroid gland autograft, which is usually placed in the non-dominant forearm. Potential additional sites for implantation include the sternocleidomastoid muscle or subcutaneous abdominal adipose tissue. This is the preferred technique for patients with strong reasons to avoid repeated neck surgeries. This technique has also the

potential of treatment failure if the implant hypertrophies and becomes autonomous. However, the implants are usually more surgically accessible than parathyroid remnants, making the repeated surgery easier to accomplish. On the other hand, total PTX with auto-transplantation may cause severe hypocalcemia if the implant fails. In this setting, the availability of tissue cryopreservation conveys the advantage of repeat auto-transplantation at a later time if needed. Total PTX without auto-transplantation is not recommended in the kidney transplant population as the subsequent hypocalcemia becomes difficult to control for patients off dialysis. A recent registry-based Swedish study comparing subtotal with total PTX found no difference in overall mortality, hip fracture, length of stay in hospital, or 90-day readmissions. There was a higher risk of cardiovascular events after total PTX compared to subtotal PTX (29% vs 14%,  $p < 0.001$ ) [80].

Controversy persists regarding the usefulness of intra-operative PTH (ioPTH) monitoring. As opposed to primary HPT where established protocols exist for ioPTH monitoring, no such protocols have been validated for ESRD-related HPT. This may be in part related to delayed renal clearance of PTH in the ESRD population [81–83]. Intact PTH (iPTH) assays cross-react with PTH fragments, which can experience reduced clearance leading to an overestimation of PTH concentration. Whole PTH (wPTH) assays cross-react with 1–84 PTH molecules only, thus providing more accurate data [9]. However, there is clinical evidence showing similar ability to detect surgical failure; thus, there is no recommendation to perform the more expensive test of wPTH [84, 85].

The PTH value is typically measured once excision is completed and compared to pre-surgical values. In general, a decline of 80% predicts cure [82]. A small study of 42 patients undergoing PTX found that ioPTH at 30 min post-excision was very accurate at predicting the persistence of SHPT. A 30-min ioPTH level  $> 12\%$  from baseline and a concentration  $> 166$  pg/mL predicted persistent SHPT with a sensitivity of 100%, specificity 71% and a negative predictive value of 100% [86].

A pre-surgical cervical ultrasound can assist with perioperative planning by describing the anatomy, guiding the sequence of exploration, and facilitating the choice of a parathyroid remnant. Ultrasound can also facilitate the decision regarding PTX as glands  $> 1$  cm in diameter or volume  $> 500$  mm<sup>3</sup> strongly suggest nodular transformation, which is usually refractory to medical treatment [87]. Additionally, ultrasound can uncover thyroid abnormalities that may need attention in the perioperative state. Ectopic parathyroid glands have been reported in up to 14% of cases, with the thymus being the most common location [88, 89]. The presence of ectopic glands increases the chances of PTX failure and the need to re-operate. Further neck imaging with Tc-MIBI-scintigraphy and SPECT/CT can help detect this hyperfunctioning tissue. However, it is unclear if extra



**Table 3** Complications after parathyroidectomy

Complication	Percentage
Hypocalcemia	42–97
Failure to achieve durable cure	1–5
Symptomatic hematoma	0.3–1
Recurrent laryngeal nerve injury	< 1–2
Mortality	0.8–1.7

imaging improves overall outcomes in hyperparathyroidism related to kidney disease [90–93].

Known complications after PTX are described on Table 3. The rate of complications is higher for surgeons with limited experience. Thirty-day readmissions post-PTX have been reported around 24%, but reduced to 13% in the hands of an experienced surgeon [73, 94]. Hypocalcemia, due to hungry bone syndrome, defined as serum total calcium concentration < 8.4 mg/dL and/or prolonged hypocalcemia for > 4 days post-PTX, is the most commonly reported complication (27%) [95]. Risk factors include higher body weight, younger age, higher preoperative serum alkaline phosphatase and lower preoperative serum calcium levels [96, 97]. Hungry bone disease has been linked to prolonged length of stay and requires aggressive treatment with calcium and vitamin D supplementation. If hypoparathyroidism persists, the use of cryopreserved parathyroid tissue, when available, can be used. Reduced renal function has also been reported in the early post-operative period. This reduction in GFR is thought to be hemodynamically mediated as PTH has a positive regulatory effect on renal perfusion [98]. However, long-term graft survival is the same as recipients without PTX [70, 98].

## 6 Conclusion

Hyperparathyroidism is common among kidney transplant recipients due to the almost ubiquitous development of SHPT and enlarged parathyroid glands during the late-stage CKD and dialysis period. Sequelae of pre-transplant SHPT in the post-transplant kidney patient include hypercalcemia, hypophosphatemia, persistently elevated PTH, and FGF23. We offer the following practical management of PT-HPT. We agree with KDOQI guidelines and recommend regular laboratory evaluation of serum calcium, phosphorus, PTH, and alkaline phosphatase post-transplant. Conservative management of avoiding calcium supplements, maintaining high urine output, and occasional low-dose phosphate supplements, is usually sufficient, and the SHPT improves with time. More severe PT-HPT is usually seen in those with more severe SHPT prior to transplant and the use of a calcimimetic during the dialysis period, as these are markers of larger gland size. Pre-transplant, we typically use a PTH

cutoff of 1000 pg/mL without calcimimetic use, or 500 pg/mL with calcimimetic use, as an indication that the parathyroid glands are enlarged, making improvement post-transplant unlikely. In these patients, we ask their nephrologists to consider pre-transplant PTX. We usually avoid the use of calcimimetics in the early post-transplant period. The majority of our post-transplant recipients will receive cholecalciferol 2000 IU daily. We recommend allowing PTH for at least 12 months post-transplant to normalize. If, despite employing conservative management, the patient's PTH remains persistently elevated with a normal vitamin D level, then we consider vitamin D analogues with monthly lab monitoring. Hypercalcemia limits the use of vitamin D analogues as treatment. These patients may be treated post-transplant with a calcimimetic, but this rarely leads to regression of the hyperparathyroidism, and does not improve BMD. PTX normalizes hypercalcemia and hypophosphatemia and has beneficial effects on bone mineral density. Treatment should be individualized, and while parathyroidectomy is recommended for persistent PT-HPT, patients considered at high risk for surgery can alternatively be treated with cinacalcet.

## Compliance with Ethical Standards

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