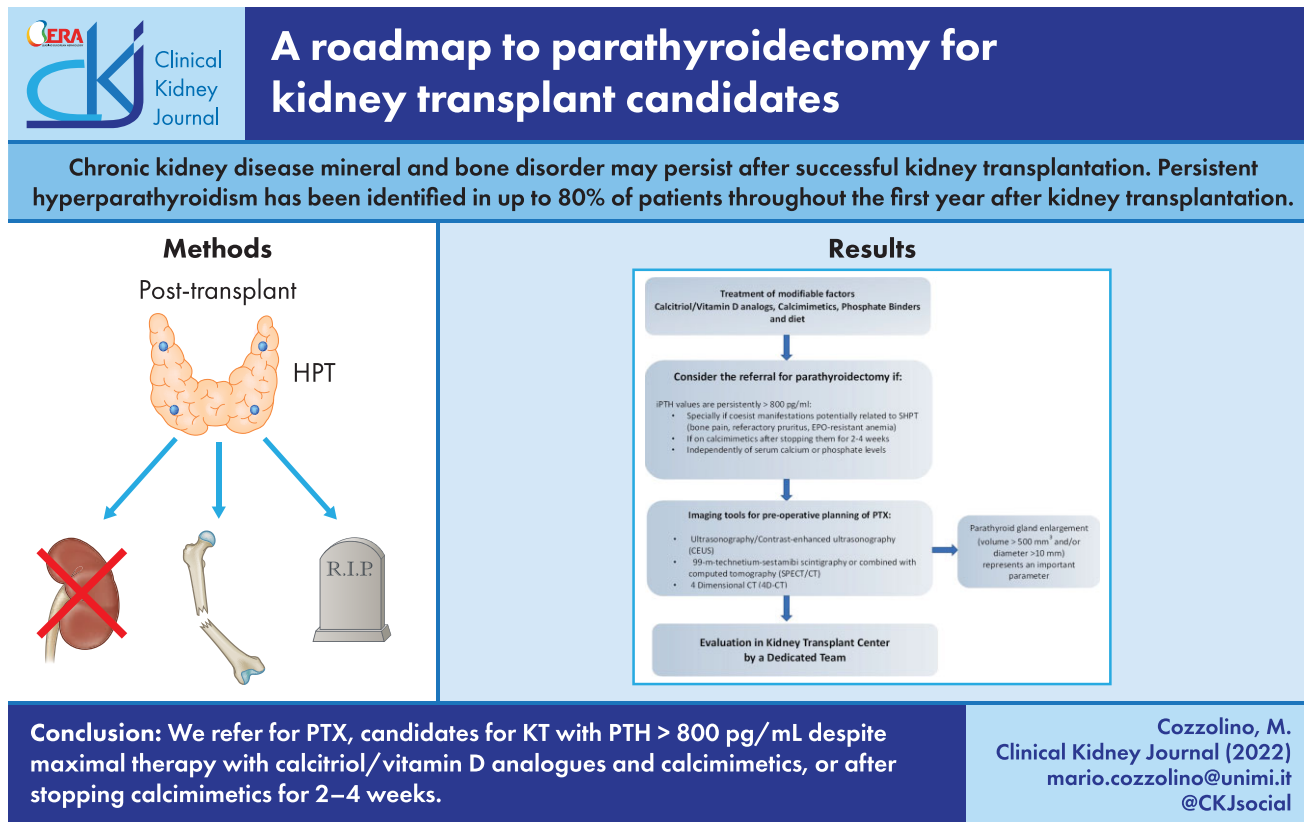


GRAPHICAL ABSTRACT



Keywords: kidney transplant, parathyroidectomy, secondary hyperparathyroidism

INTRODUCTION

Kidney transplantation (KT) is the gold standard renal replacement therapy for kidney failure. Kidney transplant recipients (KTRs) have better survival, reduced cardiovascular risk, improved quality of life and reduced health economic costs than dialysis-dependent patients [1–3]. However, KTRs are burdened by the lasting effects of their previous chronic kidney disease (CKD). Although successful KT was deemed to correct CKD-mineral and bone disorder (CKD-MBD) to a large extent, CKD-MBD persists in KTRs, although the phenotype evolves. Post-KT CKD-MBD depends on previous bone damage, persistent secondary hyperparathyroidism (SHPT), *de novo* CKD-MBD and immunosuppressive therapy. The contribution of each of these components changes over time [4] (Figure 1).

Persistent HPT is present in up to 80% of patients throughout the first year after KT and its clinical and biochemical consequences may persist for years if not appropriately treated [5–7]. International guidelines lack strict recommendations about the management of high pretransplant PTH levels, but the negative effects of persistent HPT on graft and patient outcomes make it necessary to define a roadmap in the management of SHPT in patients eligible for KT by analyzing both old and new evidence.

SHPT and tertiary HPT (THPT): pathophysiology

HPT is very common in CKD patients. It is present in ~50% of patients with stage 3 or 4 CKD and in >90% of those with

kidney failure [8]. The knowledge on the pathophysiology of SHPT has greatly expanded in recent decades. Both parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are key contributors to SHPT that share the same kidney effects on calcium (enhanced reabsorption) and on phosphate (increased excretion) but have an opposite effect on the metabolism of vitamin D [9].

PTH. PTH plays a pivotal role in calcium handling: when the serum calcium level falls below the normal set point, the calcium-sensing receptor (CaSR) is activated to promote release of PTH from the parathyroid glands. PTH increases bone resorption, releasing calcium in the blood; activates the conversion in tubular cells of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D [1,25(OH)₂D] and the reabsorption of calcium; and enhances FGF-23 production by upregulation of nuclear receptor related 1 in osteocytes (Figure 2). In proximal tubules, PTH leads to internalization of the sodium-phosphate cotransporters NPT1a and NPT1c, increasing phosphaturia and lowering serum phosphate [10, 11]. The return of serum calcium to normal values silences the CaSRs, normalizing PTH values [12, 13]. These compensation pathways are not effective in CKD because several factors persist as a result of SHPT and CKD progression: hypocalcemia, hyperphosphatemia, low levels of active vitamin D and high FGF-23 levels. The bone response to PTH is markedly deranged in advanced CKD, a phenomenon known as hyporesponsiveness or PTH resistance (Figure 3). The main

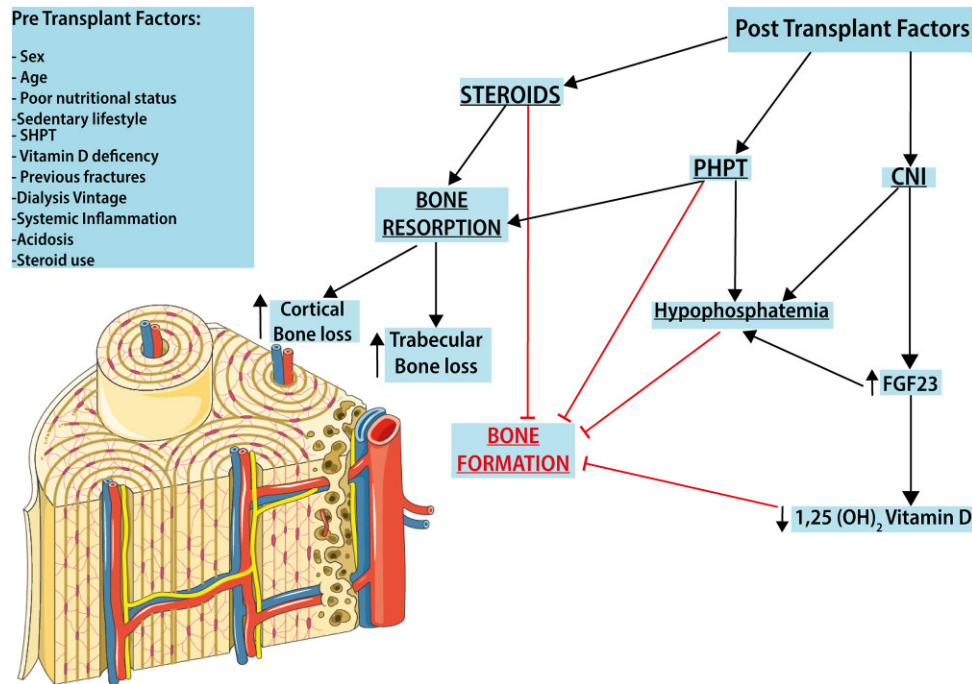


FIGURE 1: Post-KT CKD-MBD. In KTRs, the progression of bone disease results from the evolution of pre-existing CKD-MBD with several risk factors already present in the pretransplantation period. The successive evolution of post-KT bone disease is conditioned by several posttransplant factors, including the use of immunosuppressive drugs, the degree of graft dysfunction and disturbances in mineral metabolism, including an increased level of FGF23, ongoing SHPT and vitamin D deficiency. The two factors that mainly impact bone health in the posttransplant phase are steroid therapy and persistent hyperparathyroidism (PHPT). While PHPT involves mainly cortical bone, in the early posttransplant period, bone loss affects the trabecular side following decreased bone formation as a result of steroid therapy.

factors involved in PTH resistance are phosphate loading, calcitriol deficiency, oxidative stress, parathyroid hormone 1 receptor (PTH1R) downregulation and dysfunction, accumulation of PTH fragments, antagonists of the Wnt/ β -catenin pathway and uremic toxins. The presence of PTH fragments in association with the desensitization of PTH1R may explain the high prevalence of low-turnover bone disease during SHPT and the consequent persistent hypocalcemia [14].

FGF-23. FGF-23 increases very early in CKD to prevent phosphate accumulation [13] by compensating for decreased phosphate glomerular filtration. FGFs signal through four different FGF receptors (FGFR1–4), which are all tyrosine kinase receptors. FGFR1c is probably the most important FGFR for FGF-23 signaling, at least under physiological conditions, and requires the presence of coreceptor α -Klotho [15].

In proximal tubular cells, FGF-23 binding to the FGFR1–Klotho complex promotes phosphaturia by decreasing the expression of phosphate transporters NPT1A and NPT1C and also decreases gut absorption of phosphate by decreasing CYP27B1 activity [i.e. 1,25(OH)₂D generation] [9, 10]. FGF-23 also suppresses 1- α -hydroxylase both in a Klotho-dependent fashion (FGFR1) and through FGFR3 and FGFR4 in a Klotho-independent manner [16].

Decreased 1,25(OH)₂D availability in turn, enhances PTH synthesis [17]. Additionally, inflammation, albuminuria [18] and other factors also decrease kidney Klotho expression early in CKD, leading to resistance to FGF-23 [19]. In advanced CKD, the phosphaturic effects of PTH and FGF-23 are no longer evident and high serum phosphate levels also increase PTH levels [20, 21].

FGF-23 activates FGFRs through two main pathways: a Klotho-dependent activation of the mitogen-activated protein kinase (MAPK) cascade and a Klotho-independent cascade char-

acterized by activation of calcineurin–nuclear factor of activated T-cells (NFAT) (Figure 2). Specifically, in parathyroid glands, FGF-23 downregulates PTH secretion principally through classic Klotho-dependent activation or secondarily through the Klotho-independent cascade [22]. In severe SHPT, this inhibitory effect is lacking as a result of the reduced FGF-23–Klotho-dependent receptors in parathyroid glands [23, 24].

Sequential stages in the development of SHPT. HPT development is characterized by four sequential patterns of parathyroid hyperplasia. The first polyclonal proliferation phase is characterized by diffuse hyperplasia or early nodularity in diffuse hyperplasia. If not appropriately and aggressively managed, parathyroid glands develop progressive monoclonal expansion with nodular hyperplasia or a single nodular gland [23, 25]. Long-lasting and poorly controlled HPT leads progressively to a shift from diffuse to nodular hyperplasia (Figure 4). These nodules usually manifest functional features of autonomous adenomas as in primary HPT. Nodular hyperplasia is characterized by reduced expression of vitamin D receptor, CaSR, FGFR1 and its co-receptor Klotho, making SPHT refractory to medical treatments such as vitamin D agents and calcimimetics. This is the point of no return, termed THPT [25]. THPT is typically found post-KT, although it may be observed in patients on dialysis. In dialysis patients, THPT must be distinguished from SHPT with associated iatrogenic hypercalcemia and/or hyperphosphatemia related to overtreatment, e.g. with vitamin D [23].

Post transplant HPT

Successful KT was considered to reduce CKD-MBD to a large extent, but MBDs are common in KTRs, changing only the CKD-MBD phenotype. High PTH levels are observed in up to 80% of

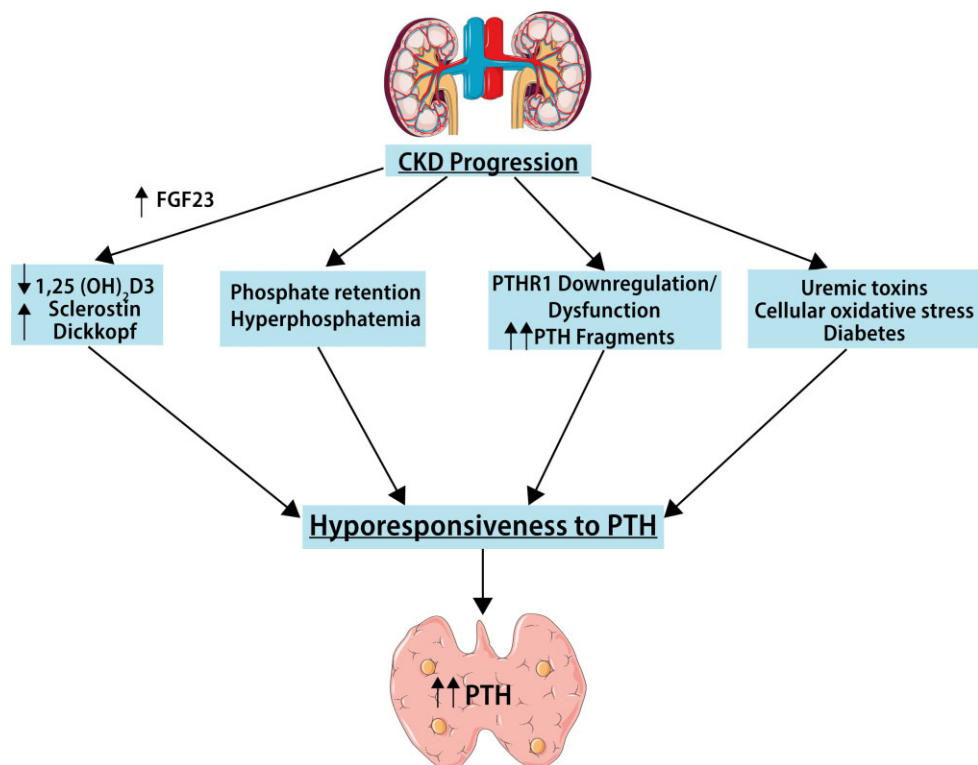


FIGURE 2: FGF23 and PTH interaction. FGF23 and PTH mutually regulate each other in a negative feedback loop, where PTH stimulates FGF23 production and FGF23 suppresses PTH synthesis. PTH increases FGF23 expression by the nuclear orphan receptor Nurr1. In the parathyroid glands, FGF23 either binds to an FGFR1 and membrane-bound Klotho, to elicit activation of the MAPK pathway, or acts via a calcineurin-dependent signaling pathway. CNI that blocks calcineurin signaling may worsen PHPT in patients with reduced Klotho levels such as in CKD. In the kidney, PTH and FGF23 share the same effect on phosphorus and calcium handling. PTH raises urinary phosphorus excretion, downregulating NPT2a and NPT2c in the kidney. PTH also enhances calcium absorption through the direct effect on bones and kidneys, indirectly upregulating 1,25(OH)₂D synthesis by increasing 1 α -hydroxylase. FGF-23 inhibits renal phosphorus reabsorption through FGFR1–Klotho signaling on NaPi-2a and 2c at the proximal tubule. FGF-23 suppresses in both a Klotho-dependent pathway (FGFR1) and through FGFR3 and FGFR4 in a Klotho-independent manner 1,25(OH)₂D production by decreasing 1 α -hydroxylase expression and increases in a Klotho-dependent pathway the expression at distal tubulus of glycosylated TRPV5, leading to increased calcium reabsorption (see text for details). NaPi-2, type II sodium–phosphate cotransporters; TRPV5, transient receptor potential vanilloid-5.

patients throughout the first year after KT [26]. Complete resolution of SHPT was observed in only 30% and 57% of recipients within the first and second years post-transplantation, respectively [27]. In 1000 consecutive KTRs, nearly 17% of patients were hypercalcemic at 12 months post-transplant and 10% were hypercalcemic at 48 months. In addition, ~50% and ~40% of patients had high PTH levels at months 12 and 48 post transplant, respectively [6]. The main predictive factors of persistent SHPT are dialysis vintage, high pre-KT PTH levels and the size of the parathyroid glands. The rapid growth of kidney failure prevalence is prolonging dialysis vintage before KT and this contributes to increasing the prevalence of persistent HPT in those on the KT waiting list [28–30]. In living donor KT, which is usually characterized by a shorter dialysis vintage prior to KT, mineral metabolism normalizes faster than in deceased donor KT [31]. Differences in prevalence may be explained by different definitions of persistent HPT, the assessment time point as well as the study era [27, 32–35]. In this regard, the ideal range of PTH and calcium levels after transplantation is not yet well defined.

Posttransplant HPT can be differentiated into persistent HPT (maladaptive response) versus *de novo* HPT (compensatory adaptive response). Persistent HPT results from preexisting CKD-MBD with SHPT, while *de novo* HPT results from decreasing graft function, leading to elevated PTH levels to maintain normophosphatemia and normocalcemia [31], reproducing the pathophysiology of CKD-MBD as observed in progressive CKD in native kidneys.

PTH levels. There is no consensus about the safe level of PTH, the PTH cut-off level that identifies persistent HPT or the ‘ideal’ timing of PTH assessment after transplantation. Most nephrologists wait up to 12 months after transplantation for PTH to normalize. Beyond 12 months, a PTH level >100 pg/mL [36, 37] or 70 pg/mL [32] is consistent with persistent HPT. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that KTRs should have the same therapeutic approach for CKD-MBD abnormalities, including PTH, as for patients with CKD stages 3–5. This implies having PTH levels within the reference range defined by each assay [38].

THPT. THPT is a misleading term that originally denoted the occurrence in the same patient of adenoma and hyperplasia in different glands, but classifying a gland as an adenoma in a patient with four enlarged parathyroid glands is questionable [33]. Some authors consider THPT to be a distinct though less frequent (21.5%) phenotype of persistent HPT, detectable in a subset of KTRs with both elevated PTH (>70 pg/mL) and hypercalcemia (serum calcium >10 mg/dL) at 1 year post-KT [32, 39].

Pre-KT PTH levels >300 pg/mL, high serum calcium (before and after KT), the use of calcimimetics, dialysis vintage or enlarged parathyroid glands pre-KT have been associated with the development of persistent HPT and THPT [32, 36, 40–42].

Parathyroid gland size. The proportion of parathyroid tissue that develops nodular hyperplasia increases as gland

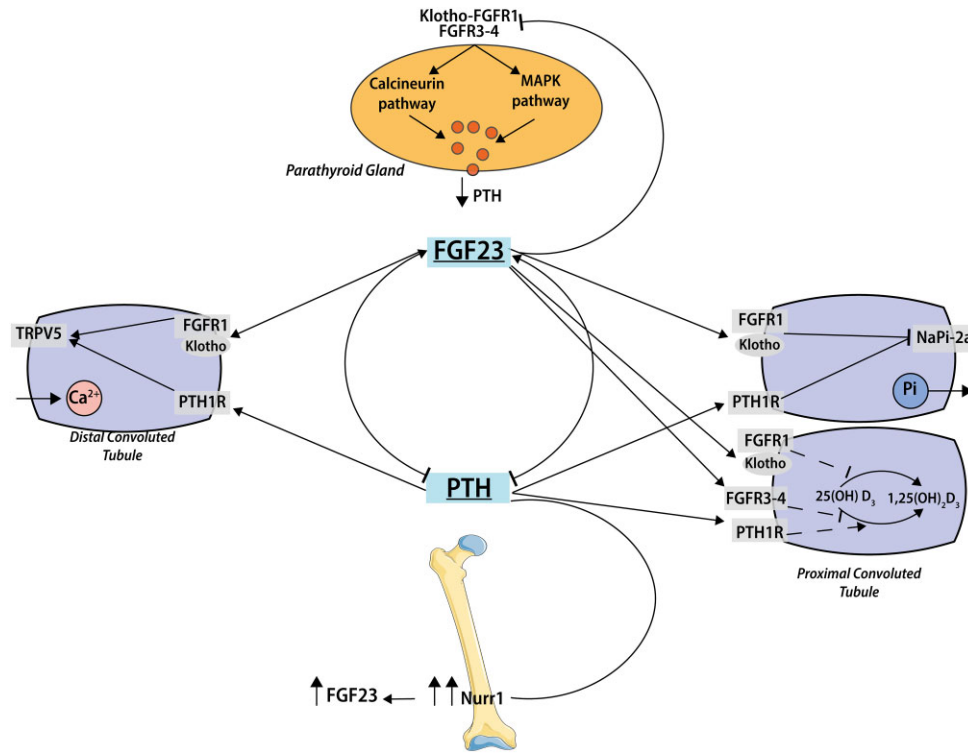


FIGURE 3: PTH resistance. The target organs' responses to the action of PTH are progressively impaired in CKD, a condition commonly referred to as PTH resistance. Multiple factors are involved, including phosphate loading, calcitriol deficiency, oxidative stress, PTH1R downregulation and dysfunction, accumulation of PTH fragments, antagonists of the Wnt/ β -catenin pathway and uremic toxins and accumulation of PTH fragments and uremic toxins.

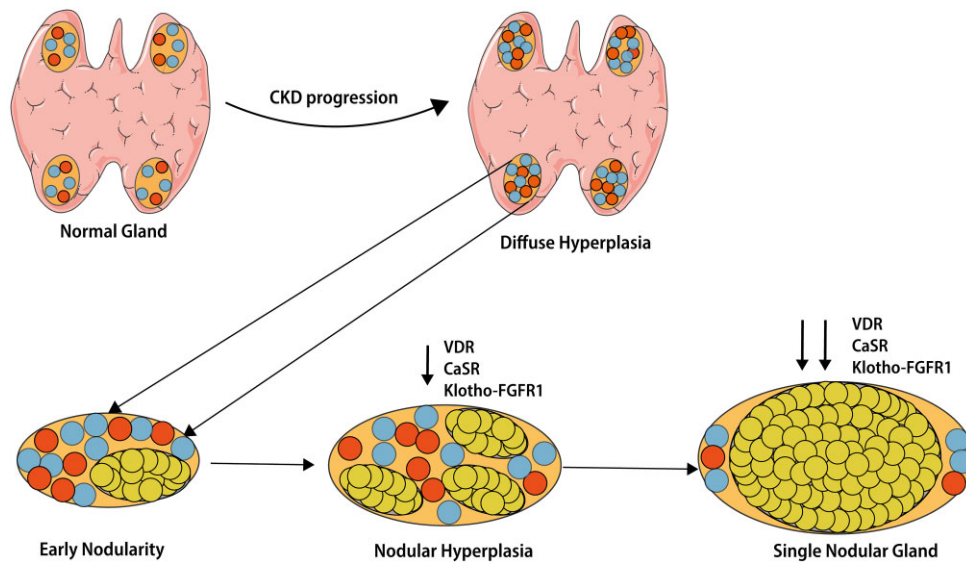


FIGURE 4: Pathophysiology of secondary hyperparathyroidism in CKD. Initially in SHPT, the parathyroid glands grow diffusely with polyclonal parathyroid cell proliferation (diffuse hyperplasia). At this stage, VDRAs activators and calcimimetics are effective in lowering PTH concentrations. Afterward, cells in the nodules are transformed monoclally and proliferate. In parallel are four patterns of parathyroid hyperplasia: diffuse hyperplasia, early nodularity in diffuse hyperplasia, nodular hyperplasia and single nodular glands. In the advanced stages of SHPT, downregulation of calcium sensing receptor (CaSR), VDR and Klotho-FGFR 1 makes parathyroid cells resistant to the inhibitory effect of calcimimetics, calcitriol and FGF-23.

weight/size increases, despite diffuse hyperplasia often being observed in small glands in patients with SHPT [43, 44]. In enlarged parathyroid glands (volume ≥ 500 mm³ or diameter ≥ 10 mm), nodular hyperplastic lesions are likely present and associated with a poor response to treatment with vitamin D re-

ceptor activators (VDRAs) and cinacalcet in dialysis-dependent patients [25, 45–52], likely as a consequence of reduced expression of both VDR and CaSR in nodular hyperplastic lesions in the transition from polyclonal to monoclonal proliferation that leads to nodular hyperplasia [23]. Thus long-term drug therapy

with VDRA alone or VDRA plus cinacalcet may be helpful in patients with parathyroid glands <10 mm but useless if the size is >10 mm [48, 50]. Few studies have analyzed the predictive value of enlarged parathyroid glands, assessed pre-KT, in the development of persistent HPT after transplantation [42, 53, 54]. Parathyroid glands of patients with persistent HPT after renal transplantation contained more than one nodular hyperplasia and restoration of VDR and CaSR expression after transplantation was observed only in diffuse hyperplasia. Therefore, in KT candidates, one enlarged parathyroid gland likely reflects nodular hyperplasia that is unlikely to regress [55]. Previous studies have demonstrated that therapy for persistent HPT should be started 3 months after KT since the most significant reduction of PTH occurs within the first 3 months after KT and PTH levels are unlikely to return to normal when elevated between 6 months and 1 year post-KT [33, 56–58]. However, the diagnosis is often not established until up to 2 years post-KT, causing increased morbidity from delayed treatment [32].

Persistent HPT and graft and patient outcomes

Persistent HPT contributes to posttransplant complications such as hypercalcemia, hypophosphatemia, high FGF-23 and nephrocalcinosis and is associated with unfavorable graft and patient outcomes [5, 26, 33, 59]. Studies on the impact of persistent HPT on graft and patient outcomes are marred by different definitions of persistent HPT based on PTH thresholds and timing of assessment, with most studies assessing PTH 10 weeks–12 months after transplantation.

Bone density and fractures. Persistent HPT in KTRs is associated with decreased bone density and an increased fracture rate [60–62]. Moderate bone mineral density (BMD) losses or BMD changes are observed in the first year after transplantation in the peripheral skeleton but not at the central skeleton. Steroid withdrawal and/or steroid minimization regimens decrease the negative effects of steroid therapy on bone health and persistent HPT is emerging as the main risk factor for bone fragility in KTRs [63, 64]. In particular, persistent HPT and high remodeling rates result in cortical and trabecular bone loss and decreased bone strength at the peripheral skeleton [65, 66].

Graft and patient survival. Studies on the association between persistent HPT and long-term graft and patient survival are limited, and results are contradictory. The pathways linking persistent HPT to graft dysfunction are not well known. Potential mechanisms include excessive vasoconstriction and tubulointerstitial calcification [36, 67].

Studies focused on pre-KT PTH values have reported divergent results. High pre-KT PTH levels have been linked to increased risk of graft failure censored for death [36, 68]. However, a retrospective analysis of >10 000 primary KTRs found no link between pre-KT PTH levels and death or graft loss after transplantation [69].

In 984 KTRs, FGF-23 was a strong and independent risk factor for the composite endpoint of death and graft loss, but the association between PTH and outcome was significant only in univariate analyses and disappeared when adjusting for estimated glomerular filtration rate (eGFR) [70].

The association of persistent HPT, defined as PTH >1.5 times the upper limit of the assay (100 pg/mL) 1 year after KT, with long-term graft outcomes was evaluated in 911 KTRs. Persistent HPT was an independent risk factor for graft loss. Moreover, a PTH level >150 pg/mL at 6 months predicted 1-year persistent HPT with 92% specificity [36].

A similar cut-off value (PTH \geq 150 pg/mL) at 3 months after KT was associated with worse allograft function up to 3 years posttransplant and to increased risk for death or death with a functioning graft [71]. In a retrospective analysis of 522 KTRs, intact PTH (iPTH) levels during the early posttransplant period (10 weeks) predicted a composite endpoint of cardiovascular events, graft loss and death. Moreover, patients with the highest levels of iPTH had the highest risk for the composite endpoint, the highest levels of calcium and the lowest levels of phosphate [72].

In a large cohort of 1840 KTRs from the ALERT trial, recruited with a mean of 5.1 years after KT and with a follow-up time of 6–7 years, persistent HPT after KT was significantly associated with all-cause mortality (4% increased risk) and allograft loss (5% increased risk) but not with major cardiovascular events [73]. No significant associations between PTH and serum calcium or phosphate were observed. These results are in agreement with another study showing that the correlation between serum PTH and serum calcium early after transplantation is gradually lost over time [58], but they differ from previous studies showing an association of hypercalcemia with graft loss and nephrocalcinosis [5, 74, 75].

Medical treatment versus parathyroidectomy before or after KT: association with outcomes

Persistent HPT post-KT often requires parathyroidectomy with a prevalence range from 0.6 to 5.6% [76]. However, there are no clear guidelines on how to treat waitlisted dialysis patients to reduce the risk of persistent HPT post-KT [77]. Moreover, the appropriate strategy in KTRs is debated, with particular focus on the risk of worsening of graft function related to medical and surgical therapy [39].

SHPT before KT can be treated by medical (VDRAs, phosphate binders and calcimimetics) or surgical (parathyroidectomy) approaches. Both reduce PTH values, although parathyroidectomy provides better long-term control of calcium and PTH values [77]. Medical treatment is generally the first step.

Calcimimetics. Calcimimetics are positive allosteric modulators of CaSRs that increase the sensitivity of the parathyroid glands to circulating calcium and VDR expression [23]. Randomized studies on cinacalcet have demonstrated its efficacy in the control of SHPT in patients on dialysis compared with vitamin D analogs and placebo [78, 79]. The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events study had a primary composite end point of time to death, myocardial infarction, hospitalization for unstable angina, heart failure and peripheral vascular events. The unadjusted intention-to-treat analysis of the 3883 dialysis patients treated with cinacalcet and placebo did not demonstrate differences in the primary endpoint (48.2% of patients treated with cinacalcet and 49.2% of patients treated with placebo) [80]. A prespecified analysis by age categories (\geq 65 years and <65 years) showed a reduction in major cardiovascular events {hazard ratio [HR] 0.70 [95% confidence interval (CI) 0.60–0.81], $P \leq .001$ } and all-cause mortality [HR 0.68 (95% CI 0.58–0.81), $P \leq .001$] in older patients [81]. Further analysis did not disclose differences in the risk of fractures, although after adjusting for baseline characteristics, multiple fractures and discontinuation of therapy, cinacalcet reduced the frequency of clinically evident fractures by 16–29% [82].

The use of calcimimetics pre-KT is frequently associated with the onset of mild hypercalcemia after KT, although this is present in 30% of KTRs (treated in dialysis with cinacalcet or not) and is potentially related with rebound of SHPT and nephrocalcinosis may develop months after KT [83]. In dialysis patients

with PTH levels well controlled by cinacalcet, there is a direct relationship between cinacalcet dosage and the development of hypercalcemia after KT [83].

Etelcalcetide is an intravenous direct CaSR agonist to treat SHPT in hemodialysis patients. In two recent cases, severe hypercalcemia developed in KT patients who had been on etelcalcetide in dialysis, requiring parathyroidectomy about 1 month after KT [84].

Parathyroidectomy. There are no clear guidelines on parathyroidectomy for patients on dialysis suffering from SHPT, beyond the notion that it is reserved for patients not responding to medical therapy [23]. Thus there are no clear indications on the optimal PTH targets to be achieved or the timing of parathyroidectomy. In the USA, between 2004 and 2016, the number of parathyroidectomies performed for SHPT in patients with kidney failure decreased by 40% [85]. In both KTRs and kidney failure patients, parathyroidectomy decreased from 7.9 to 5.4 per 1000 patients between 2002 and 2011, a major reduction being observed in 2004 (3.3 per 1000 patients), the year of cinacalcet release [85]. Evidence on the timing of parathyroidectomy in transplant candidates is also limited.

Post-KT parathyroidectomy and graft function. Post-KT parathyroidectomy has been associated with worse graft function outcomes than pre-KT parathyroidectomy. In a retrospective single-center study of 123 patients (67 pre-KT parathyroidectomy and 56 post-KT parathyroidectomy), parathyroidectomy after KT was associated with a decrease in eGFR following surgery. Post-KT parathyroidectomy was an independent risk factor for recipient graft function worsening. The risk decreased when parathyroidectomy was performed 1 year post-KT or, even better, before KT [86]. Similarly, graft function decreased in transplant patients who underwent post-KT parathyroidectomy, but the lipid profile and blood pressure control improved [87]. The negative impact of parathyroidectomy performed <1 year post-KT on renal function persisted for 5 years after transplantation when compared with parathyroidectomy performed pre-KT or 1–5 years post-KT [88]. In 76 KT patients who underwent parathyroidectomy, worsening of renal function was related to the change in PTH decline before and after surgery: a reduction in PTH >80% was followed by an important reduction of creatinine clearance. A retrospective study of 108 patients did not observe differences in graft survival between pre-KT and post-KT parathyroidectomy. However, post-KT parathyroidectomy was an independent risk factor for persistent hypocalcemia, due to hungry bone disease or hypoparathyroidism, and for the reduction of eGFR by 20% 12–36 months after transplantation ($P = .029$) [67].

In other studies, renal function in patients undergoing post-KT parathyroidectomy stabilized after an initial worsening [87, 89]. In patients who underwent post-KT parathyroidectomy [median time from KT 11 months (range 1–167)], serum creatinine increased in the first month post-parathyroidectomy compared with patients transplanted in the same period who did not require parathyroidectomy (1.91 ± 0.72 versus 1.76 ± 0.63 mg/dL, $P < .01$). In the long term, however, renal function stabilized and no differences in graft survival were observed [87]. Similar results were obtained when comparing 102 patients who underwent pre-KT parathyroidectomy with 83 patients who underwent post-KT parathyroidectomy [89].

The reason for the deterioration of graft function is unclear, but a hemodynamic mechanism has been suggested [87]. Thus, PTH induces afferent arteriole vasodilatation and efferent vaso-

constriction. This would result in glomerular hyperfiltration and the sudden removal of PTH may decrease GFR [59]. In this case, however, parathyroidectomy would also be expected to be protective in the long term, as is the case for nephroprotective interventions that decrease glomerular hyperfiltration.

Cinacalcet versus post-KT parathyroidectomy. To our knowledge, only a study compared cinacalcet and parathyroidectomy in KT patients. A 12-month prospective, multicenter, open-label, randomized study compared subtotal parathyroidectomy ($n = 15$) and cinacalcet ($n = 15$) in KT patients with hypercalcemia and HPT. The primary outcome was the normalization of calcium values, achieved in 100% of patients undergoing parathyroidectomy and in 67% of patients treated with cinacalcet ($P = .04$). Secondary outcomes included normalization of PTH values, which was achieved in 10 of 15 patients undergoing parathyroidectomy ($P = .002$) and in none of those receiving cinacalcet. Cinacalcet decreased PTH values, but they remained above the normal range: this was hypothesized to result from an increase in calcitonin with consequent hypocalcemia and persistence of HPT. BMD did not improve in patients treated with cinacalcet but increased in the femoral neck in patients undergoing parathyroidectomy ($P = .01$): BMD improvement was associated with the normalization of PTH and bone turnover marker values and the administration of calcium and vitamin D to avoid hungry bone syndrome. eGFR decreased in both groups and neither treatment decreased vascular calcifications [90]. In a 5-year extension study, parathyroidectomy had a lower risk of recurrence of THPT [91].

In a retrospective study in 92 patients treated with parathyroidectomy or cinacalcet pre-KT, parathyroidectomy resulted in better control of PTH and calcium values after transplantation ($P < .01$), although no statistically significant differences were observed in serum calcium, phosphate and graft and overall survival at 10 years [92].

Safety. In studies that compared cinacalcet and parathyroidectomy, the most frequent side effect of cinacalcet was gastric intolerance, which may have limited dosing and compliance [88]. Complications after parathyroidectomy include surgical wound infection, temporary or permanent recurrent laryngeal nerve palsy and transient or permanent hypocalcemia, the most frequent being transient hypocalcemia related to hungry bone syndrome [93, 94]. Other parathyroidectomy complications include mortality during hospitalization or within 1 month of parathyroidectomy (2%), rehospitalization (24% required), the need for intensive care (29%) and a 39% increase in 1-year hospitalizations, according to United States Renal Data System information on parathyroidectomies performed from 2007 to 2009. The most frequent disorders were hypocalcemia, myocardial infarction and arrhythmias. The number of adverse events varied significantly based on the patient's clinical history [93].

In conclusion, there are no long-term studies on the impact of parathyroidectomy or medical therapy for HPT, especially in kidney failure patients awaiting KT. However, available studies show that parathyroidectomy is more effective in controlling HPT. Pre-KT parathyroidectomy is preferable to decrease the risk of persistent HPT and protect graft outcomes [86].

International guidelines. Table 1 summarizes the main guidelines since 2001 that address or should have addressed parathyroidectomy in KTRs or in patients waitlisted for KT.

Table 1. Main guidelines since 2001 for parathyroidectomy in kidney transplant candidates

Guidelines	Year	Indication	Grade of evidence
The Evaluation of Renal Transplantation Candidates: Clinical Practice Guidelines	2001	Calcium, phosphorous, and PTH should be measured as part of the pretransplant evaluation and should be repeated periodically while patients are on the transplant waiting list.	A
		Parathyroidectomy should be considered for renal transplant candidates who have failed medical management and/or have severe, persistent, complications of hyperparathyroidism (e.g., refractory hypercalcemia, refractory hyperphosphatemia, severe intractable pruritus, serum calcium-phosphorus products that persistently exceed 70–80 mg/dL with progressive extra skeletal calcifications, and calciphylaxis).	B
Kidney Transplant Working Group of the Canadian Society of Transplantation. Canadian Society of Transplantation: Consensus Guidelines on Eligibility for Kidney Transplantation	2005	Calcium, phosphorus and PTH levels should be measured as part of the pretransplant evaluation.	A
		Parathyroidectomy should be considered for those in whom medical management has not worked or those with severe, persistent, complications of hyperparathyroidism.	B
European Renal Best Practice Guideline on Kidney Donor and Recipient Evaluation and Perioperative Care	2015	We recommend not refusing a cadaveric graft only because of uncontrolled hyperparathyroidism in the recipient.	1D
		However, for patients on the waiting list, efforts should be made to comply with existing CKD–metabolic bone disease guidelines, including parathyroidectomy, when indicated.	Ungraded statement
KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation	2020	Measure serum PTH at the time of transplant evaluation.	Not graded
		We suggest not transplanting patients with severe hyperparathyroidism until they are adequately treated (medically or surgically), as per the KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) guideline.	2D
		BMD should not be measured as part of the transplant evaluation.	Not graded

There are no clear guidelines on the indication and timing of parathyroidectomy versus pharmacological treatment, therapeutic targets or primary outcomes [95].

In the 2001 American Society of Transplantation Guideline, serum calcium, phosphate and PTH should be evaluated periodically in patients waitlisted for KT and parathyroidectomy should be considered when medical management fails and/or patients have severe, persistent, complications of HPT [96]. Similarly, the 2005 Canadian Society of Transplantation Consensus Guidelines on eligibility for KT suggested assessing calcium, phosphate and PTH levels as part of pre-KT evaluation (Grade A) and parathyroidectomy for patients not responding to medical therapy or those with severe, persistent, complications of HPT (Grade B) [97].

The 2006 Caring for Australians and New Zealanders with Kidney Impairment guidelines on management of CKD-MBD suggest considering parathyroidectomy for patients in whom cinacalcet does not achieve target levels of calcium, phosphate and PTH (<800 pg/mL) without mentioning patients waitlisted for KT [98]. Instead, more recent 2011 UK Renal As-

sociation and British Transplant Society Guidelines on KTRs give no advice about CKD-MBD and parathyroidectomy during evaluation for KT eligibility [99], as well as 2013 Kidney Health Australia-Caring for Australians and New Zealanders with Kidney Impairment Guidelines [100].

In 2015, the European Renal Best Practice Guideline on kidney donor and recipient evaluation recommends not refusing a cadaveric graft only because of uncontrolled HPT in the recipient (1D). However, it also recommends that for patients on the waiting list, efforts should be made to comply with existing CKD-MBD guidelines, including parathyroidectomy, when indicated (ungraded statement) [101].

The 2017 KDIGO CKD-MBD guidelines advise parathyroidectomy in patients with G3a–G5D with severe HPT who fail to respond to medical or pharmacological therapy (2B) [102]. The UK Renal Association commentary on the KDIGO 2017 CKD-MBD guidelines agrees on the indication of parathyroidectomy but does not mention preparation for KT [103].

Only the 2019 Chinese guidelines for CKD-MBD considered radiological parathyroid gland enlargement as a parameter to be



FIGURE 5: Four-dimensional parathyroid CT scan of a patient with SHPT before parathyroidectomy. The image in the coronal planes shows three hyperplastic parathyroid glands (black arrows).

considered before parathyroidectomy, although no suggestion is made for KTRs despite dealing with transplant bone disease [104].

The 2020 KDIGO clinical practice guidelines on evaluation of candidates for KT contains a chapter dedicated to the preparation of the KT candidate with CKD-MBD. The rationale is that severe HPT needs to be treated before KT, and if medical therapy fails, pre-KT parathyroidectomy is indicated. These new guidelines suggest measuring serum PTH at the time of transplant evaluation and not transplanting patients with severe SHPT until they are adequately treated (medically or surgically) as per the 2017 KDIGO CKD-MBD guidelines (2D) [38]. Nevertheless, in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) US Commentary on the 2020 KDIGO guidelines on evaluation of candidates for KT, there is no comment on management of pre-KT parathyroidectomy [105].

From the analysis of different guidelines emerges the need for new guidelines that clarify the indications for pre-KT parathyroidectomy and its role in the prevention of graft failure and transplant bone disease.

Preoperative imaging

Although the diagnosis of SHPT is biochemical and does not require imaging confirmation, in the era of minimally invasive parathyroid surgery, preoperative detection of pathological parathyroid glands is essential for a targeted surgical approach [106, 107]. Diagnostic imaging techniques routinely used include ultrasound, scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI). No studies have evaluated the newer 4-dimensional CT (4D-CT) [108] (Figure 5).

Ultrasound and scintigraphy are two of the imaging techniques most widely used to locate pathological parathyroid tissue, and they are first-line localization methods [109]. Their diagnostic accuracy is similar or even superior to second-line localization methods like CT or MRI [110–112]. Parathyroid scintigraphy uses technetium (^{99m}Tc) sestamibi (MIBI) as radiopharmaceutical to evaluate enlarged or ectopic parathyroid glands and its combination with CT (SPECT/CT) guarantees more sensitivity in parathyroid evaluation during SHPT [108, 113].

Scintigraphy has greater sensitivity than ultrasound in locating enlarged parathyroid glands, while ultrasound has higher specificity. The combination of scintigraphy and ultrasound allows 95% specificity in the diagnosis of enlarged parathyroid glands. Thus, scintigraphy and ultrasonography are complementary and should be used together [114].

Ultrasound identifies parathyroid tumors and potential concomitant thyroid disease and locates suspected parathyroid glands [115, 116]. In earlier studies, the sensitivity of parathyroid ultrasound ranged from 20 to 79% [117, 118], but in a recent review the sensitivity and positive predictive value (PPV) of ultrasound ranged from 51 to 96% and from 50 to 100%, respectively [119]. In this regard, ultrasound devices keep evolving and providing better quality imaging. Factors that decrease the sensitivity and PPV of ultrasound include concomitant thyroid nodules and multiple parathyroid adenomas or parathyroid hyperplasia.

Parathyroid ultrasound is performed with high-frequency linear transducers (9–15 MHz) and the entire anterior cervical region should be examined. Parathyroid tissue is usually found along the posterior margin of the thyroid lobes or near their lower poles. Normal parathyroid glands are small and isoechoic relative to the thyroid parenchyma and cannot be visualized. The pathological parathyroid tissue (or more simply ‘adenoma’) becomes visible due to its increased size and altered echogenicity. Parathyroid adenomas appear as well-circumscribed, oval masses whose echogenicity is clearly inferior to the adjacent thyroid gland (Figure 6A). Larger parathyroid adenomas sometimes present partially liquid echo structures that reflect areas of cystic involution. Colour Doppler imaging reveals vascular patterns (Figure 6B) that can be helpful for differentiating parathyroid adenomas from enlarged lymph nodes and for identifying parathyroid adenomas within the thyroid gland.

The role of contrast-enhanced ultrasonography (CEUS) prior to surgery in patients with primary HPT is still debated [120, 121]. CEUS for parathyroid adenomas and hyperplasia is characterized by a strong early contrast enhancement beginning 12 s after bolus injection at the margin of parathyroid glands in the arterial phase, a short enhancement of the noncystic parenchyma followed by an early wash out beginning at 50 s (Figure 6C). Sensitivity was \sim 96–97% while specificity and PPV were \sim 98% [121–123].

Conventional ultrasound has low sensitivity in assessing the severity of SHPT because it cannot display the dynamic perfusion characteristics. CEUS could address this deficiency and detect nodular hyperplastic parathyroid glands before SHPT becomes resistant to medical therapy through time–intensity curves that illustrate the dynamic features of tissue vascularization and blood flow (wash-in time, intensity and wash-out time) [124] (Figure 6D).

Ultrasound performed by experts should be sufficient in most cases to discover abnormal parathyroid glands. The high PPV of CEUS is helpful in doubtful cases for the differential diagnosis between multiple findings.

Planning parathyroidectomy in SHPT

Parathyroidectomy is suggested for patients with SHPT refractory to medical therapy [112].

Surgical approaches. There are three surgical approaches: total parathyroidectomy with or without thymectomy, subtotal parathyroidectomy (3/4 glands or 7/8 glands), and total parathyroidectomy with heterotopic autotransplantation [89, 125].

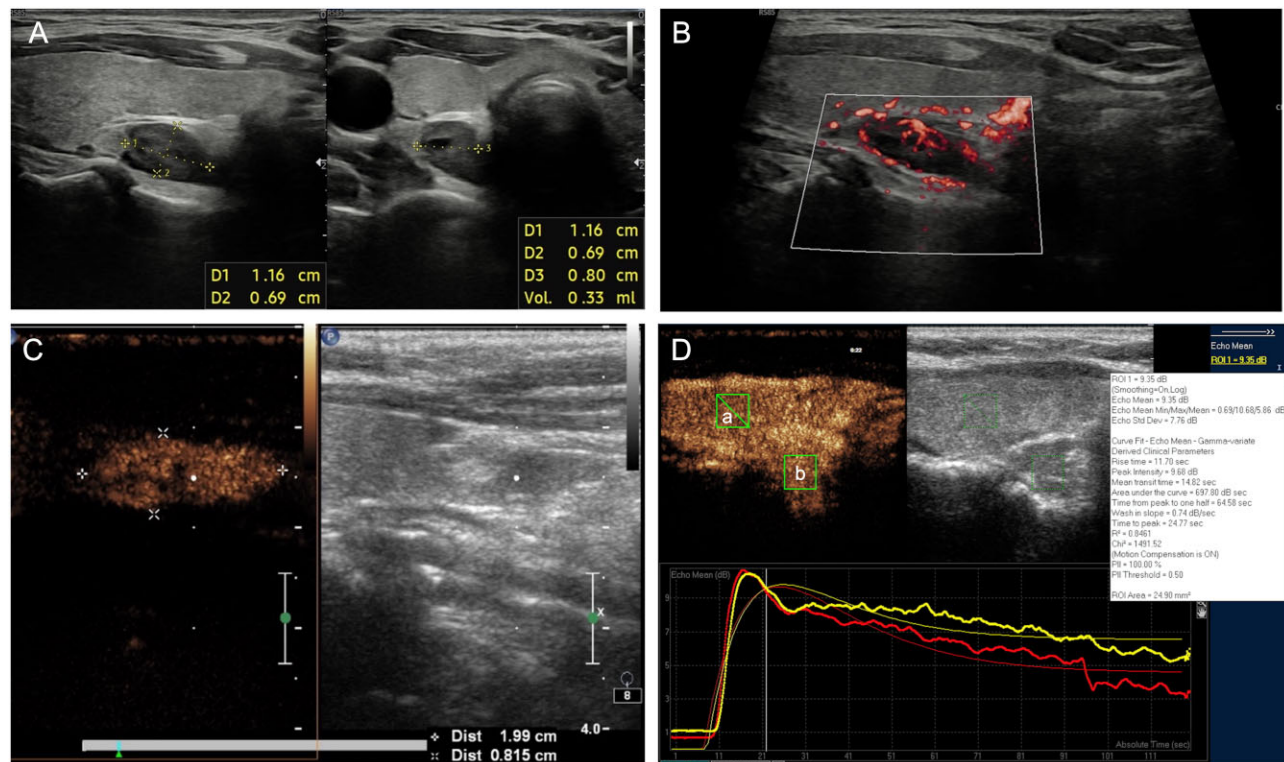


FIGURE 6: (A) Ultrasound of the neck showing inferior parathyroid adenomas (roughly 1.16×0.69 cm) located behind the thyroid. The parathyroid adenoma appears as a well-circumscribed, oval mass, hypoechoic in comparison to the adjacent thyroid gland. Longitudinal (left) and transverse (right) scans. (B) An inferior parathyroid adenoma located behind the thyroid with color Doppler imaging (longitudinal scan). (C) Longitudinal scan demonstrating an inferior parathyroid adenoma located near the inferior pole of the thyroid lobe (left). The CEUS examination is characterized by a strong early contrast enhancement in the arterial phase beginning 15 s after the bolus injection (right). (D) CEUS time-intensity curves: the wash-in (arterial phase in the figure, 0–30 s after application of contrast agent) and wash out (venous phase, 30–120 s) of the adenomas (a), represented in the graph by the red line, compared with the thyroid gland (b), represented by the yellow line.

Usually, in SHPT, all four glands are enlarged and total parathyroidectomy decreases the risk of relapse, but increases the risk of permanent hypocalcemia and hungry bone syndrome [108]. Thus, to balance the risks of persistent or recurrent disease versus permanent hypoparathyroidism with hypocalcemia, most centers have opted in recent years for subtotal parathyroidectomy or total parathyroidectomy + autotransplantation to preserve mineral homeostasis by leaving a small residue of parathyroid tissue [23].

There is no consensus on the indications for total versus subtotal parathyroidectomy, and on the amount of remnant parathyroid tissue in subtotal parathyroidectomy. In 34 consecutive kidney failure patients with SHPT, 3/4 subtotal parathyroidectomy seemed effective and safer than 7/8 subtotal parathyroidectomy, as assessed by lower rates of irreversible hypoparathyroidism and shorter hospital stays [126]. The prevalence variability between parathyroidectomy and subtotal parathyroidectomy reflects, in part, different approaches in dialysis practices [127, 128].

Postoperative morbidity and mortality do not differ significantly between total parathyroidectomy + autotransplantation and subtotal parathyroidectomy [129]. However, reoperations for recurrent HPT after subtotal parathyroidectomy entail more potential complications given the need of a neck reexploration under general anesthesia, whereas after total parathyroidectomy + autotransplantation, patients with parathyroid graft-dependent recurrent disease undergo resection of the autograft under local anesthesia only [129].

Parathyroid gland autotransplantation. There are different protocols for parathyroid gland autotransplantation. Usually the parathyroid tissue is fragmented and then autotransplanted by injection into the arm. However, since autotransplanted parathyroid tissue will not be functional until it has an adequate blood supply by neovascularization, some surgeons mobilize a portion of one parathyroid gland and place the tissue anteriorly, superficial to the strap muscles. The blood supply in this case is guaranteed and the gland is easily accessed in case of reoperation by placing a surgical clip easily identified on X-ray [130].

Autotransplantation may be immediate or delayed. Immediate autotransplantation allows for maintenance of PTH levels following parathyroidectomy. However, not all patients will develop hypoparathyroidism. This implies that some patients will undergo unnecessary autotransplantation with the risk of persistent HPT. The alternative is parathyroid cryopreservation [131]. Cryopreservation preserves cellular function (up to 5 years) and allows the storage of parathyroid tissue for potential reimplantation in patients who develop hypoparathyroidism [132].

Assessing effectiveness. The effectiveness of parathyroidectomy is usually determined by a rapid decrease in PTH values, although there is no clear numerical definition. Rapid intraoperative PTH (ioPTH) testing can guide an adequate resection of parathyroid tissue [133]. A reduction of 60–70% of the pre-excision ioPTH value 10–30 minutes after excision was strongly

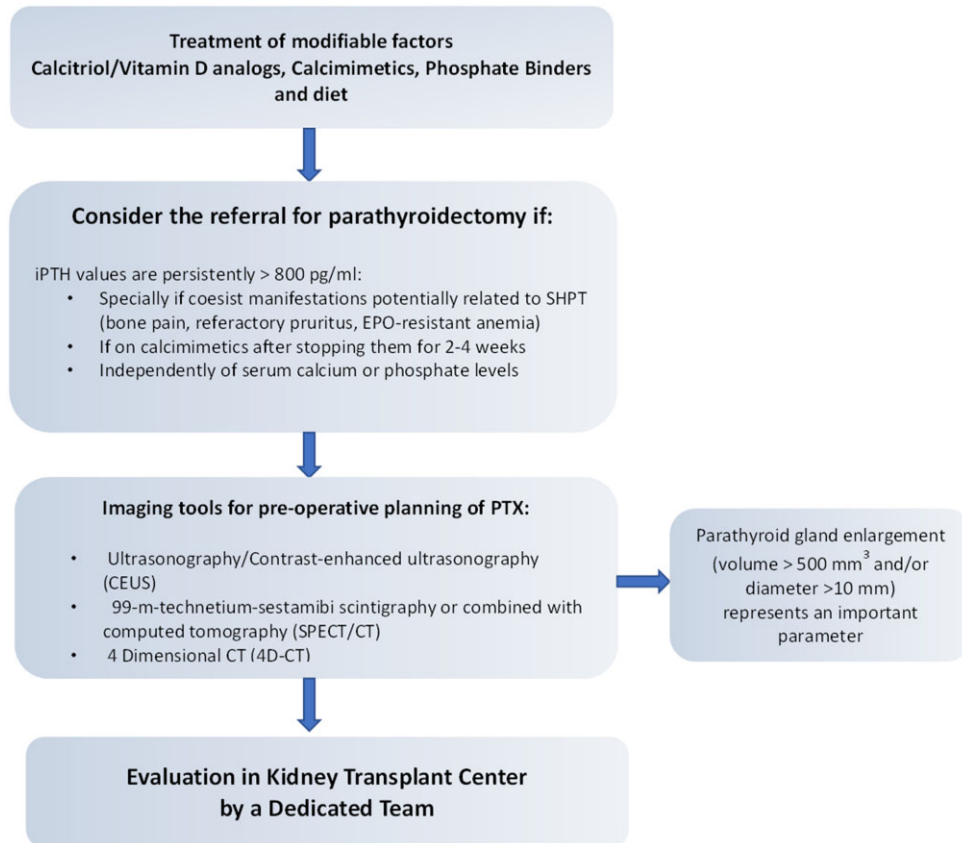


FIGURE 7: Roadmap to parathyroidectomy for kidney failure patients with SHPT candidates to KT. The first step to reduce the risk of persistent HPT in KT candidates is the correction of modifiable factors: hypocalcemia, hyperphosphatemia, hyperparathyroidism (PTH target values 2–9 times the upper limit of normal in dialysis patients). If PTH levels are >800 pg/mL with or without hypercalcemia and/or hyperphosphatemia and symptoms or complications coexist related to SPHT, referral for parathyroidectomy should be considered. Imaging is necessary for preoperative parathyroidectomy planning, aimed to localize and define the size of parathyroid glands. Enlarged parathyroid glands (volume > 500 mm³ and/or diameter >10 mm) represent a further parameter, in addition to high PTH levels, in the decision-making regarding parathyroidectomy. In our centers, a multidisciplinary team (nephrologists, otolaryngologists, radiologists) decides on the indication of parathyroidectomy based on preoperative findings. In all cases, CEUS is performed a few days before surgery by an expert and dedicated sonographer in the presence of the nephrologist and surgeon to verify helpful landmarks (skin, vascular axis, trachea, esophagus, upper and lower thyroid poles) for surgery. EPO, erythropoietin; 4D-CT, 4-dimensional computed tomography.

correlated with resolution of HPT, while the Miami criteria (50% reduction in PTH compared with the highest pre-excision value 10 min after excision) were not predictive [108]. However, the ioPTH value after excision does not predict the risk of postoperative hypoparathyroidism. Severe hypoparathyroidism and hypocalcemia have been observed even if patients have a PTH >2-fold above the upper limit of normal 15–20 min after excision [108, 134].

A roadmap for parathyroidectomy in patients waitlisted for KT: why not?

After successful KT, some CKD-MBD indexes [calcium, phosphate, 1,25(OH)₂D] normalize or improve in most KTRs, although persistently high levels of PTH and FGF-23 can worsen bone and mineral homeostasis and negatively impact graft and patient outcomes. Once graft function has recovered, parathyroid gland hyperplasia and SHPT improve over 6–12 months, thus most nephrologists consider it safe to wait 12 months post-KT before considering parathyroidectomy. However, SHPT may not completely resolve in ~70% and 40% of KTRs within the first and second years posttransplantation, respectively [27].

The KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation suggests not transplanting patients with severe HPT until they are adequately treated (medically or surgically) as per the KDIGO CKD-MBD guidelines [38]. Indeed, patients who fail to respond to medical therapy or have severe, persistent complications of HPT [38] should undergo parathyroidectomy before transplantation. Beyond the generic indications of the KDIGO guidelines, there is no agreement on the definition of adequacy of SHPT control in patients waitlisted for KT. Indeed, the KDIGO transplantation guidelines identify the need for studies addressing the association between pre-KT PTH levels and clinically important post-transplant outcomes [35].

Indications of pre-KT parathyroidectomy. Persistent HPT is usually associated with pre-KT PTH levels above the target of KDOQI guidelines (PTH >300 pg/mL, which is well below the KDIGO target), the use of calcimimetics while on dialysis and the presence of enlarged parathyroid glands [32, 36, 40–42]. We propose that pre-KT parathyroidectomy should be preferred in KT candidates to prevent persistent HPT and to protect graft function. In KT candidates, similar to patients with stage 5D CKD,

parathyroidectomy should be considered when PTH levels are >800 pg/mL for >6 months despite maximized medical therapy, especially if associated with persistent hypercalcemia or hyperphosphatemia, tissue or vascular calcification including calciphylaxis and/or worsening osteodystrophy.

Timing of pre-KT PTH assessment. While calcimimetics reduce PTH, they also lower serum calcium and thus can mask THPT. There is debate as to how to measure PTH in patients waitlisted for KT. Coyne and Delos Santos [135] suggest that calcimimetics should be stopped for 2–4 weeks before measuring PTH in KT candidates as part of the assessment for transplantation. If the PTH is >800 pg/mL, the patient's risk of persistent HPT appears to be high. A cut-off for PTH of 1000 pg/mL without calcimimetic use or 500 pg/mL with calcimimetic use has also been proposed: higher values would suggest enlarged parathyroid glands, making improvement post-KT unlikely and, thus, making pre-KT parathyroidectomy preferable [37].

Parathyroid gland size. In our opinion, pre-KT determination of PTH levels is not the optimal tool for decision-making about parathyroidectomy for KT candidates, as parathyroid gland size can not be assessed. Enlarged parathyroid glands (volume ≥ 500 mm³ or diameter ≥ 10 mm) frequently present nodular hyperplastic lesions that are unlikely to regress.

Assessment of parathyroid gland size requires imaging tools that additionally inform of parathyroid gland localization, which is especially relevant for ectopic glands. Imaging tools include ultrasound and scintigraphy, often combined with CT (i.e. SPECT/CT) [108]. CEUS allows estimation of parathyroid gland size and a differential diagnosis through the interpretation of dynamic microvascular features.

Multidisciplinary teams. Given the high expertise required from each specialist involved, it is desirable to create multidisciplinary teams composed of nephrologists, radiologists and surgeons for the optimal management of pretransplant SHPT in KT candidates, as well as of persistent/tertiary HPT in KTRs.

A roadmap for parathyroidectomy in patients waitlisted for KT. We refer for parathyroidectomy (preferably subtotal parathyroidectomy) candidates for KT with PTH >800 pg/mL despite maximal therapy with calcitriol/vitamin D analogs and calcimimetics or after stopping calcimimetics for 2–4 weeks. Both these conditions have to be associated with enlarged parathyroid glands (diameter >10 mm), independent from the presence or absence of hypercalcemia or hyperphosphatemia (Figure 7). A further item in the decision-making process by a multidisciplinary team is the number of prior KTs. Thus patients waitlisted for a second or more KT are usually burdened by longer-lasting CKD and dialysis vintage and may be highly sensitized with multiple preformed anti-human leukocyte antigen antibodies and therefore may also remain longer on the waitlist compared with unsensitized transplant candidates, in particular those with a greater number of HLA mismatches in prior grafts [136].

CONFLICT OF INTEREST STATEMENT

M.C. is a member of the CKJ editorial board.

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