Review

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Timing of parathyroidectomy for kidney transplant patients with secondary hyperparathyroidism: A practical overview

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SUMMARY Kidney transplantation remains the best treatment for patients with end-stage kidney disease, and it could partially mitigate systemic disorders of mineral and bone metabolism caused by secondary hyperparathyroidism. However, persistent hyperparathyroidism is still observed in 30-60% of patients 1 year after kidney transplantation, leading to impairment of allograft function and a disturbance of mineral metabolism. The timing of parathyroidectomy varies among transplant centers because the possible negative effects of parathyroidectomy on allograft outcomes are still unclear. This review provides a comprehensive and detailed overview of the natural course of hyperparathyroidism following kidney transplantation and the effects of the timing and extent of parathyroidectomy on allograft function. It aims to provide useful information for surgeons to propose an appropriate intervention strategy to break the vicious cycle of post-kidney transplantation hyperparathyroidism and deterioration of allograft function.

Keywords persistent hyperparathyroidism, allograft function, hemodynamic fluctuation, nephrocalcinosis

1. Introduction

As a common and formidable complication in end-stage renal disease (ESRD), chronic kidney disease-mineral and bone disorder (CKD-MBD) is initially stimulated by phosphorus retention, combined with a low calcium level, and abnormalities in 1.25-hydroxyvitamin D synthesis, together with a progressive increase in parathyroid hormone (PTH), which eventually results in secondary hyperparathyroidism (SHPT) (*1,2*). SHPT is likely to develop to an advanced stage that is resistant to medical treatment such as drug therapy, dialysis, and diet. Untreated or treatment-resistant SHPT results in serious complications such as kidney stones, osteoporosis, vascular calcification, and pathological fractures (*3-5*), affecting the quality of life in most patients with ESRD (*5,6*).

Kidney transplantation (KT) remains the best treatment for patients with ESRD (*7*). By restoring renal function, successful KT is thought to ameliorate the endocrinal and metabolic effects of SHPT and at least partially mitigate systemic disorders of mineral and bone metabolism, thus improving quality of life and increasing patient survival (*5,7-9*). However, in the early post-transplant period, persistence of preexisting hyperparathyroidism and related biochemical alterations are still observed in some patients. Hyperparathyroidism after KT may influence changes in allograft function and further disturb mineral metabolism (*4,7*), which leads to a vicious cycle involving the persistence of post-transplant hyperparathyroidism and impairment of allograft function. Two concerns regarding the management of hyperparathyroidism in kidney transplant recipients have been raised: (*i*) Which strategy is feasible and acceptable? To prevent potential persistent hyperparathyroidism (PHPT) in a KT candidate, or to treat a definite PHPT in a kidney transplant recipient? and (*ii*) If treatment of PHPT is ensured, what is the appropriate timing for surgery? Early or late?

The current review includes recent findings and it discusses the effects of the timing and extent of parathyroidectomy on allograft function.

2. Natural course of hyperparathyroidism following KT and prevalence of post-transplant PHPT

The preexisting mineral imbalances that lead to SHPT are usually normalized within several days to several weeks after KT (*7*), but changes in serum PTH levels usually take several months to manifest. Recent retrospective studies (*10,11*) have described the long-term natural history of SHPT after KT. The PTH level dropped significantly during the first 3 months post-transplant and decreased gradually throughout the

year, typically stabilizing thereafter. The development of hyperparathyroidism was determined based on the pre-transplant PTH level and the renal function at each checkpoint during follow-up. This indicated that remission of hyperparathyroidism following KT depended on the restoration of renal function. A decrease in the PTH level by 33% in the first 6 months of the first year after transplantation and by 57% in the second half indicated that the restoration of renal function might accelerate the remission of hyperparathyroidism (*10*). Studies have noted a significant correlation between PTH and the estimated glomerular filtration rate (eGFR) (*12,13*). With the restoration of a more normal eGFR, SHPT might resolve in mild cases or remain stable until the end of the first year post-transplant (*11,14*). Even with adequate allograft function, PHPT is still observed in 30-60% of kidney transplant recipients 1 year after KT and in 20% of patients even at 5 years (*4,14,15*). The direct and most prominent impact of PHPT is on the serum calcium level (*12,14*). Although the serum calcium level normalizes a few days after KT, hypercalcemia may develop as soon as 1 week after transplantation (*7,14*). Hypercalcemia is closely associated with PHPT in the majority of cases and is usually considered to be an indicator of PHPT, with a incidence between 10% and 30% (*9,14,15*). This variability in incidence may be attributable to various factors such as the use of different serum calcium levels for diagnosis, evaluation of the ionized or total calcium level, regardless of whether the calcium levels are corrected based on albumin, and the timing of diagnosis (*15*). A point worth noting is that the prevalence of hypercalcemia may decrease over time, but 5-10% of patients continue to have persistently high serum calcium levels over the long term (*7*).

3. Post-KT PHPT and its clinical significance

Like hypercalcemia, the divergence in the prevalence of post-KT PHPT also reflects the fact that the diagnostic cut-offs and evaluation time-points are inconsistent (*9,14,16-22*). In many studies, post-KT PHPT was referred to as tertiary hyperparathyroidism (THPT). There is a lack of a consensus regarding the exact definition for THPT. "THPT" refers to an advanced stage – and especially autonomous secretion of PTH – but does not necessarily define hyperparathyroidism as that occurring only after KT. Concomitant hypercalcemia is an indispensable criterion for THPT but not for PHPT. KT itself is just like a screening procedure, eliminating all of the hyperplastic parathyroid tissue that might return with re-established calcium-phosphate homeostasis, leaving only autonomous tissue that does not respond to feedback (*11*). Different percentages of THPT components remain in PHPT parathyroid glands at different time-points post-transplant (*22*). Even with small parathyroid glands, nodular hyperplasia might still be very severe (*20,22,23*). Therefore, THPT is considered a subset of PHPT post-KT (*22*), and the term PHPT has been used in a review of the relevant literature throughout this paper.

PHPT endangers both patient and allograft survival. First, PHPT is also associated with increased mortality, cardiovascular complications, fractures, and decreased quality of life (*11*). In a multivariate analysis comparing kidney transplant recipients with serum PTH>65 pg/mL to those with normal or low levels, an increase of 46% for all-cause death was noted (*24*). Second, with respect to specific concern about allograft survival, PHPT contributes to deterioration of allograft function. A longitudinal study of 911 kidney transplant recipients with a mean follow-up time of 47 months reported that the rate of allograft failure (defined as a return to dialysis) was 49/538 in the PHPT group *vs*. 10/343 in the non-PHPT group, and death-censored allograft survival was lower in the PHPT group (*19*). Another analysis of 1,609 kidney transplant recipients found that PHPT was independently associated with delayed allograft function and worse allograft survival (*5*). PHPT and hypercalcemia have a close causal relationship and both affect three aspects of allograft function: (*i*) PHPT and hypercalcemia promote nephrocalcinosis, which is characterized by tubular and interstitial deposits of calcium in the form of calcium oxalate or calcium phosphate. As the duration and severity of hypercalcemia increases, the extent of tubulointerstitial calcification increases, which may contribute to allograft dysfunction over the long term, and especially when the calcium level rises rapidly (*14,15*). (*ii*) Hypercalcemia promotes vascular calcification. PHPT-related hypercalcemia is associated with the development of vascular calcification, which then stiffens the vasculature and impairs arterial distensibility, thereby compromising perfusion of the allograft. Because vasculature supplying the allograft may also be involved, the possibility of allograft failure increases (*24,25*). Severe hypercalcemia can also cause acute injury of the allograft due to low perfusion by direct vasoconstriction (*14*). (*iii*) PHPT leads to hyperfiltration injury. The hemodynamic effect of PTH seems to significantly vasodilate preglomerular vessels while constricting efferent arterioles at the same time, resulting in hyperfiltration and consequent progressive deterioration of renal function.

4. To prevent PHPT in KT candidates, is pre-transplant parathyroidectomy an appropriate or excessive treatment?

There is a wide divergence of clinical practice and a lack of consensus in the area of surgical management of KT candidates with hyperparathyroidism (*4,26*). In a survey conducted in the United States in 2018, questions about the use of parathyroid surgical procedures to prepare patients for KT indicated that more than two-thirds of respondents did not consider a PTH level > 800 pg/mL as

an absolute or relative contraindication for transplantation (*26*). Approximately 66% of respondents answered that they occasionally recommended parathyroidectomy for SHPT prior to KT, and only 5% answered that they always recommended it in the context of SHPT. Sixty-three percent indicated that < 10% of their KT candidates underwent pre-transplant parathyroidectomy at their facilities. Sixty-six percent recommended post-transplant parathyroidectomy based on persistent, unsatisfactory PTH levels post-transplant.

4.1. Pre-transplant parathyroidectomy might be superior to post-transplant parathyroidectomy in terms of ensuring allograft function

Whether the parathyroidectomy is performed before or after KT, a sustained decrease in PTH and calcium levels was consistently achieved (*18,27,28,29-31*). However, the altered mineral metabolism and endocrine function associated with pre-KT parathyroidectomy might be more conducive to allograft survival compared to that associated with untreated SHPT. This could explain why pre-KT parathyroidectomy was considered to be superior to post-KT parathyroidectomy in terms of ensuring allograft function according to several comparative studies (*11,25,27,28,32,33*). First, the degree of metabolic and endocrine disturbances that an allograft is subjected to is more severe in patients not undergoing pre-KT parathyroidectomy than in those undergoing that procedure. Almost all of the studies noted that the pre-KT PTH level (the post-parathyroidectomy PTH level in the pre-transplant group roughly compared to the pre-parathyroidectomy level in the post-transplant group) and the prevalence of hypercalcemia, which were both risk factors contributing to worsening allograft function, were significantly higher in the post-transplant groups (*18,27,28*). This likely indicates that patients undergoing post-transplant parathyroidectomy usually have severe PHPT and impaired allograft function should be promptly remedied. Second, post-KT parathyroidectomy results in additional and drastic hemodynamic fluctuation in the allograft, related mainly to an abrupt reduction in PTH. Given that PTH has important preglomerular vasodilatory action as well as efferent vasoconstrictive action, a steep decline in PTH action on the renovascular system could lead to perivascular ischemia and cause irreversible interstitial tubule cell damage. In a study by Jeon *et al*., patients with impairment of > 25% 1 month after transplantation had a significantly lower baseline eGFR and significantly greater changes in the PTH level after parathyroidectomy (*27*). Third, the incidence of interstitial calcium deposition was significantly higher in the post-KT group than in the pre-KT group (*31*). This progressive nephrocalcinosis likely correlates with a high risk of reduced allograft function (*11,34*). The potential cause of further deterioration of allograft function after parathyroidectomy and whether parathyroidectomy halts the progress of interstitial calcification need to be examined further; information from a kidney biopsy might help in the differential diagnosis of allograft dysfunction after parathyroidectomy (*27*).

4.2. There are doubts about the need for pre-transplant parathyroidectomy to preclude the regression of mild or moderate SHPT in transplant candidates

In the literature, few KT candidates have undergone a parathyroidectomy (*22,25*). There are 3 doubts about the necessity for pre-transplant parathyroidectomy in transplant candidates:

1) *Spontaneous regression of SHPT after successful KT*: Clinical studies comparing the effect of pre- or post-transplant parathyroidectomy on allograft function have yielded inconsistent results. Should PHPT be prevented before KT or be treated after KT? Some authors believe that because SHPT can regress in up to 57% of patients with correction of mineral homeostasis after successful KT, spontaneous resolution may be expected in some patients (*5,16*), so parathyroidectomy can be postponed for some candidates (*30*).

2) *The alternative role of calcimimetics in the treatment of SHPT*: Since their approval for clinical use in 2004, calcimimetics have gained wide acceptance at both efficaciously and safely ameliorating SHPT, and the rate of prescription has increased over the years (*35*). Calcimimetics both contribute to normalization of PTH and calcium levels and also eliminate the complications of parathyroidectomy. The use of calcimimetics provides an opportunity for surgeons to decide whether to perform post-transplant parathyroidectomy based on the impact of successful KT on parathyroid function.

3) *Unpredictable changes in parathyroid function after pre-transplant parathyroidectomy*: The serum level of PTH is one of the most important indices with which to evaluate patients with hyperparathyroidism, but it is still the most difficult index to control by parathyroidectomy. The rate of hypoparathyroidism following surgical intervention in SHPT varied between 16.6% and 18.1% (*36*). Low levels of PTH before KT were associated with an increased risk of post-KT vascular events (*37*). Marked hypoparathyroidism and hypocalcemia related to pre-KT parathyroidectomy might also lead to slow allograft function, and suboptimal allograft function is significantly related to the diffuse hypoperfusion of the glomeruli (*38*). Conversely, the risk of hyperparathyroidism recurrence is always present if renal disease is not fully cured. A study reported that hyperparathyroidism recurred after subtotal parathyroidectomy in one-third of patients on chronic hemodialysis at the end of a 10-year follow-up (*39*). If hyperparathyroidism recurs and persists after KT, PHPT and hypercalcemia are confirmed risk factors for poor allograft outcomes (*15,40,41*). Thus, a trade-off between the possible benefit and this potential risk of

parathyroidectomy has to be evaluated in KT candidates.

Therefore, the relatively low proportion of patients who undergo pre-transplant parathyroidectomy could be partially explained by two reasons: (*i*) its necessity in light of the potential effect of KT on the regression of SHPT and (*ii*) its curative effect regarding unpredictable changes in mineral metabolism and parathyroid function.

4.3. The risk factors for development of PHPT should be evaluated before pre-transplant parathyroidectomy

Okada *et al*. (*31*) suggested the superiority of pre-transplant parathyroidectomy over post-transplant parathyroidectomy in terms of stabilizing post-KT PTH levels within the normal range and preserving renal allograft function. This means that the main significance of pre-transplant parathyroidectomy is to cure SHPT and to prevent post-KT PHPT, thereby allowing KT candidates to avoid post-transplant parathyroidectomy. Therefore, KT candidates with risk factors for PHPT are eligible for pre-transplant parathyroidectomy. The risk factors for development of PHPT that should be evaluated before surgery include a high pre-KT PTH level, a long history of dialysis, and treatment with calcimimetics. Patients with pre-KT PTH levels of 300-599 pg/mL are likely to develop PHPT, and the higher the preoperative level, the more possibility PHPT developing (*22*). In addition, a dialysis vintage > 6 years is a strong predictor of PHPT (*21,42*). The parathyroid mass grows gradually and progresses over time in patients undergoing longterm dialysis, indicating a high possibility of parathyroid gland autonomy (*42*). Tominaga *et al*. (*43*) reported that in SHPT patients on dialysis, an enlarged parathyroid gland weighing > 500 mg had a > 90% probability of containing nodular hyperplastic tissue, whereas a gland weighing < 150 mg mostly had diffuse hyperplastic tissue. Paradoxically, usage of calcimimetics was also cited as a risk factor. Some studies have reported a "rebound" effect on PTH because of the cessation of calcimimetics at the time of KT, leading to subsequent hyperparathyroidism and hypercalcemia (*8,21,22*). The deceptive action of calcimimetics blurred the true status of SHPT, thereby further hampering evaluation of the PHPT risk before KT. Once severe hyperparathyroidism is diagnosed, post-KT parathyroidectomy is the only option to treat that condition.

5. To cure PHPT in kidney transplant recipients, should post-transplant parathyroidectomy be performed early or late?

SHPT was not cured in all patients with KT, and PHPT was observed in 10-66% of patients 1 year after transplantation despite improvement in renal function (*16,19,44*). In a study by Lou *et al*. (*5*) with a more contemporary cohort with 1,609 cases, KT cured hyperparathyroidism in only 30.3% of cases at 1 year and 56.9% of cases at 2 years. PHPT has negative effects on allograft survival and can only be cured by surgical intervention. The current indications for post-KT parathyroidectomy include THPT, enlarged (> 500mg) parathyroids on imaging, persistent hypercalcemia, rapidly worsening vascular calcification, unexplained deterioration of allograft function, and progressive loss of bone mineral density (*27,44,45*). Although parathyroidectomy is intended to correct PHPT as well as hypercalcemia and to reverse the progression of allograft impairment, it is a double-edged sword in terms of its effect on allograft function. In most studies, parathyroidectomy preformed within 12 months after KT was classified as "early parathyroidectomy;" otherwise, it was classified as "late parathyroidectomy" (*18,28,30*). In addition, there is also debate over the impact of early versus late parathyroidectomy after KT on allograft function. The current guidelines and practice for PHPT recommend close observation, frequent monitoring, and waiting until 12 months after transplant prior to considering parathyroidectomy (*11*). How does post-transplant parathyroidectomy effect allograft function, and is late parathyroidectomy superior to early parathyroidectomy as current practices recommend?

5.1. The negative effect of post-transplant parathyroidectomy on allograft function is mainly by transient impairment and rarely by permanent deterioration

Several studies have reported that allograft function declined significantly 1-3 months after parathyroidectomy, it gradually recovered, and then it finally improved to the baseline level 12-15 months after parathyroidectomy (*3,16*). Long-term outcomes were comparable to those in patients who did not undergo parathyroidectomy, and permanent graft dysfunction was rare (*6,8,10,45*). Patecki *et al*.(*45*) reported that the median annual change in the eGFR between KT and parathyroidectomy was -0.5 mL/min, and then a significant drop of 25% in the eGFR was observed. In the interval between parathyroidectomy and 3 years later, a stable annual increase in the eGFR of 1.0 mL/min reflected improvement or recovery of renal function after the correction of hyperparathyroidism. A multicenter retrospective study including 185 patients compared the eGFR 5 years after transplantation in pre- and post-transplant parathyroidectomy groups, and it noted no differences in allograft function regardless of the timing of parathyroidectomy. Even though the post-transplant group had a > 25% decrease in the eGFR 3 months after parathyroidectomy, eGFR gradually recovered to the level in the pre-transplant group 1 year post-parathyroidectomy (*30*). In another multi-center study including 100 patients, acute deterioration of renal function was alleviated and stabilized 1 week after

parathyroidectomy in most patients; however, persistent impairment of renal function was noted in around 20% of patients. There were no significant differences in the eGFR in the pre- and post-transplant groups from 1 month to 5 years after transplantation (*27*). The decrease in the eGFR post-parathyroidectomy was associated with abnormalities of hemodynamics induced by parathyroidectomy-related hypoparathyroidism, and the decline might be transient. Therefore, post-transplant parathyroidectomy is necessary when PHPT impairs graft function, even though a transient decline in the eGFR may occur.

5.2. Late post-transplant parathyroidectomy provides a reasonable timeframe to allow spontaneous regression of hyperparathyroidism but it delays alleviation of allograft impairment due to PHPT

A marked decrease in the PTH level usually indicates the success of parathyroidectomy, but it is a significant predictor of allograft dysfunction (*40*). A decline in the PTH level of more than 80% is followed by a significant drop in creatinine clearance (*9,46*). In the initial phase after KT, PTH may be a driving force for glomerular filtration, simultaneously vasodilating preglomerular vessels and constricting efferent arterioles (*13*). A decline in PTH results in a reverse of glomerular hyperfiltration and reduced renal perfusion. This early hemodynamic injury induced by a low PTH after early post-transplant parathyroidectomy is certainly the main cause for early deterioration of renal function (*46*). Littbarski *et al*.(*28*) reported that parathyroidectomy within the first year post-transplant was more closely associated with compromised allograft function compared to pre-transplant parathyroidectomy, whereas late post-transplant parathyroidectomy was not. Late post-transplant parathyroidectomy allowed hyperparathyroidism to spontaneously regress in a considerable proportion of KT patients within a reasonable timeframe. A drastic hemodynamic fluctuation in the allograft due to post-transplant parathyroidectomy may be avoided in these patients.

However, in patients who required a post-transplant parathyroidectomy, PHPT is present at the time of transplantation and abnormal mineral metabolism may persist for several years. Chronic exposure to high PTH and calcium levels in patients with allograft calcification can facilitate further tubulointerstitial calcification and allograft impairment (*15,47*). Parathyroidectomy should be performed before PHPT progresses to an advanced stage (*20,45*). Research has indicated that achievement of a normal PTH level has a positive impact on overall allograft survival. Patients whose PTH levels normalized within 12 months displayed improved overall allograft survival compared to those whose levels normalized after 12 months (*5*). Normalization of calcium levels may contribute to regression of calcification in some patients (*15,41*). Therefore, the earlier an intervention is implemented, the better the prognosis with respect to the deteriorative role of PHPT and hypercalcemia (*47*).

5.3. Relatively limited parathyroidectomy (subtotal parathyroidectomy) is a procedure with proven effectiveness and safety in the early post-transplant period

Before considering a parathyroidectomy in the early period post-transplant, an important issue is to identify and treat patients who are prone to developing severe, non-resolving post-transplant hyperparathyroidism. A PTH level ≥ 150 pg/ml at 3 months post-transplant was found to be an independent predictor for allograft loss, decreased overall survival, and death with a functioning allograft during the period studied (*41*). In patients with severe hyperparathyroidism early after transplantation, the current guidelines consider severe hypercalcemia (serum calcium > 2.87 mmol/L) to be a strong indication for early parathyroidectomy (*48*). Limited parathyroidectomy might offer less possibility of a significant change in PTH (*7*) and lower the risk of hypoparathyroidism (*49*), thus having a positive effect on the rapid return of the eGFR to preoperative levels (*34,50*). Moreover, intraoperative PTH (ioPTH) monitoring provides a more precise profile of the PTH level (*51*). Von Beek *et al*.(*52*) found that there was a strong correlation between ioPTH and early postoperative PTH levels, indicating that ioPTH was a potentially useful index for predicting surgical effectiveness. In patients with functioning allografts, ioPTH levels 10 min and 20 min after resection of the parathyroid glands were equivalent to 2.6 times and 2.3 times the post-operative PTH levels, respectively, and were considered to possibly fall within the expected target range (*52*). With accurate monitoring, an acute decline in renal function after parathyroidectomy can be avoided and a stable renal function can be achieved throughout the 1-year follow-up (*51*).

The current issues on this topic are summarized in Figure 1. To prevent or to treat, that is the question. There is uncertainty about the necessity of surgery to prevent potential PHPT. When treating definite PHPT, there is a risk of endangering allograft function due to either a delayed surgical intervention or surgery with an abrupt drop in the PTH level.

The indications for surgical treatment of SHPT have been well-defined. Based on the current authors' own experience, parathyroidectomy should be performed, if indicated, to alleviate CKD-MBD-related symptoms, regardless of whether patients are KT candidates or not. A pre-KT parathyroidectomy would not affect the timetable for a planned KT but it would create relatively favorable conditions for a future allograft. The only additional consideration is the amount of residual parathyroid tissue. A subtotal parathyroidectomy or a

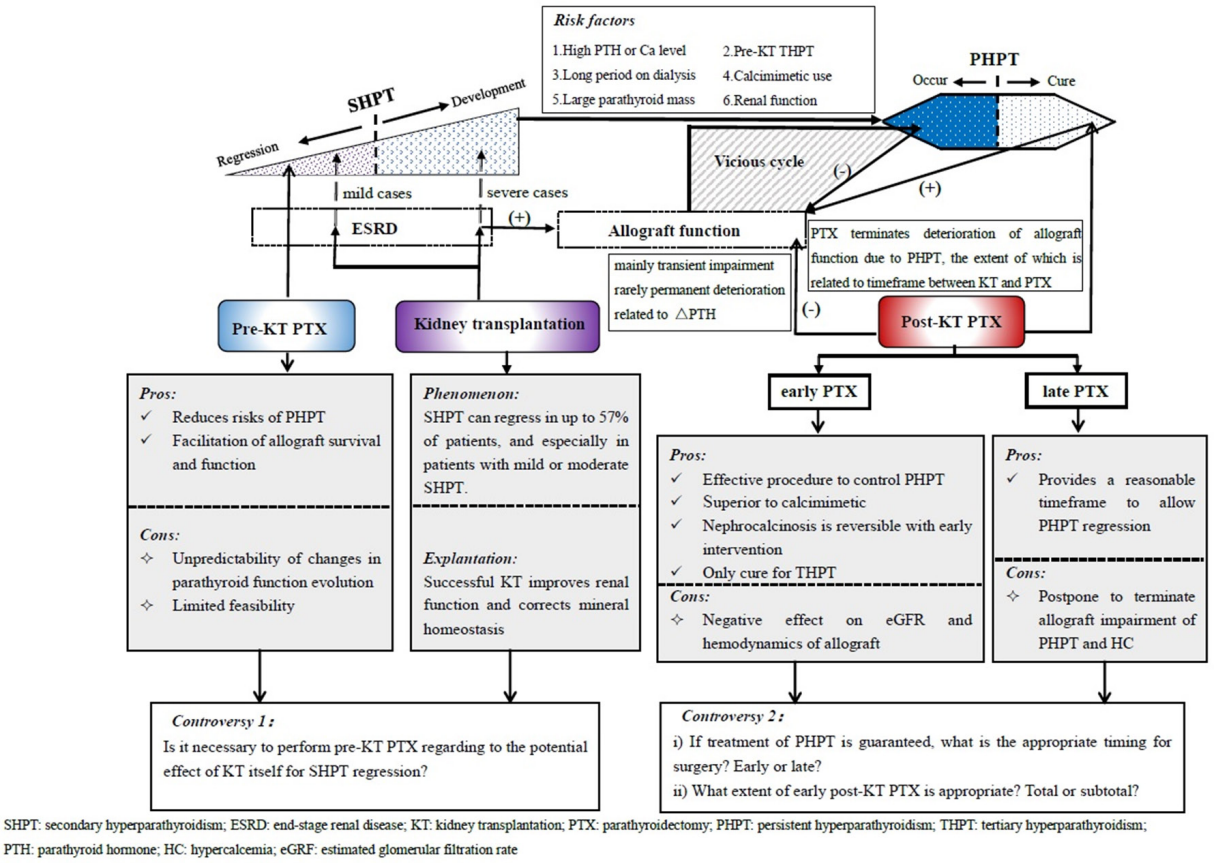

Figure 1. Flowchart showing current controversies pertaining to the timing of parathyroidectomy for kidney transplant patients with secondary hyperthyroidism.

total parathyroidectomy with auto-transplantation is a rational choice.

An "early" and "limited" surgical intervention is recommended for the treatment of PHPT. Several clinical indexes are feasible at predicting and confirming PHPT in the first six months post-KT; further observation has less value in confirming the diagnosis of PHPT and it has many adverse effects on allograft function. Thus, breaking this vicious cycle as soon as possible has clinical significance. A limited parathyroidectomy can reduce the negative impact of surgery on allograft function with a relatively mild change in the PTH level. Therefore, subtotal parathyroidectomy in the early period post-transplant may be a safe choice.

6. Conclusion

KT remains the best treatment for patients with ESRD but hyperparathyroidism might persist in a fairly large number of patients. To prevent or treat PHPT requires a consensus between doctors and patients. To determine the appropriate surgical intervention for PHPT, various factors for allograft impairment such as PHPT, hypercalcemia, the donor source, and parathyroidectomy itself should be evaluated. The rational timing of parathyroidectomy for KT patients with PHPT remains controversial with regard to the preservation of both allograft function and serum Ca levels. Additional studies with a large sample size and prospective trials should be conducted in the future.

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