



Persistent hyperparathyroidism after kidney transplantation; updates on the risk factors and its complications

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Successful kidney transplantation can bring back the ability to create active (1, 25 dihydroxy-vitamin) D, respond to homeostatic phosphate signals, and improve the balance of essential stimuli that were subjected to secondary hyperparathyroidism (HPT) (1), leading to a decline in parathyroid hormone (PTH) especially during the first three months after kidney transplantation (1,2). Nevertheless, the amendments in these metabolic abnormalities do not regularly result in normalization of PTH and some of the aspects of mineral and bone disorders may persist in a number of kidney transplant recipients (3). Elevated post-transplant PTH exceeding three months may be suggestive of persistent HPT that may or may not improve over time (3).

Interestingly, even with satisfactory allograft function, a notable proportion of kidney transplant recipients continue to have elevated PTH levels (1). In long-term kidney transplant recipients with a considerably functioning allograft, with estimated glomerular filtration rate (eGFR) greater than 30 to 45 mL/min, elevated PTH level can still be found in 30% to 60% at one-year following transplantation (3-8), and about 20% of patients have persistently elevated PTH levels at five years after kidney transplantation (9), resulting in persistent secondary HPT or progresses to tertiary HPT post-transplantation (6,10). Thus, Kidney Disease Outcomes Quality Initiative (KDOQI) guideline has suggested early and routine monitoring of PTH (monthly through the first 3 months, and once every 3 months from 3 months to 1 year after transplantation) (11).

Among advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients with HPT, after kidney transplantation, we may classify them in to three groups (3); 1) recipients without persistent post-transplant HPT (HPT subsided within three months after transplantation; 2) recipients with persistent secondary HPT due to hyperplastic parathyroid glands; and 3) recipients with tertiary HPT due to monoclonal development of parathyroid cells before kidney transplantation.

■ Implication for health policy/practice/research/medical education

Successful kidney transplantation leads to a decline in parathyroid hormone (PTH) especially during the first three months after kidney transplantation. However, elevated PTH level can still be found in 30% to 60% at one-year following transplantation. Persistent hyperparathyroidism after kidney transplantation may lead to significant complications including bone diseases/fracture, vascular calcification, cardiovascular disease, and allograft dysfunction. Risk factors for persistent hyperparathyroidism include long dialysis duration, high PTH level before transplantation, post-transplant high calcium, post-transplant high alkaline phosphatase, and impaired kidney function post-transplant.

■ **Keywords:** Hyperparathyroidism, Parathyroid, Kidney transplantation, Risk factor, Transplantation

Effects of persistent hyperparathyroidism on outcomes after kidney transplantation

Neglected uncontrolled, persistent HPT after kidney transplantation may lead to significant complications (Box 1) (3,11-16). It may cause or worsen pre-existing osteopenia/osteoporosis, progressive bone damage, and fracture in renal transplant recipients (3,11-13). Moreover, studies have also demonstrated higher rates of vascular calcification, cardiovascular disease (3,11), allograft dysfunction (12,13), and graft loss (14). In addition, persistent HPT has been associated with renal calcinosis, leading to poor allograft function (16). Bleskestad et al (15) demonstrated that elevated iPTH levels (>14.4 pM) were associated with a significant 2.6 fold increased the risk of the composite clinical outcomes including cardiovascular events, graft loss, and all-cause mortality.

Risk factors for persistent hyperparathyroidism after kidney transplantation

Reported risk factors for persistent HPT after kidney transplantation are shown in Box 2 (1,17-22). Persistent post-transplant HPT is thought to be primarily attributed

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to some degree of CKD and parathyroid gland hyperplasia retained by kidney-transplant patients (9,23). Post-kidney transplant recipients have eGFR approximately 30 to 60 mL/min/1.73 m² (9,23) and hence manifest some degree of reduced kidney function, resulting in CKD-related HPT(19). In addition, recovery of calcium sensing receptor (CaSR) and vitamin D receptor (VDR) expression following transplantation, with subsequent reduction of gland size, occurs only in non-nodular hyperplastic glands, not in nodular hyperplastic glands, which are resistant to PTH control mechanisms (24-26). High PTH level before transplantation can also prognosticate the severity of persistent HPT and the requirement for parathyroidectomy after transplantation (1,9,20,22). Because of the prolonged life span (nearly 20 years) of parathyroid cells with a cell regeneration rate of just 5% per year, the reduction in PTH level after the first three months happens at a very slow rate (2). Accordingly, recipients with very high PTH level before transplantation are prone to develop long-term persistent HPT after kidney transplantation.

Studies have also shown long dialysis duration before transplantation (1,18) and older age (21) as risk factors for persistent HPT after kidney transplantation. In a recent retrospective study of 520 kidney transplant recipients by Yamamoto et al (17), long dialysis duration prior to kidney

transplantation, large maximum parathyroid gland size before transplant, pre-transplant high PTH levels, post-transplant (less than 2 weeks) hypercalcemia, and post-transplant high alkaline phosphatase were demonstrated as independent risk factors for persistent HPT after kidney transplantation (17).

Conclusion

In summary, persistent HPT is common occurring up to 60% at 1-year following kidney transplantation, and is associated with poor outcomes after kidney transplantation including osteopenia/osteoporosis, fracture, vascular calcification, cardiovascular disease, allograft dysfunction, and graft loss. Risk factors for persistent HPT include long dialysis duration, high PTH level before transplantation, post-transplant high calcium, post-transplant high alkaline phosphatase, and impaired kidney function post-transplant.

Authors' contribution

All authors had access to the data and a role in writing the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflicting interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Box 1. Effects of persistent hyperparathyroidism on outcomes after kidney transplantation

Reported complications of persistent HPT in kidney transplant recipients (3,11-16).

- Osteopenia/osteoporosis
- Fracture
- Vascular calcification
- Cardiovascular disease
- Allograft dysfunction, and graft loss
- Renal calcinosis
- Increased the risk of the composite clinical outcomes including cardiovascular events, graft loss, and all-cause mortality

Box 2. Risk factors for persistent hyperparathyroidism after kidney transplantation

Reported risk factors for persistent HPT in kidney transplant recipients (1,17-22).

- Long dialysis duration
- High PTH level prior to transplantation
- Post-transplant high calcium
- Post-transplant high alkaline phosphatase
- Impaired kidney function post-transplant
- Parathyroid gland hyperplasia
- Older age
- Large maximum parathyroid gland size before kidney transplant
- Monoclonal transformation (nodular hyperplasia) of parathyroid glands

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