KI REPORTS
KIReports.org

Is Hyperparathyroidism a Concern for Allograft Dysfunction in Pediatric Kidney Transplantation?

Sheena Kaul[1] and Catherine Quinlan[1,2,3]

[1]Department of Pediatric Nephrology, The Royal Children's Hospital, Melbourne, Victoria, Australia; [2]Murdoch Children's Research Institute, Melbourne, Victoria, Australia; and [3]School of Medicine, University of Melbourne, Melbourne, Victoria, Australia

Kidney Int Rep (2023) **8,** 8–9; https://doi.org/10.1016/j.ekir.2022.11.009

See Clinical Research on Page 81

Parathyroid hormone (PTH) is a polypeptide protein released by the parathyroid gland, and is essential for calcium and phosphate homeostasis and bone mineralization.[1] PTH allows for tubular calcium reabsorption in the kidneys, calcium absorption in the gastrointestinal tract, calcium mobilization from the bones, and phosphate excretion by the kidneys.[1] PTH synthesis and secretion is mainly influenced by the extracellular free (ionized) calcium, and contributory effects from inorganic serum phosphate, 1,25-dihy droxycholecalciferol, fibroblast growth factor-23 (FGF-23), and osteoblast-derived phosphaturic hormone.[1]

In patients with chronic kidney disease, there is a dysregulation of calcium and phosphate homeostasis, which leads to decreased phosphate excretion by the renal tubules causing a rise in serum phosphate, elevated levels of FGF-23, and reduced synthesis of 1,25-dihydroxycholecalciferol.[1,2] These changes then cause an increased synthesis and secretion of PTH and parathyroid hyperplasia, resulting in the development of a vicious cycle.[2] Patients with early stages of chronic kidney disease often have no changes in their serum calcium and phosphate levels, and the PTH level may be only slightly elevated than the reference values.[2]

The elevated calcium and phosphate levels associated with secondary hyperparathyroidism have been associated with the formation of vascular calcification that is strongly associated with increased morbidity and mortality.[2] In addition, patient age and duration of dialysis have been linked to an increased risk of developing vascular calcification.[2]

Secondary hyperparathyroidism is a common complication of chronic kidney disease, and patients at time of kidney transplant would often have hyperphosphatemia, elevated FGF-23, and low level of 1,25-dihydroxycholecalciferol.[3]
Following kidney transplant, the general functional response is improvement or reversal of these abnormalities, but persistent abnormalities in PTH and FGF-23 can contribute to changes in bone and mineral homeostasis.[3] Studies have demonstrated that patients will develop mild to moderate hypophosphatemia, likely because of the phosphaturic effect of PTH and FGF-23, within the first 3 months posttransplant.[3,4] Hypophosphatemia generally improves in most patients over the first 12 months posttransplant.[3,4]

Wolf *et al.*[4] studied the change in PTH levels following kidney transplant in the following 2 groups of patients with secondary hyperparathyroidism at the time of transplant: patients with a low PTH (defined as PTH $>$ 65 and $<$ 300 pg/ml), and those with a high PTH (defined as PTH $>$ 300 pg/ml).[4] Within the first 3 months posttransplant, both groups had a significant decline in PTH from baseline levels, and a slower improvement over the subsequent months.[4] At 12 months posttransplant, PTH was still elevated above normal values (high PTH group, 146 pg/ml; low PTH group 118 pg/ml).[4] In the same study, within 1 week of transplant, hypercalcemia developed in 21% of patients with low PTH and 30% of those with high PTH.[4] The proportion of patients with hypercalcemia peaked at 29% for low PTH patients and 48% for high PTH patients by 2 months posttransplant, and then steadily decreased.[4] Within 12 months posttransplant, there were 11% of patients in the low PTH group and 25% of patients in the high PTH group who continued to have hypercalcemia.[4]

Muirhead *et al.*[5] described that in their study of long-term follow-up of 1000 consecutive transplant recipients, approximately 48% of patients had an elevated PTH at 12

Correspondence: Sheena Kaul, The Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville Victoria 3052, Australia. E-mail: Sheena.Kaul2@rch.org.au

months posttransplant, and approximately 39% continued to have an elevated PTH at 2 years posttransplant.[5]

Pihlstrøm *et al.*[6] evaluated the association between persistent hyperparathyroidism and mortality, cardiovascular disease, and renal allograft survival in 1840 stable kidney transplant recipients aged 30 to 75 years who participated in The Assessment of LEscol in Renal Transplantation trial.[6] They reported that 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.[6] Because of the significant morbidity and mortality associated with persistent hyperparathyroidism post kidney transplant, the recommendation is to obtain PTH measurement that is appropriate to the graft function, and to normalize serum levels of calcium, phosphate, and 1,25-dihydroxycholecalciferol.

In this issue of *KI Reports*, Prytula *et al.*[7] examined the relationship between PTH, serum calcium and phosphate, and 25-hydroxyvitamin D and allograft outcome in pediatric kidney transplant recipients who were registered in the Cooperative European Pediatric Renal Transplant Initiative Registry.[7] This was a retrospective, multicenter, longitudinal cohort study over a period of up to 5 years. Study data were collected at baseline, months 1, 3, 6, 9, and 12 posttransplant, and every 6 months thereafter up to 5 years.[7] Allograft dysfunction, defined as either graft loss, eGFR $\leq$ 30 ml/min per 1.73 m^2 or a $\geq$50% decline from baseline eGFR at 1 month posttransplant, was used a primary outcome measure.[7]

The association between hyperparathyroidism and allograft dysfunction was present in the conventional Cox model (hazard ratio 3.13; 95% confidence interval 1.99–4.92; $P < 0.001$) and in the marginal structural model (hazard ratio 2.79; 95% confidence interval 1.80–4.34; $P < 0.001$).[7] The association between hyperphosphatemia and allograft dysfunction was present in the conventional Cox model (hazard ratio 1.99; 95% confidence interval 1.36–2.91; $P < 0.001$) but not in the marginal structural model (hazard ratio 1.32; 95% confidence interval 0.87–2.00; $P = 0.193$).[7]

There was no association between 25-hydroxyvitamin D and time to allograft dysfunction.[7] However, the analysis was partly limited because of 67% to 88% of missing values. There was no association between early posttransplant hypophosphatemia at 1 month and allograft dysfunction ($P = 0.95$).[7] When adjusted only for time-varying eGFR in the marginal structural model, analyses demonstrated that hyperparathyroidism and hypocalcemia were associated with a higher risk of allograft dysfunction.[7]

In summary, Prytula *et al.*[7] present in this issue of *KI Reports* that hyperparathyroidism is an independent risk factor, after adjustment for covariates that can affect graft survival such as allograft rejection, for allograft dysfunction in pediatric kidney transplant recipients. Further studies, especially prospective studies with interventions aimed at a strict PTH control, would provide further insight into the causal relationship between hyperparathyroidism and allograft dysfunction.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Habas E Sr., Eledrisi M, Khan F, Elzouki AY. Secondary hyperparathyroidism in chronic kidney disease: pathophysiology and management. *Cureus*. 2021;13:e16388. https://doi.org/10.7759/cureus.16388
2. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol*. 2011;6:913–921. https://doi.org/10.2215/CJN.06040710
3. Delos Santos R, Rossi A, Coyne D, Maw TT. Management of post-transplant hyperparathyroidism and bone disease. *Drugs*. 2019;79:501–513. https://doi.org/10.1007/s40265-019-01074-4
4. Wolf M, Weir MR, Kopyt N, et al. A prospective cohort study of mineral metabolism after kidney transplantation. *Transplantation*. 2016;100:184–193. https://doi.org/10.1097/TP.0000000000000823
5. Muirhead N, Zaltman JS, Gill JS, et al. Hypercalcemia in renal transplant patients: prevalence and management in Canadian transplant practice. *Clin Transpl*. 2014;28:161–165. https://doi.org/10.1111/ctr.12291
6. Pihlstrøm H, Dahle DO, Mjøen G, et al. Increased risk of all-cause mortality and renal graft loss in stable renal transplant recipients with hyperparathyroidism. *Transplantation*. 2015;99:351–359. https://doi.org/10.1097/TP.0000000000000583
7. Prytula A, Shroff R, Krupka K, et al. Hyperparathyroidism is an independent risk factor for allograft dysfunction in pediatric kidney transplantation. *Kidney Int Rep*. 2023;8:81–90.