Editorial

Persistent Hyperparathyroidism: A Reality Calling for Additional Evidence

Hanne Skou Jørgensen and Pieter Evenepoel

In this issue of *AJKD*, Wang et al[1] report on the incidence, trends, and consequences of treatment of posttransplant hyperparathyroidism in a nationwide registry encompassing 30,127 Medicare-insured US patients who received a

first kidney transplant. The 2 treatments of interest were cinacalcet use and parathyroidectomy in the first 3 years following kidney transplantation. The authors report that cinacalcet use was common (18%) and increased by 20% from 2007 to 2013, with treatment most often initiated early in the posttransplant course (a median of 6.8 weeks). In contrast, surgical parathyroidectomies were much less common (1.8%), did not increase in frequency, and were typically performed >12 months posttransplant.

These findings confirm that hyperparathyroidism is a common complication after kidney transplantation—and that its incidence is increasing. The latter likely reflects a shift toward medical therapy first in controlling secondary hyperparathyroidism in patients with late-stage chronic kidney disease, including those on the kidney transplant waiting list.[2] One-third of the patients enrolled in the study by Wang et al had been treated with cinacalcet prior to kidney transplantation. These patients are at risk for rebound hyperparathyroidism when calcimimetic therapy is discontinued at the time of transplantation,[3] especially when exposure time is short. Although it is reassuring to observe that in a substantial subset of patients in the study from Wang et al, cinacalcet withdrawal at time of transplantation was without complications, there remains a clear window of opportunity for better control of secondary hyperparathyroidism *pre*-transplant.

The clinical consequences of hyperparathyroidism posttransplant remain uncertain. Observational studies indicate unfavorable outcomes, with increased risk of fracture,[4] cardiovascular disease,[5] and kidney graft loss,[5] but intervention studies are limited and, so far, yielded unequivocal results.[6,7] A first question to be tackled in kidney transplant recipients presenting with hyperparathyroidism is whom to treat? Clearly, it is important to discriminate *persistent* (or tertiary) from *secondary* hyperparathyroidism when considering treatment posttransplant, as the first is likely a maladaptive condition, while the latter can be considered a beneficial adaption to maintain normocalcemia and normophosphatemia in the face of kidney graft dysfunction. To complicate matters further, the phenotype of persistent hyperparathyroidism posttransplant often mimics familial hypocalciuric hypercalcemia, with lower levels of calciuria than what is

typically seen for primary hyperparathyroidism.[8] Pathophysiological mechanisms underlying this atypical presentation remain to be defined, but both calcium-sensing receptor dysfunction and skeletal parathyroid hormone (PTH) resistance may be hypothesized to be involved. According to a recent bone biopsy study, the majority of kidney transplant recipients have normal bone turnover at 1 year posttransplant, and hyperparathyroidism with hypercalcemia is not necessarily indicative of high bone turnover, as was also found in previous reports.[9,10] In clinical practice, we want to identify patients with negative effects of PTH on target organs—such as high bone turnover with risk of bone demineralization, or excessive calciuria with risk of kidney stones and nephrocalcinosis. To that end, besides routine mineral metabolism parameters, bone turnover markers and the calcium to creatinine clearance ratio may be of help. As the positive predictive value of bone turnover markers for high bone turnover is rather disappointing,[11,12] the threshold for performing a bone biopsy in a patient with hyperparathyroidism and elevated bone biomarkers prior to referral for a parathyroidectomy should be low.

Having identified patients with maladaptive hyperparathyroidism, we should next consider how to treat. Lack of hard outcome trials precludes formal treatment recommendations, and so, benefits and risks of calcimimetics versus parathyroidectomy should be considered, in order to define the best treatment option at the individual level (Table 1). Cinacalcet has been shown to normalize mineral metabolism parameters posttransplant, but its effect on bone mineral density is limited.[7] In a small randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients, subtotal parathyroidectomy induced greater reductions in PTH and calcium and was associated with a significant increase in femoral neck bone mineral density.[13]

Any intervention carries inherent risks. In the study by Wang et al, 1 in 4 patients (25%) were hospitalized within 90 days of parathyroidectomy and a similar number (28%) after their first prescription of cinacalcet. To counter the earlier initiation of cinacalcet (at a median of 6.8 weeks) compared to parathyroidectomy (at a median of 13.9 months), a sensitivity analysis was performed restricting to patients starting therapy >12 months posttransplant. In this analysis, hospitalizations were more common following a parathyroidectomy (24%) than after cinacalcet prescription (15%). The most feared complications of PTH suppressive therapy are hypocalcemia and kidney dysfunction. Hypocalcemia results from decreased

Table 1. Considerations for Medical Versus Surgical Treatment of Persistent Hyperparathyroidism After Kidney Transplantation

	Calcimimetics	Parathyroidectomy
Benefits and Risks		
Advantages	Noninvasive; can be withdrawn	Radical treatment; proven skeletal benefit
Disadvantages	Tolerability not assured; adherence not assured; treatment duration unknown	Invasive; peri- and postsurgical risks; initial cost
Effect Parameters		
Parathyroid hormone	Reduced (by 25%)	Normalized
Calcium	Normalized (for 70%); low risk of hypocalcemia	Normalized (for 100%); high risk of hypocalcemia
Phosphate	Normalized	Normalized
Bone turnover markers	No change/initial increase	Decrease
Bone mineral density	No change	Substantial gain
Vascular calcification	No change	No change
Kidney function	No reduction	Possible reduction

skeletal calcium efflux and even, in the case of hungry bone syndrome, from net skeletal calcium influx. The timing, severity, and duration of hypocalcemia relate directly to the dynamics of the PTH signaling changes and degree of bone mineralization defect at baseline. Thus, not surprisingly, the hypocalcemia following (sub)total parathyroidectomy differs from that following calcimimetic therapy: by occurring earlier (acutely) and being more pronounced, often symptomatic, and of longer duration. Accordingly, in the study by Wang et al, the risk of hypocalcemia was clearly higher after parathyroidectomy than after cinacalcet initiation (44% vs 2%). Kidney graft dysfunction has been reported following parathyroidectomy and calcimimetic therapy in some, but not all, case series—and likely has a hemodynamic origin.[14] Wang et al report a similar risk of acute kidney injury necessitating admission with both treatment options (7.8% vs 10.8%). These absolute risks are hard to interpret without knowledge of the baseline risk. A recent meta-analysis is reassuring, as it demonstrated no sustained kidney dysfunction with either therapy.[15]

Whereas a successful parathyroidectomy offers a permanent solution,[9,10] the effect of cinacalcet is only for the duration of the treatment, with a risk of rebound hyperparathyroidism after discontinuation.[8] Although some degree of spontaneous resolution of hyperparathyroidism is expected posttransplant, the prevalence seems fairly stable from 1 year posttransplant and onward.[11] Thus, the duration of treatment with cinacalcet may well be indefinite. From a health economic perspective, this is relevant, as it has been calculated that surgery would be more cost-effective if cinacalcet duration reached 14 months.[9]

To conclude, the study by Wang et al provides helpful information regarding the current clinical practice of treating hyperparathyroidism after kidney transplantation. A main limitation is the lack of biochemical data on the prevalence and severity of mineral metabolism disturbances and indications for initiation of, and choice of, therapy. The consequences of persistent hyperparathyroidism in the posttransplant period still need to be defined, and this information is a prerequisite to establishing both treatment indications and targets for therapy. Considering the increasing utility of calcimimetics posttransplant, studies are urgently needed to determine whether they are safe and efficient in the early posttransplant period, whether treatment can be withdrawn or should continue indefinitely, and, most importantly, whether treatment benefits the patient by reducing the risk of fractures and cardiovascular events or improving kidney graft and overall survival.

Article Information

Authors' Full Names and Academic Degrees: Hanne Skou Jørgensen, MD, PhD, and Pieter Evenepoel, MD, PhD.

Authors' Affiliations: Department of Microbiology, Immunology and Transplantation; Nephrology and Renal Transplantation Research Group, KU Leuven, Leuven, Belgium (HSJ, PE); Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark (HSJ); and Department of Medicine, Division of Nephrology, University Hospitals Leuven, Leuven, Belgium (PE).

Address for Correspondence: Pieter Evenepoel, MD, PhD, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium. Email: pieter.evenepoel@uzleuven.be

References

1. Wang AX, Liu S, Montez-Rath ME, Chertow GM, Lenihan CR. Parathyroidectomy and cinacalcet use in Medicare-insured kidney transplant recipients. *Am J Kidney Dis*. Published online September 23, 2022. doi:10.1053/j.ajkd.2022.07.015
2. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clin J Am Soc Nephrol*. 2015;10:98-109. doi:10.2215/CJN.12941213
3. Evenepoel P, Sprangers B, Lerut E, et al. Mineral metabolism in renal transplant recipients discontinuing cinacalcet at the time of transplantation: a prospective observational study. *Clin Transplant*. 2012;26:393-402. doi:10.1111/j.1399-0012.2011.01524.x
4. Perrin P, Caillard S, Javier RM, et al. Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant*. 2013;13:2653-2663. doi:10.1111/ajt.12425

5. 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. doi:10.1097/TP.0000000000000583

6. Trillini M, Cortinovis M, Ruggenenti P, et al. Paricalcitol for secondary hyperparathyroidism in renal transplantation. *J Am Soc Nephrol*. 2015;26:1205-1214. doi:10.1681/ASN. 2013111185

7. Evenepoel P, Cooper K, Holdaas H, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant*. 2014;14:2545-2555. doi:10.1111/ajt.12911

8. Marx SJ. Familial hypocalciuric hypercalcemia as an atypical form of primary hyperparathyroidism. *J Bone Miner Res*. 2018;33:27-31. doi:10.1002/jbmr.3339

9. Borchhardt K, Sulzbacher I, Benesch T, et al. Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Transplant*. 2007;7:2515-2521. doi: 10.1111/j.1600-6143.2007.01950.x

10. Jørgensen HS, Behets G, Bammens B, et al. Patterns of renal osteodystrophy 1 year after kidney transplantation. *Nephrol Dial Transplant*. 2021;36:2130-2139. doi:10.1093/ndt/ gfab239

11. Jørgensen HS, Behets G, Viaene L, et al. Diagnostic accuracy of noninvasive bone turnover markers in renal osteodystrophy. *Am J Kidney Dis*. 2022;79:667-676.e1. doi:10.1053/j.ajkd. 2021.07.027

12. Keronen SM, Martola LAL, Finne P, et al. Clinical prediction of high-turnover bone disease after kidney transplantation. *Calcif Tissue Int*. 2022;110:324-333. doi:10.1007/s00223-021-00917-1

13. Cruzado JM, Moreno P, Torregrosa JV, et al. A randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. *J Am Soc Nephrol*. 2016;27:2487-2494. doi:10. 1681/ASN.2015060622

14. Evenepoel P, Claes K, Kuypers D, et al. Impact of parathyroidectomy on renal graft function, blood pressure and serum lipids in kidney transplant recipients: a single centre study. *Nephrol Dial Transplant*. 2005;20:1714-1720. doi:10. 1093/ndt/gfh892

15. Frey S, Goronflot T, Kerleau C, et al. Parathyroidectomy or cinacalcet: do we still not know the best option for graft function in kidney-transplanted patients? A meta-analysis. *Surgery*. 2021;170:727-735. doi:10.1016/j.surg.2021.02. 048