The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e3532–e3533
https://doi.org/10.1210/clinem/dgac211
Advance access publication 15 April 2022
Commentary

Parathyroidectomy Versus Calcimimetic: The Lower the PTH the Better?

Pieter Evenepoel,[1,2] and Hanne Skou Jørgensen[1,3]

[1]Department of Microbiology, Immunology and Transplantation; Nephrology and Renal Transplantation Research Group, KU Leuven, 3000 Leuven, Belgium
[2]Department of Medicine, Division of Nephrology, University Hospitals Leuven, 3000 Leuven, Belgium; and
[3]Department of Kidney Diseases, Aarhus University Hospital, 8200 Aarhus, Denmark

Correspondence: Pieter Evenepoel, MD, PhD, Dienst nefrologie, Universitair Ziekenhuis Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Email: Pieter.Evenepoel@uzleuven.be.

Key Words: cinacalcet, fracture, hemodialysis, mortality, parathyroidectomy, secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT) is ubiquitous in later stages of chronic kidney disease (CKD). It is an integral part of the CKD-mineral and bone disorder, contributing to bone disease and to vascular and soft-tissue calcifications. The biologic actions of PTH may extend beyond maintaining mineral and bone metabolism to include metabolic, immunological, and cardiovascular effects. Controlling sHPT is, therefore, a major concern for the nephrologist. The current choice of therapies for sHPT include native and active vitamin D compounds, phosphate control by diet or phosphate-binders, calcimimetics, and parathyroidectomy (PTX). The lack of randomized, controlled trials comparing these therapies means there is no clear priority between them. However, most would consider the surgical option of PTX mainly for severe or refractory sHPT (1).

As a proxy of a head-to-head trial, Komaba et al recently performed a prospective cohort study addressing the question of whether survival in dialysis patients with sHPT differs according to PTH-lowering treatment strategy. Using data from the Japanese Society for Dialysis Therapy Renal Data Registry, patients with PTH levels ≥ 300 pg/mL who underwent PTX or started treatment with cinacalcet during 2 consecutive years (January 1, 2008, to December 31, 2009) were matched by an extensive propensity score model. During a 6-year follow-up period, 22.5% in the PTX group and 27.4% in the cinacalcet group died, translating to a hazard ratio of 0.78 (95% CI, 0.67-0.91, $P = 0.002$) (2).

This observation of a 22% survival benefit in patients treated with PTX is intriguing, particularly when considering that the indication for PTX was a PTH level much lower than the upper Kidney Disease: Improving Global Outcomes (KDIGO) PTH target for dialysis patients. Because the treatment strategy in the study by Komaba et al was not based on random allocation, results may have been subject to selection bias and confounding. The authors applied a range of statistical methods to minimize these risks and test the robustness of the results; nevertheless, residual confounding cannot be completely excluded. Further, results should be confirmed in other populations because PTH responsiveness and treatment strategy show great variability across regions and ethnicities.

Exploratory analyses indicated that the survival benefit by PTX could be explained by a better control of sHPT, whereas improved calcium and phosphate control, or active vitamin D therapy, seemed to play a marginal role at best. Mediation analysis revealed that posttreatment reductions in PTH levels could explain 64.1% of the survival benefit of PTX vs cinacalcet. This finding aligns with a bunch of experimental and clinical evidence demonstrating that PTH may cause harm to the musculoskeletal, cardiovascular, and immune systems. Although posttreatment fibroblast growth factor 23 (FGF23) levels were not available, it may be speculated these would be lower in PTX- vs cinacalcet-treated patients because the former presented both lower PTH levels and calcium-phosphate product. Acknowledging the growing evidence linking FGF23 to dismal outcomes, lower posttreatment FGF23 levels in PTX-treated patients may represent another explanation for the survival benefit (3).

For many years, the optimal PTH target in patients with late-stage CKD has been a matter of intense debate. Recommended target ranges vary considerably between guidelines; for example, the Japanese Society for Dialysis Therapy recommends a PTH target of 60 to 240 ρg/mL, or approximately 1 to 4 times the upper normal limit (4), which is substantially lower than what is recommended by the KDIGO guidelines (2-9 times the upper normal limit) (5). In the absence of randomized controlled trials, these recommendations originate from observational studies, examining the relationship between PTH levels and mortality. Such studies carry a high risk of residual confounding and are limited by artificial constraints induced by statistical modeling (1).

Remarkably, in the study by Komaba et al, the survival benefit in PTX- vs cinacalcet-treated patients was most pronounced in the lowest postoperative PTH tertile (<35 pg/mL).

Received: 30 March 2022. **Editorial Decision:** 30 March 2022. **Corrected and Typeset:** 29 April 2022

This finding adds credit to the theory that residual confounding accounts for the association between low PTH and high mortality, and supports a notion of "the lower, the better" for PTH suppressive therapy. Similar to the association between (bone-specific) alkaline phosphatase and outcomes, the true relationship between PTH levels and mortality may be linear—not U-shaped—and conditions causing suppression of PTH (inflammation, malnutrition) may be the true culprits behind the association of low PTH and poor outcomes (6). In aggregate, these data indicate that the Japanese strategy to aim for lower PTH levels in late-stage CKD might confer a survival benefit. One may speculate that a better PTH control, at least partly, explains the lower mortality and fracture risk consistently demonstrated in Japanese patients receiving hemodialysis.

No survival difference could be demonstrated when further matching PTX and cinacalcet treated patients for PTH, calcium, and phosphorus control. This observation is remarkable because the calcium-sensing receptor (CaSR) is expressed not only in the parathyroid glands, but also in many other tissues, including the skeleton and vasculature. In these tissues, CaSR signaling may confer health-promoting effects such as the attenuation of vascular calcification (7). The absence of a survival benefit in cinacalcet- compared with PTX-treated patients questions the clinical relevance of extraparathyroid CaSR activation. This conclusion does warrant caution because the study was not designed to address this issue. Head-to-head outcome studies comparing different PTH-lowering strategies, such as active vitamin D analogs against calcimimetics or PTX, are nonexistent.

Altogether, the study by Komaba et al calls for continued efforts to identify the optimal PTH treatment targets in late-stage CKD and should be seen as encouragement to embark on randomized controlled trials to provide solid evidence for PTH targets and treatment strategies. Balancing treatment strategies, it should be acknowledged that PTX, overall, allows for more pronounced PTH suppression compared with medical therapy (8).

Disclosures

The authors declare no funding or conflicts of interest.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Ketteler M, Block GA, Evenepoel P, *et al*. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int*. 2017;92(1):26-36. doi:10.1016/j.kint.2017.04.006.
2. Komaba H, Hamano T, Fujii N, *et al*. Parathyroidectomy versus cinacalcet among patients undergoing hemodialysis. *J Clin Endocrinol Metab*. 2022. In Press.
3. Musgrove J, Wolf M. Regulation and effects of FGF23 in chronic kidney disease. *Annu Rev Physiol*. 2020;82(1):365-390. doi:10.1146/annurev-physiol-021119-034650.
4. Fukagawa M, Yokoyama K, Koiwa F, *et al*. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial*. 2013;17(3):247-288. doi:10.1111/1744-9987.12058.
5. 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(1):98-109. doi:10.2215/CJN.12941213.
6. Haarhaus M, Evenepoel P. Differentiating the causes of adynamic bone in advanced chronic kidney disease informs osteoporosis treatment. *Kidney Int*. 2021;100(3):546-558. doi:10.1016/j.kint.2021.04.043.
7. Massy ZA, Hénaut L, Larsson TE, Vervloet MG. Calcium-sensing receptor activation in chronic kidney disease: effects beyond parathyroid hormone control. *Semin Nephrol*. 2014;34(6):648-659. doi:10.1016/j.semnephrol.2014.10.001.
8. 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(8):2487-2494. doi:10.1681/ASN.2015060622.