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Fracture Risk in Patients on Hemodialysis: the Lower the Parathyroid Hormone the Better?

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Secondary hyperparathyroidism has been recognized for more than 50 years as a cause of bone fractures.[1] More recently, the term chronic kidney disease-mineral and bone disorder (CKD-MBD) was coined by Kidney Disease: Improving Global Outcomes (KDIGO) because of the growing evidence that there is a complex interplay between bone, various mineral metabolism parameters, including parathyroid hormone (PTH), and cardiovascular calcifications in CKD, with an obvious impact on cardiovascular complications and survival.[2]

With the availability of increasingly effective and safe drugs to control secondary hyperparathyroidism, including active vitamin D derivatives and more recently, calcimimetics (initially cinacalcet, then i.v. agents such as etelcalcetide, favoring drug adherence),[3] the PTH target level in patients on dialysis became an important question. The Kidney Disease Outcomes Quality Initiative guidelines recommended in 2003 a target of intact PTH (iPTH) level of 150 to 300 pg/ml.[4] This was revised by the 2009 KDIGO CKD-MBD guideline.[5] The Workgroup suggested to maintain iPTH level in the range of approximately 2 to 9 times the upper limit of normal (corresponding approximately for most iPTH assays to 130 to 600 pg/ml). Several findings contributed to this much broader range. First, multiple studies showed that iPTH levels within the 150 to 300 pg/ml range did not accurately predict bone histology. Second, there were no randomized controlled trials showing that treatment to achieve a specific PTH level improves clinical outcomes. However, in observational studies, the inflection point at which PTH level becomes significantly associated with increased all-cause mortality varied, ranging from >400 to >600 pg/ml. The KDIGO Workgroup further wisely recommended that therapeutic decisions be based on trends rather than on single laboratory values.

The KDIGO CKD-MBD guideline has been widely adopted globally. However, the 2013 Japanese Society of Dialysis Therapy CKD-MBD Clinical Practice Guideline suggested a target range of iPTH of 60 to 240 pg/ml in patients on dialysis, again based on observational studies.[6]

In this issue of KI Reports, Komaba *et al.*[7] used the Japanese Society of Dialysis Therapy Registry to perform a retrospective study of the association of PTH levels with the risk of any fracture and site-specific fracture. They were able to include 180,333 patients on hemodialysis (HD) or hemodiafiltration thrice weekly for 3 or more months at the end of 2016. Baseline covariates (including demographics, comorbidities, and mineral metabolism parameters) were registered at that time. The registry recorded in 2017 all hospitalizations and their cause. During 1 year of follow-up, a total of 3762 fractures required hospitalization. In an adjusted analysis, higher baseline PTH levels were associated with an increased risk of fracture (odds ratio per doubling of iPTH: 1.06); (95% confidence interval: 1.03–1.09). This association was most pronounced for hip fractures (a substantial cause of morbidity and mortality) and absent for vertebral fractures. This preferential sensitivity of cortical bone (among others, at the hip level) versus trabecular bone (at the vertebral level) is perfectly in line with the mechanism of action of PTH.[8] More importantly, the risk of fracture was lowest for iPTH levels < 39 pg/ml, thus within the normal range and much lower than the KDIGO target range and even the Japanese target range for patients on dialysis.

The study[8] has definite strengths, including a large sample size, nationwide extension, and well-defined outcomes. It also has multiple limitations: 69,000 patients had to be excluded because data on hospitalizations were not available; follow-up was limited to

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1 year; only fractures requiring hospitalization were recorded; and some important potential confounders were missing, such as data on active vitamin D derivatives and calcimimetics treatment, on type of laboratory test used to measure both albumin[9] and serum PTH[S1] levels. Bone turnover markers such as alkaline phosphatase was also not available.[S2] Finally, like in any observational study, there may be additional unmeasured confounders accounting for the provocative results of the authors.

The demonstration by Komaba *et al*.[8] that normal levels of iPTH associate with the lowest adjusted risk of fractures in patients on HD is provocative and even broadens the gap between Japan and the rest of the world. As mentioned above, the gap already existed and was poorly understood, despite efforts by various investigators. An attractive hypothesis was that bone would be more sensitive to high turnover induced by PTH in Japanese patients on HD than in patients on HD elsewhere. However, with a case-control design, Evenepoel *et al*.[S2] recently matched patients from 2 prospective HD cohorts from Japan and Belgium. They found that Japanese patients had lower levels of PTH and of 2 markers of bone turnover, bone alkaline phosphatase and tartrate-resistant acid phosphatase isoform. Importantly, Japanese patients receiving HD had lower bone turnover than their European counterparts, even at similar PTH levels.[S2] Interestingly, practice patterns and therapeutic targets are significantly different between Japan and the rest of world not just for CKD-MBD. As another example, hemoglobin targets and erythropoiesis-stimulating agents dosages are much lower in Japan than elsewhere; however, adjusted survival on HD has repeatedly been shown to be best in Japan.[S3,S4] Lastly, Yamamoto *et al*.,[S5] using the DIalyses Outcomes Practice Patterns Study database, recently came to the conclusion that total alkaline phosphatase is a more robust exposure of adverse outcomes (all-cause mortality, cardiovascular mortality, and fractures) than PTH in patients on HD; thus suggesting that it may be useful to evaluate target organ response rather than PTH alone when considering the consequences of secondary hyperparathyroidism. Interestingly, in this study, the association of PTH level with the risk of fractures was very weakly linear, whereas multiple previous studies[S6–S8] found a U-shaped association of PTH level with the risk of fractures, in line with the KDIGO target of the 2009 Guideline, not modified in 2017.[S9]

Overall, the authors should be congratulated for this well-designed retrospective large-sized registry-based study. Nevertheless, their results cannot be generalized. Thus, the study should not prompt the revision of any clinical practice targets, especially outside Japan, but calls, like any good study, for additional well-designed studies to unravel the reasons for the Japanese specificities. Indeed, at present one can only speculate about the potential role(s) of differences in genetic background, environmental exposures (such as diet, physical activity, medications, etc.). Their understanding might very well have implications outside Japan.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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