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Letter to the Editor Response

Response to Letter to the Editor From Sumi et al: "Lower Bone Turnover and Skeletal PTH Responsiveness in Japanese Compared to European Patients Receiving Hemodialysis"

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Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone; sHPT, secondary hyperparathyroidism.

To the Editor,

We would like to thank Sumi and colleagues (1) for their interest in our recently published paper "Lower Bone Turnover and Skeletal PTH Responsiveness in Japanese Compared to European Patients on Hemodialysis" (2). We hereby offer our response to their letter.

In our paper, we find that bone turnover markers are lower, even for a given level of parathyroid hormone (PTH) in Japanese vs European patients, indicating a lower skeletal response to PTH. Sumi et al comment that this could be due to more frequent use of active vitamin D and calcimimetics in Japanese patients, as they previously demonstrated that these treatments associate with a lower bone turnover marker/PTH ratio (3). However, as our findings, and those of others (4), indicate that skeletal responsiveness to PTH decreases with rising levels of PTH, more severe secondary hyperparathyroidism (sHPT) could also account for an apparent inverse relationship with these medications. To examine any independent effects, it would be necessary to take into account the degree of sHPT, for example by matching on PTH levels. We attempted this approach in a case-control analysis and found that bone turnover markers are higher in patients receiving cinacalcet compared to controls, at similar PTH levels (5). These findings are in line with experimental data demonstrating direct effects of calcimimetics in bone (6).

Sumi et al ask whether, in the face of reduced skeletal responsiveness, PTH levels should be kept higher to maintain normal bone turnover. They point out that despite lower PTH treatment targets, Japanese patients on dialysis have consistently better outcomes than their European counterparts. Actually, we believe it is worth considering whether lower bone responsiveness to PTH in chronic kidney disease (CKD) is an *adaptation*—a desensitization of the skeleton to protect against excessive bone resorption in the face of sHPT. Further, the clinical consequence of low bone turnover in CKD is not established. While the gold standard for diagnosing renal bone disease is the transiliac bone biopsy, studies informing on the prospective value of bone biopsy findings are not available. If we look to studies investigating the relationship between bone turnover markers and adverse outcomes, they consistently show greater risk of all-cause mortality, cardiovascular events, and fractures as bone turnover marker levels increase (7). Importantly, there does not seem to be any signal of harm at lower levels of bone biomarkers. If we compare these data to the complicated U-shaped relationship between PTH levels and outcomes (8), we could hypothesize that it may be more useful to evaluate the *effects* of PTH on target organs, rather than PTH levels alone.

To conclude, we do not believe that the mere existence of reduced skeletal responsiveness to PTH in CKD justifies targeting above normal PTH levels, and we fully agree with Sumi et al that further research is needed to establish treatment targets for sHPT. Prospective studies investigating the

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predictive value of PTH and bone turnover markers—alone and in concert—on clinically relevant outcomes, would be particularly welcome.

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Disclosures

S.M., M.V., and E.C. are members of the ERA CKD-MBD working group. H.K. and M.F. are members of the Japan CKD-MBD Forum. M.F. is a member of the CKD-MBD working group of the Japanese Society of Nephrology. P.E. reports institutional grants from Vifor FMC, Sanofi, and Amgen, honoraria from Vifor FMC and Amgen, and participation on Medice advisory board. E.C. is a consultant for IDS, DiaSorin, Nittobo, Fujirebio, bioMérieux and Werfen. Remaining authors report no conflicts of interest.

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