Serum PTH levels in dialysis: better safe than sorry

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Secondary hyperparathyroidism (SHPT) results in high parathyroid hormone (PTH) levels, induced by low calcium (Ca), high phosphate (P), and reduced calcitriol production in chronic kidney disease (CKD) patients.[1,2] Clinically, this "syndrome" is called CKD-MBD (Mineral Bone Disorder), with enhanced risk of renal osteodystrophy, progressive arterial calcification, and cardiovascular morbidity and mortality.[3] Both the Ca-sensing receptor (CaSR) and the vitamin D receptor (VDR) are fundamental regulators of parathyroid (PT) gland function and PTH secretion, and their activation induced by either increased serum Ca levels or calcitriol administration, reduces PTH expression and synthesis and PT gland hyperplasia rapidly in experimental models of chronic renal failure.[4] On the contrary, both reduced serum Ca and calcitriol levels result in decreased CaSR and VDR activity, which promotes PTH synthesis and secretion. In addition, CaSR regulates PTH gene expression and upregulates VDR. VDR activation in the gastrointestinal tract enhances Ca absorption, increasing serum Ca levels and reducing PTH through CaSR activation.[5] In summary, both high serum phosphate (P) and low serum Ca levels, together with low levels of calcitriol levels, typically in advanced CKD, are key players into the pathogenesis of SHPT,[6,7] and greatly down-regulation of both PT CaSR and VDR play an important role in the development of SHPT.[8] Intuitively, CaSR and the VDR are biologically targets for CKD-MBD treatment.

In their study, Yu et al. show that hemodialysis patients with low PTH level (<60 pg/ml) had a higher incidence of mortality and non-fatal cardiovascular events than those with SHPT (>600 pg/ml).[9] Authors found a significant difference in age between the two groups, but the incidence of the composite outcome remained significantly higher in the low PTH group than in the SHPT group (50% *versus* 27.8%). Interestingly, these data reflect results that we published a few years ago,[10] from the analysis of the FARO survey, suggesting that low doses of paricalcitol an active vitamin D treatment associates with reduced overall mortality as well as factor-adjusted mortality risks among dialysis patients with SHPT, even when serum iPTH levels are ⩽150 pg/ml. Moreover, in this analysis, patients who did not receive treatment had a poorer prognosis.[10]

It remains largely unknown while some subjects do develop low PTH (or lack of "ideal" rise of PTH, between 150 and 600 pg/ml. Similarly, having a "low" PTH <50 pg/ml, after surgical parathyroidectomy does not have the same clinical meaning as "spontaneous" suppression of PTH.

A few studies using heterogeneous methods that included patients with different dialysis vintages showed an association between low PTH levels and all-cause mortality.[11,12] Also, it is well known that at present, a high proportion of patients receiving dialysis therapy have relatively low serum PTH levels.[13] Potentially, the observation that vascular calcifications are more prevalent in patients undergoing dialysis who have low PTH levels than in those with normal or moderately elevated levels, in association with low-turnover bone disease, supports the hypothesis that this condition favors mineral deposition in extra-skeletal tissues instead of bone.

In summary, Yu and coauthors are showing that, in dialysis patients serum, PTH levels lower than 100 pg/ml are associated with poor outcomes.[9] Therefore, all the causes that potentially contribute to over-suppress PTH, such as high Ca concentration in dialysis bath, high doses of calcium-based P-binders, and high doses of active vitamin D and/or calciminetics, should be considered in this population. Low doses of vitamin D might be maintained.[10]

Furthermore, other therapies should be considered. The calcimetic cinacalcet can provide salutary effects on CKD-MBD in severe SHPT and might be an initially effective PTH-lowering therapy prior to surgical parathyroidectomy as well as an alternative treatment in the patients unsuitable for surgery.[14] The emerging importance of RANK ligand inhibitor (denosumab) to promote calcium influx into bone (independent of PTH) may be considered even in CKD patients.

In conclusion, SHPT management has rapidly progressed in the last decade. The introduction of targeted therapies, such as selective VDR and CaSR modulators, offers an increased opportunity to adequately control elevated PTH, without over suppression, especially in patients with CKD receiving dialysis.

Conflict of interest statement

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