Do calcimimetics directly alter bone remodeling?

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Secondary hyperparathyroidism is an almost inevitable consequence of untreated chronic kidney disease (CKD), resulting in disordered skeletal remodeling and mineralization defects. Thus, due to the high circulating levels of parathyroid hormone (PTH), both osteoblast and osteoclast surfaces may be augmented and ultimately bone volume may be reduced (11). In CKD, synthesis of 1,25-dihydroxyvitamin D [1,25(OH)2D] is impaired. This occurs at least in part due to suppression of renal 25-hydroxyvitamin D-1α-hydroxylase [the enzyme synthesizing 1,25(OH)2D] by retained phosphate and by elevated concentrations of FGF23 (16), and in part because of loss of renal parenchyma. As a consequence, low levels of 1,25(OH)2D develop in stage 3 CKD leading to reduced calcium absorption (1). The low 1,25(OH)2D and resultant hypocalcemia can lead to the development of secondary hyperparathyroidism mainly due to the fact that 1,25(OH)2D via the vitamin D receptor, and extracellular ionized calcium [Ca2+]e, by activating the calcium-sensing receptor (CaSR), coordinately regulates PTH biosynthesis and parathyroid cell growth. The CaSR is a G protein-coupled receptor that responds to [Ca2+]e in particular, but also to multiple extracellular cations (2). In addition to modulating parathyroid function, CaSR also regulates renal calcium reabsorption. More recently, CaSR has also been reported to function in vitro in a variety of skeletal cells, including osteoblasts, bone marrow stromal cells, monocyte macrophages, and osteoclasts (3). Furthermore, in vivo studies showed that transgenic mice with a constitutively active mutant CaSR targeted to mature osteoblasts demonstrate enhanced bone resorption (4), whereas mice with deletion of both CaSR and 25-hydroxyvitamin D-1α-hydroxylase exhibit reduced bone resorption (5). Other studies noted the importance of an alternate extracellular cation-sensing G protein-coupled receptor in bone and specifically in osteoblasts (13) and targeted deletion of the gene encoding this receptor has been reported to produce either osteopenia (14) or no skeletal phenotype (18).

Calcimimetics are small orally active agents that act as positive allosteric modifiers of the CaSR. As type II agonists, they do not activate the receptor directly but instead increase receptor sensitivity to the type I agonists calcium and polycations (e.g., neomycin, gadolinium) (6). One such calcimimetic, the phenylalkylamine derivative cinacalcet HCl, has been approved for clinical use in the treatment of secondary hyperparathyroidism in CKD and in the treatment of parathyroid carcinoma.

In the American Journal of Physiology-Renal Physiology, Finch and colleagues (5) report a comparison between cinacalcet and a potent analog of 1,25(OH)2D, paricalcitol, on bone and mineral metabolism in uremic rats. These animals have creatinine clearances “equivalent” to patients with CKD 3–4 and manifest secondary hyperparathyroidism. Although both agents suppressed elevated serum PTH levels, among their findings was that bone resorption was increased and bone volume was reduced after treatment with cinacalcet. This observation has great translational importance because a direct negative effect of calcimimetics on the skeleton would be of major concern for the use of these agents to control parathyroid disease.

What can we learn from the existing literature that may help in placing this observation in context? Using the phenylalkylamine derivative NPS R-568 that acts as an agonist at the CaSR, it has been reported that peritrabecular fibrosis in bone of uremic rats with secondary hyperparathyroidism was reduced and that volumetric cortical bone mineral density (BMD) was improved (17). Nevertheless, the elevated osteoclast and osteoblast surfaces characteristic of hyperparathyroidism which were observed in these animals were not significantly reduced by this calcimimetic even though PTH was reduced. In a more recent study using the arylalkylamine calcimimetic AMG 641 in an adenine-induced uremic rat model of secondary hyperparathyroidism, reductions in trabecular bone volume and trabecular number and increases in trabecular spacing were prevented. Again, however, although osteoblast surface/bone surface was significantly decreased, consistent with the decrease in secondary hyperparathyroidism induced by the calcimimetic, there were no significant decreases in bone resorption (osteoclast surface/bone surface) (7).

What has been the experience in humans? In a year-long placebo-controlled trial in patients with primary hyperparathyroidism, cinacalcet administration increased biomarkers of bone turnover (although they remained in the normal range) despite a drop of ~20% in serum PTH levels. Furthermore, there were no positive effects on BMD after 1 yr compared with placebo (12). Several small studies in hemodialysis patients (8–10, 19) have now demonstrated that as cinacalcet treatment decreases circulating PTH levels, cinacalcet may also decrease biomarkers of bone turnover. However, most of these studies may have been confounded by the concurrent use of vitamin D and/or phosphate binders in the treatment of these patients.

Clearly therefore, the work of Finch et al. (5) on the resorptive effects of cinacalcet on the skeleton needs first to be confirmed in further animal studies. Additionally, the mechanism of action of calcimimetics in bone needs to be clarified; that is, whether this effect occurs via the CaSR, some other skeletal calcium receptor, or some other direct or indirect mechanism. Finally, the skeletal effect of cinacalcet in humans needs to be clarified in larger studies of patients with CKD and renal osteodystrophy. Overall, such studies should shed light on important new physiology of bone remodeling but would also be paramount in clarifying the therapeutic role of what has become an important part of our armamentarium for managing hyperparathyroidism.

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