Decreased Circulating Sclerostin Levels in Renal Transplant Recipients With Persistent Hyperparathyroidism: Who's Conducting the Orchestra?

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Mature osteocytes are the conductors of the bone orchestra, and make up over 90% of skeletal cells. They sense mechanical stimuli and changes in levels of serum 1,25-dihydroxyvitamin D, PTH and indirectly, serum phosphate. In response, they regulate the balance between osteoblast and osteoclast activity to improve bone strength and to maintain systemic mineral homeostasis.

Osteocyte products include FGF 23 and sclerostin, a soluble protein encoded by the SOST gene. FGF23 influences bone by modulating phosphate balance and vitamin D metabolism; with higher levels reducing phosphate reabsorption in the proximal tubule, reducing the activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and influencing PTH production. On the other hand, sclerostin is involved in the response of bone to mechanical strain, and by signaling to cells on bone remodeling surfaces, sclerostin controls the balance between osteoclast resorption and osteoblast formation of bone.

Before proceeding further, to understand the role of sclerostin in bone, one needs a quick sketch of some important bone biology. Wnts are members of a family of proteins secreted by bone marrow stromal cells and osteoblast progenitors. They bind to low density lipoprotein receptor-related proteins (LRP) on cells of the osteoblast lineage[1] and activate the highly regulated Wnt/ß-catenin canonical signaling pathway (Figure 1). Stabilization of ß-catenin and its translocation to the nucleus induces osteoblast maturation, and an increase in the expression of osteoprotegerin (OPG) which promotes increased bone formation by mature osteoblasts. The increase in OPG also changes the ratio of OPG to RANKL (the receptor activator of nuclear factor kappa-B ligand), which reduces osteoclastogenesis and osteoclastic bone resorption.

When sclerostin is expressed by osteocytes, this relatively low molecular mass (~28 kDa) glycosylated protein is transported to the bone surface via the osteocyte canalicular system, where it binds to LRP 5/6 and LRP4 on immature osteoblasts.[2] This binding inhibits anabolic Wnt signaling and prevents inchoate osteoblasts from maturing. Additionally, sclerostin is reported to reduce in vitro mineralization, by down regulating endopeptidases that degrade the peptides bound to bone mineral, which inhibit further mineral deposition.[3] These changes are likely to have patient-level importance, because a number of studies have now reported that higher serum sclerostin levels predict increased fracture risk, independent of changes in bone mineral density.[4,5]

Circadian increases in PTH, and daily subcutaneous injections of teriparatide (PTH 1-34) used for the treatment of osteoporosis, are anabolic to bone. Although many signaling pathways are involved in this response, the anabolic actions of intermittent PTH are due at least in part to the activation of osteocyte PTH/PTHrP receptors, which downregulate sclerostin expression.[6] Continuous 18-hour infusions of PTH 1-34 also suppress sclerostin; although the maximum suppressant effect is seen early, whereas markers of bone resorption increase linearly throughout the 18-hour infusion.[7] Therefore, anabolic effects caused by a reduction in sclerostin may only occur early after PTH levels rise, whereas prolonged elevations of PTH, as might be found with primary hyperparathyroidism, or "tertiary" hyperparathyroidism after kidney transplantation, are likely to result in greater bone resorption than formation.[8]

Serum sclerostin values increase with reduction in eGFR,[9] and in patients on hemodialysis, sclerostin values are approximately 5-fold higher than in premenopausal women without CKD and 2-fold higher than postmenopausal women.[10] Sclerostin values are inversely correlated to serum PTH, to osteoblast number and function and to parameters of bone turnover.[10] Somewhat paradoxically, in a cross-sectional study of patients with CKD, urinary excretion of sclerostin was around 10-fold higher in patients with CKD stage 5 than patients with CKD stage 1, and the *absolute* amount of excreted sclerostin increased as kidney function declined.[11] This suggests that skeletal production of sclerostin might increase with CKD. Although this could result from skeletal resistance to PTH signaling, sclerostin values were also higher in patients who had hyperparathyroidism and high bone turnover on bone trephine.[10] Other studies suggest that sclerostin expression by calcified vasculature may contribute to circulating levels,[12] and that elevation of serum sclerostin may represent a physiological adaptation to inhibit progressive vascular calcification.[12,13]

In this issue of Transplantation, Evenepoel et al[14] exploit the dramatic changes that occur following kidney transplantation and parathyroidectomy to investigate acute and longer

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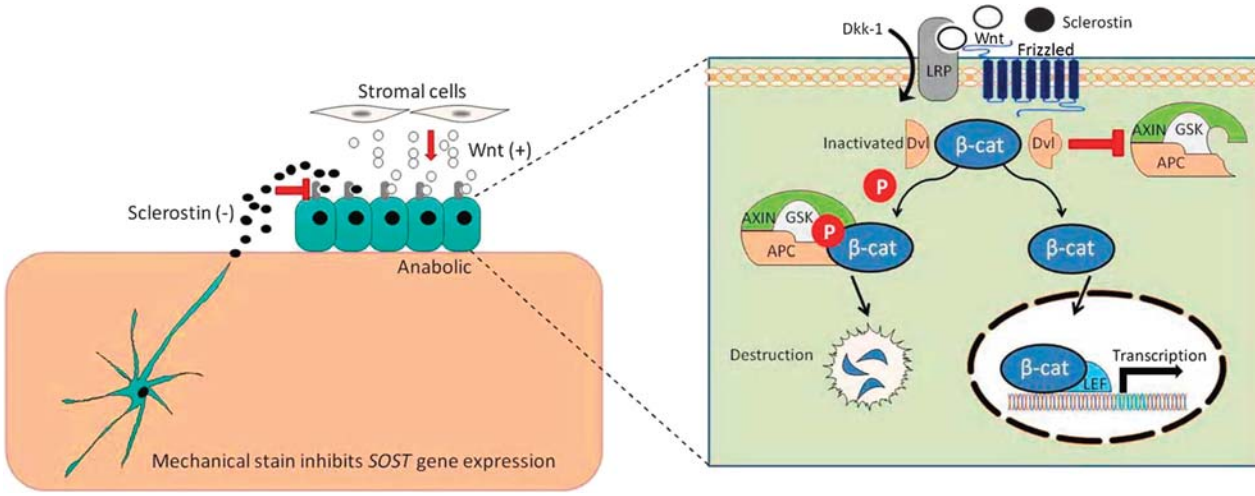

FIGURE 1. The Wnt signaling pathway is anabolic for bone. Wnts are produced by stromal cells and osteoblast progenitors and bind to the osteoblast Frizzled-LRP 5/6 receptor complex. When sclerostin binds to LRP, Wnt signaling is inhibited. Secreted frizzled-related proteins bind directly to Wnts to prevent their interaction with the receptor complex. Dkk-1 bound to LRP5/6 prevents the binding of Wnt, or when complexed with Kremen can cause the internalisation of LRP5/6, and a longer lasting inhibition of Wnt signalling. Dkk-1, Dickkopf-1; ß-cat, ß-catenin; LRP, low density lipoprotein-receptor-related protein; Dvl, dishevelled; LEF, lymphoid enhancer binding factor; APC, adenomatous polyposis coli; GSK, glycogen synthase kinase. The 'destruction complex' comprises Axin, APC, and GSK. Modified with permission from Elder GJ. Pathophysiology of CKD-MBD. *Clinic Rev Bone Miner Metab*. 10;2011:128–141.

term sclerostin responses. They show that the median decrease in sclerostin levels 3 months after transplantation is 61%, and because sclerostin is filtered and reabsorbed in the proximal tubule,[11] they hypothesize that this early reduction in sclerostin is due to posttransplant proximal tubular dysfunction. Consistent with this hypothesis, they report that sclerostin levels rise by 12 months after transplantation and are similar to levels of CKD controls. However, in transplant recipients referred for parathyroidectomy, sclerostin values are 3-fold lower than in dialysis patients matched for levels of serum PTH, and sclerostin values increase after these patients undergo parathyroidectomy, as might be expected from a reduction in PTH suppression. The authors speculate that, together with increased ionised calcium levels, lower serum sclerostin values might assist in discriminating secondary from tertiary hyperparathyroidism.

Although requesting a sclerostin level for this indication is currently premature, these data are particularly valuable in an era when sclerostin monoclonal antibodies will soon be available in the clinic. How will responses to the antibody differ in elderly osteoporotic patients with CKD and high sclerostin levels or following kidney transplantation, and will sclerostin antibodies be useful for other facets of CKD mineral and bone disorder? It will be particularly important that we develop a better understanding of sclerostin physiology in CKD and after transplantation to answer these questions and to gain greater insight into how CKD affects the bone orchestra's performance.

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