Renal osteodystrophy (ROD) is one of the three components of chronic kidney disease–mineral and bone disorder (CKD-MBD) (1). Patients with CKD may develop various types of bone disease, spanning the spectrum of extreme situations such as severe osteitis fibrosa, osteomalacia, mixed osteopathy, and adynamic bone disease. In addition, patients may have osteoporosis, which increases the risk for fractures, both in advanced and in less severe CKD stages (2–4), which, in turn, result in excess mortality (5,6). In many instances, the pathogenesis of the precise type of ROD in a given patient seems to be obvious, for instance secondary hyperparathyroidism for osteitis fibrosa, vitamin D deficiency or aluminum overload for osteomalacia, hyperparathyroidism for adynamic bone disease, and advanced age and female gender for osteoporosis. However, other factors may also play a role, including abnormal levels or functions of hormones involved in mineral metabolism (other than parathyroid hormone [PTH] and calcitriol), in gonadal function, or in energy metabolism (in particular diabetes) (7); abnormal growth factors or cytokine levels and dysfunction of their receptors (8,9); acidosis (10); oxidative stress and advanced glycation end products (11); uremic toxins (12,13); metal overload (14,15); insufficient mechanical loading (8); and inappropriate diets and malnutrition (16,17). A better understanding, at the patient level and the molecular level, of the underlying pathogenesis and the risk factors involved in ROD including osteoporosis might help to prevent this important health problem in the patient population with CKD (6).

In this issue of CJASN, Čejka et al. (18) hypothesize that sclerostin, a protein expressed by osteocytes, may play an important role in ROD, on the basis of the results of a cross-sectional bone biopsy study done in 60 patients who had stage 5D CKD and were on long-term hemodialysis treatment. Sclerostin is the gene product of SOST, discovered in 2001 (19). Inactivating mutations of the gene lead to sclerosteosis, and deletions in noncoding regions downstream of the gene were identified in van Buchem disease. The skeletal manifestations of both diseases consist in progressive generalized osteosclerosis without bone fragility. Although the SOST gene is expressed in several tissues including the heart, aorta, and liver, with high levels in the kidney, the postnatal expression of the sclerostin protein is limited to osteocytes, chondrocytes, and cementocytes. The main action of sclerostin is a decrease in bone formation. It inhibits osteoblast proliferation and differentiation and promotes osteoblast apoptosis. Whether sclerostin also acts on bone resorption, either directly or indirectly, remains to be seen. At the molecular level, sclerostin is an inhibitor of canonical wnt signaling via binding to the LDL receptor–related protein 5 and 6 (LRP5/6) co-receptors (Figure 1A). Wnts are glycoproteins that bind to receptors of the Frizzled family. Activation of these receptors leads to intracellular accumulation of β-catenin and its translocation to the nucleus and initiation of target gene transcription, via the T cell factor/lymphoid enhancer factor transcription factor, in various cells, including the osteoblast. Thus, the current hypothesis is that sclerostin is able to block canonical wnt signaling as other inhibitors do, such as Dickkopf-1 (Dkk-1), Kremen, or Wif in osteoblasts. However, the precise role of LRP5 and the Wnt pathway in bone remains a matter of controversy (20). Moreover, sclerostin is able to promote intracellular bone morphogenic protein 7 (BMP7) proteasomal degradation and thus antagonizes the BMP7 signaling pathway only in cells expressing both proteins (21).

Present understanding of the regulation of SOST/sclerostin expression by osteocytes is as yet incomplete (19). On the one hand, 1,25-dihydroxyvitamin D (calcitriol); glucocorticoids; TNF-α; and probably also BMP2, 4, and 6 are able to stimulate SOST/sclerostin expression. On the other hand, mechanical loading has been shown to decrease SOST mRNA and sclerostin levels in osteocytes. Similarly, administration of PTH reduces sclerostin expression both in vitro and in vivo, probably via a direct cAMP-dependent effect. However, the PTH–sclerostin axis is far from being fully understood because both intermittent and continuous PTH administration downregulate sclerostin expression in osteocytes, whereas only intermittent PTH is osteoanabolic (22). Recently, estrogen administration to postmenopausal women was shown to reduce circulating sclerostin levels (23). Figure 1B shows the factors involved in the regulation of SOST/sclerostin expression.

Interestingly, Čejka et al. (18) found an inverse relation between serum sclerostin and intact PTH
Moreover, sclerostin was a strong predictor of bone turnover and osteoblast number. Low sclerostin serum levels proved to be a better positive predictor than iPTH for high bone turnover and osteoblast number. In contrast, iPTH was superior to sclerostin for the negative prediction of high bone turnover. Interestingly, serum levels of Dkk-1 did not correlate with iPTH or any of the histomorphometry parameters. Of note, a similar inverse relationship between serum sclerostin and iPTH was recently reported in patients with primary hyperparathyroidism (24). As to circulating bone turnover markers, no correlation with serum sclerostin was found in patients with primary hyperparathyroidism (24) or in healthy postmenopausal women (25,26). However, the percentage changes in bone formation or resorption markers in early response to estrogen treatment in postmenopausal women

Figure 1. (A) Putative mechanisms of action on bone-forming osteoblasts of sclerostin (SOST) secreted by osteocytes through inhibition of the Wnt signaling pathway. TCF/LEF, T cell factor/lymphoid enhancer factor (Wnt co-receptors). (B) Bone formation by osteoblasts is inhibited by SOST/sclerostin, which is expressed in osteocytes. PTH, estrogen, and mechanical loading inhibit sclerostin expression and thereby stimulate bone formation indirectly. In contrast, glucocorticoids; BMP2, 4, and 6; and calcitriol stimulate sclerostin expression. The latter thus indirectly inhibit osteoblast activity and bone formation. Adapted from reference 19; bone microscopy picture from Wikipedia.
correlated significantly with those of serum sclerostin levels (23).

Of note, serum values of sclerostin were considerably higher in patients with stage 5D CKD (18) than in healthy control subjects, patients with primary hyperparathyroidism, or postmenopausal women without known CKD (23–26). As suggested by Cejka et al. (18), the difference between the population with CKD and people free of CKD may come from increased sclerostin retention secondary to renal function impairment and/or increased sclerostin production. Differences in sclerostin assay methods may also have played a role.

The demonstration that the level of serum sclerostin, which is directly produced by osteocytes, is a good predictor for bone formation in patients with CKD may be of clinical interest for at least two reasons. First, serum iPTH, which is produced elsewhere, reflects bone turnover only indirectly and its predictive value is limited. However, Cejka et al. did not compare the predictive value of sclerostin with that of other circulating bone formation markers such as bone-specific alkaline phosphatase, which may be a more appropriate marker to use in CKD (27). Most important, the determination of serum sclerostin alone does not seem to help distinguish adynamic bone disease from normal bone turnover. Clinically useful markers for this latter distinction still need to be developed. Second, sclerostin is now a promising therapeutic target for osteoporosis. Administration of anti-sclerostin antibodies has been shown to prevent and cure both cortical and trabecular bone loss and to enhance bone strength in ovariectomized rats, a model of postmenopausal osteoporosis (28), and also to increase bone mineral density in humans (29). Such a therapeutic approach might be of interest in patients with CKD and fractures as well. This may be worth testing.

Finally, correlation does not mean causation. The observed negative correlation between serum sclerostin and iPTH should stimulate further work, allowing more detailed insight into the potential role of sclerostin in impaired bone formation and the skeletal resistance to PTH seen in many patients with CKD (30).

Disclosures

None.

References


23. van Lierop AH, Witteveen JE, Hamdy NA, Papapoulos SE: Patients with primary hyperparathyroidism have lower circu-


