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Sclerostin levels in CKD patients: an important, but not definitive, step on the way to clinical use

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Sclerostin, an inhibitor of the Wnt signaling pathway, inhibits bone formation. In a study of vascular biopsies of patients undergoing kidney transplantation, Qureshi *et al.* demonstrate that circulating sclerostin levels are associated with vascular calcification (VC). This adds to an emerging body of literature implicating sclerostin as a key link between chronic kidney disease–mineral and bone disorder and cardiovascular disease. Some confounders of this association remain, and the mechanisms by which sclerostin promotes VC have yet to be elucidated.

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Sclerostin is a new and potentially important player in the well-known bone–vascular axis in chronic kidney disease (CKD) and end-stage renal disease.[1] Sclerostin, a 22-kDa protein secreted by osteocytes and chondrocytes, was originally described in human carriers of a mutation of its gene, *SOST*, at the beginning of the 21st century (Figure 1). Mutations of this gene lead to a rare genetic disease characterized by high bone mass, namely sclerosteosis, and so sclerostin was found to be a potent inhibitor of bone formation. Osteocytes effectively act as mechanoreceptors for bone formation, and sclerostin was shown to play a key role in the development of osteoporosis associated with lack of mechanical stimulation, as observed in weightless astronauts or in patients confined to bed for a long period of time. Animal studies demonstrated that sclerostin levels were dramatically increased in unloaded bones with impaired bone formation,[2] implicating sclerostin as the protein link between mechanical stress and bone formation. Sclerostin acts as an inhibitor of bone formation by inhibiting the canonical Wnt pathway, which itself promotes bone formation by dual anabolic and anticatabolic actions. Most studies, in both the general and the osteoporotic populations, suggest a positive association between sclerostin levels and bone mineral density (BMD), though the nature of this association is not yet fully understood. The assertion that circulating sclerostin may reflect the number of osteocytes remains hypothetical. Both the diabetic state and gender also influence sclerostin levels.[3]

Several clinical and biological variables have been described as determinants of sclerostin secretion. Among the most important of them, age and CKD have been found to be directly associated with increased sclerostin concentrations, whereas an inverse correlation has been observed between circulating sclerostin and parathyroid hormone levels and other bone biomarkers.[2]

In the context of CKD, sclerostin concentrations clearly increase as glomerular filtration rate decreases; whether this is due to reduced renal clearance, increased skeletal production, or both is still a subject of debate. Therefore the biological significance and interpretation of circulating sclerostin levels in CKD remain uncertain. As in non-CKD populations, most observational studies have reported a negative association between serum sclerostin and parathyroid hormone and/or other bone biomarkers in patients with CKD. Age, serum phosphorus, and body mass index (or height) are the variables that were most frequently found to be positively associated with serum sclerostin.[4] In a bone biopsy study of 60 hemodialysis (HD) patients, Cejka *et al.* demonstrated that sclerostin levels were inversely correlated with bone formation rate, and suggested that it could be a useful biomarker for the prediction of high (but not low) bone turnover.[5] A similar finding was also made in a cohort of peritoneal dialysis patients, though sclerostin did not outperform bone alkaline phosphatase as a predictor of bone turnover.[3] As in non-CKD populations, a puzzling positive association was found in observational, cross-sectional studies between circulating sclerostin levels and BMD in CKD and HD patients.[6,7] In a longitudinal study of 81 HD patients, high sclerostin levels at baseline were predictive of bone loss over a 1-year period;[7] however, these interesting results have yet to be confirmed. Although preliminary data suggest

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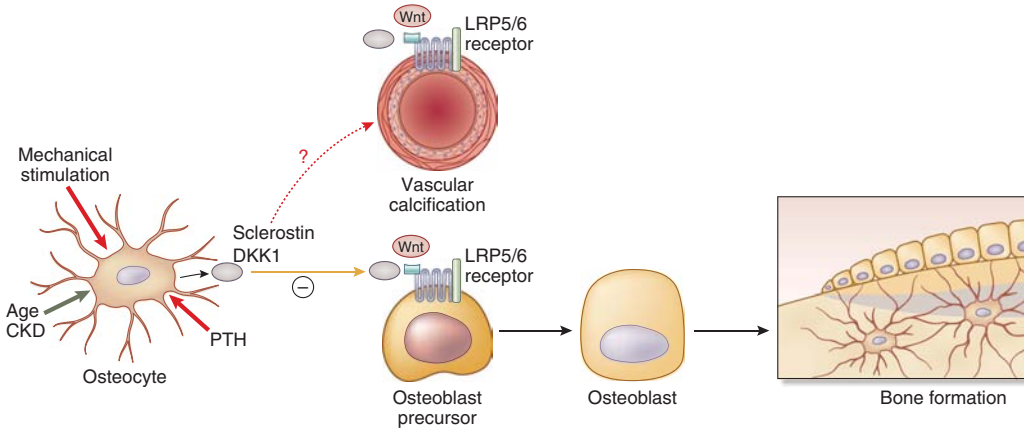

Figure 1 | Sclerostin: regulation, bone effect, and (hypothetical) link with vascular calcifications. The absence of mechanical stimulation induces sclerostin secretion by osteocytes. Sclerostin inhibits the Wnt receptor (LRP5/6), inducing inhibition of differentiation and proliferation of osteoblast precursors into mature osteoblasts. Age and CKD increase sclerostin secretion. Parathyroid hormone (PTH) decreases sclerostin production. Green arrow: Promotion of sclerostin production by osteocytes. Red solid line: Inhibition of sclerostin secretion by osteocytes. Yellow line: Inhibition of the Wnt pathway by sclerostin in bones through the LRP5/6 receptor. Black arrow: Regular way of bone formation. The link between sclerostin and vascular calcifications remains hypothetical (red dotted line). Red solid line: Inhibition of sclerostin secretion by osteocytes. Grey solid line: Stimulation of sclerostin secretion by osteocytes. Yellow line: Inhibition of the Wnt pathway by sclerostin in bones through the LRP5/6 receptor. Black arrow: Regular way of bone formation. The link between sclerostin and vascular calcifications remains hypothetical (red dotted line).

sclerostin may be a promising biomarker in assessing bone health in CKD patients, it is not clear whether it has any added value compared with existing bone biomarkers in predicting bone turnover and/or BMD. Its clinical utility in determining hard clinical end points such as fracture is unknown. Indeed, given that global bone strength is determined both by qualitative changes in bone (for instance, mineralization and turnover) and by quantitative changes in bone volume and density, it is perhaps unrealistic to expect a single biomarker to predict such outcomes.

In CKD patients, abnormalities in bone turnover as well as osteoporosis are associated with an increased risk of vascular calcifications (VCs) and cardiovascular mortality. *In vivo* data have implicated the Wnt signaling pathway in the development of VCs, and there is an increase in sclerostin expression in the media of mice that develop VCs. Increased expression of sclerostin was also shown *ex vivo* in calcified aortic valves of HD patients and in skin biopsies taken from HD patients with calciphylaxis.[1] Qureshi *et al.*[8] (this issue) examined the relationship between sclerostin and VCs in patients undergoing kidney transplantation. A particular strength of the study was the use of *both* histological assessment of inferior gastric artery calcification and quantification by spiral computed tomography of coronary artery calcification. Furthermore, the authors were able to study vascular sclerostin expression by two different methods (immunochemistry and mRNA) in calcified epigastric arteries from 89 patients undergoing kidney transplantation. They found a significant positive association between VCs and circulating sclerostin levels. Surprisingly, there was no expression of sclerostin in calcified vascular tissues. The absence of sclerostin expression *in loco* does not preclude this protein from being implicated in the pathophysiology of VCs via a systemic effect, be it direct or indirect. These results have to be interpreted in the light of conflicting previous reports. For example, while some groups found a positive correlation between circulating sclerostin levels and VC scores in HD and CKD patients without diabetes, others have described a negative correlation in patients with diabetes and in chronic HD patients, or found no correlation in peritoneal dialysis patients.[4] Thus, the true relationship between VCs and sclerostin is far from being well understood. Moreover, such discrepant results are also observed when the ability of sclerostin to predict mortality in CKD patients is studied.

How can such conflicting results be explained? First, populations studied are frequently not comparable. Dialysis status and CKD staging could play a role and influence the results. Both dialysis and predialysis patients have been included in the same analysis by Qureshi *et al.*,[8] and this could be a source of confusion. Second, as the authors themselves recognize, the method of statistical analysis can profoundly affect the results —indeed, the conclusions of Qureshi *et al.* might have been different if cardiovascular history had been included in the multivariate analysis. Third, the techniques used for scoring VCs were not always the same, with differing sensitivities. Last but not least, it is increasingly evident that measuring sclerostin in plasma is not an easy task. Durosier *et al.*, who measured sclerostin in 187 healthy subjects aged 65 years with three different enzyme-linked immunosorbent assays, found as much as a 20- to 30-fold difference in sclerostin levels between the assays.[9] These analytical differences could be even more relevant in the context of end-stage renal disease, where inactive fragments could accumulate, like with parathyroid hormone measurements.[1] There is thus an urgent need for standardization between the assays and common agreement on the different epitopes to be recognized.

The data published by Qureshi *et al.*[8] are a solid basis for future research in the putative link between bone and cardiovascular disease. The fact that sclerostin is only expressed in bones but not in the vascular wall, yet is still associated with VCs, reinforces the supposed link between bone and VCs. However, until analytical improvements in its measurement are achieved, we do not know whether sclerostin measurement is useful in clinical practice to assess bone turnover, changes in BMD, and/or VCs. Furthermore, there is a large overlap in sclerostin concentrations between calcified and noncalcified patients, and results from receiver operating characteristic curve analysis do not look particularly impressive, even if statistically significant. In other words, even if sclerostin levels are higher in patients with VCs, from a clinical perspective, the discriminating power of this biomarker is certainly too low to be useful at the individual patient level. The great interest in the field of serum sclerostin as a new biomarker is also explained by the fact that anti-sclerostin antibody therapy has recently become available and has been shown to be effective in osteoporotic patients in a recent phase 2 trial. Initial studies in animal CKD models show promising results, especially on bone parameters and in animals with normal to low bone turnover. This last point is of interest as our arsenal to treat HD patients with adynamic bone disease (and low BMD) is very limited. Benefit of such therapy, for both bone health and VC, would be the definitive proof that the associations described above are really causal and/or clinically important. Also, we simply do not know whether determining sclerostin levels would be of any value as an aid in the clinical decision of whether to initiate or monitor therapy with anti-sclerostin antibody.

The description of sclerostin as the cross-talk between bone and vasculature is at this point still an illusion from a clinical point of view, but this pathway will be the source of fascinating basic, analytical, and clinical work in the future.

DISCLOSURE
All the authors declared no competing interests.

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Chinese herbal medicines and chronic kidney disease: a positive outcome in a large patient study in Taiwan

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The worth of traditional Chinese herbal medicines for chronic kidney disease (CKD) patients remains in debate. Lin *et al.* used a research database in Taiwan to identify almost 25,000 stage 3–5 newly diagnosed CKD patients who, after diagnosis, did or did not use prescribed Chinese herbal medicines for CKD. Reduced risk of end-stage kidney disease from specific traditional medicines warrants reflection on a CKD therapy resource that is largely ignored by Western medicine.

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Current conventional-medicine treatment options for chronic kidney disease (CKD) are limited in efficacy, and often do not inhibit progression of CKD to end-stage kidney disease (ESKD), an increasing and costly disease in many societies. Nonetheless, there is continuing concern in Western medicine about the value of traditional Chinese herbal medicines as treatments for patients with CKD. Many active components