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NEPHROLOGY - REVIEW

Sclerostin: a new biomarker of CKD–MBD

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Abstract
The causes of the increased cardiovascular risk associated with kidney diseases partly reside in the chronic kidney disease–mineral bone disorder (CKD–MBD) syndrome. Three cardiovascular risk factors [hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23)] levels have been discovered within the CKD–MBD over the last decades. In addition, sclerostin is recently presented as a new bone and vascular disease biomarker. This 22-kDa glycoprotein, secreted mainly by osteocytes, is a soluble inhibitor of the canonical Wnt pathway that has a pivotal role in bone biology and turnover. CKD patients are reported with higher levels of sclerostin, and levels decrease during dialysis. Sclerostin is associated with vascular calcification and CV risk in CKD, although data are still controversial. The question whether serum sclerostin has protective or deleterious role in CKD–MBD pathophysiology, and therefore in cardiovascular risk and overall mortality, is still open and needs to be answered. The standardization of assays and the establishment of a clear cut-off values when sclerostin starts to switch from physiological to pathophysiological role have to be another important step. Further research is needed also to define its relationship with other CKD–MBD biomarkers for future diagnostic and therapeutic strategies.

Keywords Sclerostin 1 · Chronic kidney disease 2 · Bone turnover 3 · Vascular calcification 4 · Cardiovascular mortality 5

Sclerostin in physiological milieu and chronic kidney disease

Wnt/β-catenin signaling and circulating sclerostin

The kidney disease is associated with high mortality rates, mainly due to cardiovascular complications [1, 2]. The causes of the increased cardiovascular risk associated with kidney diseases partly reside in the chronic kidney disease–mineral bone disorder (CKD–MBD) syndrome [3]. Three cardiovascular risk factors [hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23)] levels have been discovered within the CKD–MBD over the last decades [4]. In addition, sclerostin is recently presented as a new bone and vascular disease biomarker.

Sclerostin is a soluble protein coded by the SOST gene (gene that encodes sclerostin) on chromosome 17q12–q21, produced almost exclusively from osteocytes and to a lesser extent by other cell types, including osteoclast precursors, renal and vascular cells. It reduces bone formation by inhibiting the anabolic canonical wingless-type mouse mammary tumor virus integration site (Wnt) pathway in osteoblasts [5] suppressing osteoblast activity and down-regulating bone turnover [6]. Activation of the Wnt/β-catenin pathway promotes osteoblastogenesis by stimulating osteoblast differentiation and blocks apoptosis and osteoclastogenesis by increasing the osteoprotegerin/receptor activator of nuclear factor kappa-B ligand (OPG/RANKL) ratio [7–9]. Sclerostin regulation in bone is complex and partially understood, regulated by growth factors and hormones that affect bone formation. Here, calcitonin and bone morphogenetic proteins

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are considered as stimulating factors, and PTH and estrogens suppress its expression [10].

In healthy bone in general population, osteocytes maintain a balance between osteolysis and osteogenesis through the control of sclerostin secretion. Serum sclerostin levels are higher in males reflecting total-body skeletal mass (osteocyte number) but are reported to increase in both genders across the adult lifespan, partially explained by declining estrogen levels with aging, occurring in both women and men (through reduced aromatization of testosterone to estradiol) [11]. However, it is generally accepted that sclerostin in postmenopausal women reflects bone mineral density [12]. Undetectable or very low levels of sclerostin in patients with sclerosteosis and Van Buchem's disease result in excessive bone growth and increased bone strength [13].

Sclerostin in relation to the renal function, and its role in bone turnover in CKD, and the kinetic in RRT

Despite its central role in bone biology, little is known about the metabolism or elimination of this molecule. Sclerostin is a small peptide of a 22-kD and 213-amino acid protein. Compared to adult individuals with normal renal function, circulating levels of sclerostin started to increase gradually as kidney function declines reported to be approximately 3–4 times higher in patients with end-stage renal failure (ESRD) [14–16]. Apart from many other peptides, renal function reduction does not seem to affect sclerostin serum levels since also tubular excretion tends to increase [17]. On the other hand, there is no clear answer if sclerostin is dialyzable. While reporting that sclerostin levels in hemodialysis (HD) correlate well with Kt/V [18], data from CONTRAST—a randomized control trial—showed that the decreased level of sclerostin in hemodiafiltration (HDF) is dependent on the magnitude of the convection volume, but those were found unaltered in HD patients [19]. In addition, in PD patients, total sclerostin elimination in the dialysate was found to be 2.5 times higher compared to urine [20]. After kidney transplantation, serum sclerostin decreases initially, but increases again over time from transplantation [21, 22]. Alternatively, it is suggested that increased circulating levels found in CKD may be the effect of the enhanced production by osteocytes [6]. Although the bone compartment is one candidate for increased production, the exact source of sclerostin detected in the circulation is not known yet. Firstly, it was suggested that an increase in osteocyte production is most likely the primary event that leads to the elevation in serum sclerostin levels observed in CKD patients [23]. Thereafter, Ishimura et al. reported significant, independent, and positive association of serum sclerostin with BMD of both cortical and cancellous bone [24]. There are several observational studies reporting significant and independent positive association between serum phosphate, FGF23, and sclerostin concentrations [14, 25] and negative relationship with PTH, qualifying sclerostin as a possible candidate to aggravate PTH resistance in CKD [26]. Kramer et al. nicely explained how much skeletal PTH actions rely upon sclerostin physiology [27]. In uremia, high sclerostin levels may exacerbate PTH resistance, which could cause and/or aggravate ABD as well. On the other hand, PTH suppresses sclerostin in osteocytes, increasing bone mass and the rate of bone remodeling. However, high sclerostin levels coexist with high PTH levels in patients with advanced CKD, possibly suggesting skeletal resistance to the action of PTH [16, 28], similar to FGF23 resistance explaining the coexistence of high FGF23 and PTH [29]. Furthermore, in line with the biological effects of sclerostin on bone, an inverse relationship between serum sclerostin and Bone ALP as bone formation marker was also noticed [29]. There is a sustained evidence that CKD–MBD has an impact on Wnt pathway and that phosphate and FGF-23 may be additional modulators of sclerostin expression [30]. Thus, sclerostin becomes an important element of the bone–kidney axis represented up to now by FGF23 and its kidney-produced coreceptor Klotho [31].

It was also shown that a high-phosphate diet decreases bone volume in an experimental model of chronic kidney disease–adynamic bone disease (CKD–ABD), possibly via changes in SOST expression through a PTH-independent mechanism [8]. These findings reinforce the role of phosphate in sclerostin regulation through a PTH-independent mechanism [32]. Hence, a thorough serum phosphate control with phosphate binders may be able to increase bone formation rates, osteoblast surfaces in the metaphyseal trabeculae of the tibia and femur, osteoid surfaces and to reverse the CKD-induced trabecular osteopenia [33].

Sclerostin increases FGF23 by inhibiting PHEX (a protein encoded by the Phosphate regulating gene with Homologies to Endopeptidases on the X chromosome) [34]. This protein stimulates FGF23 degradation and interacting with its coreceptor Klotho, increases tubular phosphate excretion and inhibits 1,25D synthesis with related clinical effects [31]. The absence of sclerostin leads to higher concentrations of the active vitamin D metabolite, likely associated with the decrease in FGF-23 concentration and/or due to a direct effect of sclerostin on cyp27B1 expression in proximal tubules [34]. Additionally, the excretion of urinary (Ca) is diminished, suggesting that apart from inhibition of 1a,25 (OH)2D synthesis, there might be a possible direct effect of sclerostin on renal Ca excretion [34, 35]. Whether plasma levels of sclerostin are regulated by dietary calcium phosphorus and vitamin D needs to be determined.

It is still an ongoing debate to what extent sclerostin may serve as a biomarker of CKD–MBD. Sclerostin levels do not always correlate as expected with observed BMD or bone turnover markers, suggesting the presence of possible

confounding variables that must be taken into account before routine clinical implementation. Another reason to be considered is the assay standardization. Substantial differences were observed in serum sclerostin levels measured by the commercially and non-commercially available assays, between various assays or between serum and plasma samples within the same assay. These intra-assay differences may be partly explained by the sclerostin presence in a protein-bound complex, with free and bound forms recognized variously by antibodies used in the assays [11]. These sources of variability may be also partly considered for frequent inconsistencies in clinical findings reported for other biomarkers such as FGF23 and PTH, pointing out the need for standard operating procedures and cross validation of various assays. The standardization of assays and the establishment of a clear cut-off values when sclerostin starts to switch from physiological to pathophysiological role have to be an important step for better understanding the mechanisms, helping clinical care decisions.

Sclerostin in CKD–MBD pathophysiology: the impact on cardiovascular and overall mortality?

Sclerostin and atherosclerosis

As previously known, patients with CKD are affected by calcification of intima and media layer of blood vessels. Additionally, atherosclerosis together with chronic inflammation process present in CKD makes a suitable environment for CV risk development. In patients with CKD, vascular calcifications occur as a result of the transition of vascular smooth muscle cells into osteoblastic-like cells, a process that is initiated by inflammatory factors in blood vessels [36]. There are several clinical studies investigating the potential role of sclerostin in CV risk and CV and overall mortality, both in patients with CKD and normal kidney function. This association was analyzed by detecting vascular and soft-tissue calcification and/or by finding the signs of atherosclerotic process in arteries, available for clinical investigation.

In patients with acute ischemic stroke, higher serum sclerostin levels compared to controls have been show and serum sclerostin appeared to be an independent predictor of ischemic stroke [37]. Similarly, higher serum sclerostin levels were associated with lower ankle–brachial index in elderly patients, indicating higher sclerostin values as risk factor for peripheral artery disease [38].

In a study of postmenopausal female patients with type 2 diabetes mellitus, there was a negative association between sclerostin and intima–media thickness (IMT) [39]. The results of our previous study did not show any association of sclerostin with IMT, although values of sclerostin were lower in patients with advanced CKD, and higher IMT values [40].

On the other hand, in population with normal kidney function, the association of serum sclerostin with the presence of vascular calcification has been observed, in type 2 diabetic patients and postmenopausal women [41, 42]. These studies suggest that sclerostin might have a certain relationship with atherosclerosis development, but the clear clinical evidence is still lacking.

Sclerostin and vascular calcifications

Vascular calcifications (VC) are well-known hallmark of increased CV risk. A couple of studies have investigated the potential link between serum sclerostin and the occurrence of vascular and soft-tissue calcifications, primarily in patients with CKD. It has been shown that patients with CKD, but also those with diabetes mellitus and rheumatoid arthritis, have higher expression of SOST gene in the wall of calcified arteries and the association of serum sclerostin with VC [43]. Similarly, a positive correlation between serum sclerostin and VC in patients CKD stages 3 and 4 has been shown [44]. Interestingly, SOST expression is reported as protective for developing aortal aneurysm and atherosclerosis [45].

Serum sclerostin levels correlated positively with aortic abdominal calcification, detected by lateral abdominal X-ray, in CKD patients stages 3–5, but negatively correlated with the severity of the calcifications [46]. Nevertheless, this study in 161 CKD patients stages 3–5 indicated negative association of sclerostin with cardiovascular events (CVEs).

High serum sclerostin values were associated with positive expression of sclerostin in radial artery medial layer [47]. In a recently published study in patients with ESRD undergoing renal transplantation, serum sclerostin was associated with the occurrence and severity of thoracic aorta calcification and with its positive expression in internal iliac arteries [48]. Another study reported that, although sclerostin was positively associated with vascular calcifications in renal transplant candidates, it did not predict major CVE, bone fracture or mortality over a period of 3.7 years of follow-up [49]. Conversely, there are also studies showing negative correlation of serum sclerostin with vascular calcifications [50, 51]. There are also data suggesting a positive correlation between serum sclerostin and CVEs [52].

Valvular calcifications are very important problem among patients with CKD and the importance of sclerostin in their development is still debatable. Some studies found sclerostin as an independent risk factor for heart valve calcification in stage 3–5 CKD patients [53]. Taken together, there is not enough clinical evidence whether sclerostin is only a marker of CV calcifications or it has potentially protective role.

Data on the importance of sclerostin in dialysis population are also inconsistent. In Chinese patients on hemodialysis, sclerostin was positively associated with carotid intima–media thickness (CIMT) and patients with higher sclerostin values had shorter survival [54]. Another study did not show sclerostin as predictor of long-term mortality in prevalent hemodialysis patients, whereas higher levels of FGF23, alkaline phosphatase, PTH and lower levels of 25(OH)vitamin D were associated with mortality [55]. The same study indicated negative association of sclerostin with these parameters.

Furthermore, other studies showed a potential protective role of sclerostin in CKD–MBD where patients on hemodialysis with higher sclerostin levels had lower aortic calcification scores and better survival rate [51]. Serum sclerostin levels predicted the calcification of arteriovenous fistula (AVF) in hemodialysis patients with tendency of protective effect on AVF patency [56]. In contrast, Gong et al. reported that patients on peritoneal dialysis with higher sclerostin values had more frequent CVE and cardiovascular deaths during 6-year follow-up period compared to those with lower sclerostin levels [57].

The role of serum sclerostin has been investigated also in patients after kidney transplantation. It has been reported that serum sclerostin is inversely associated with VC (coronary artery and aorta calcification) and progression in renal transplant recipients over a period of 4.4 years, after adjustment for traditional risk factors [58]. These findings would also support the theory of local sclerostin production as protective mechanism for further VC progression.

Despite the suppressive effect of PTH on sclerostin and the fact that sclerostin is dialyzable, the serum values remain higher in patients with CKD compared to the levels in healthy population [59, 60]. Indeed, a few studies attempted to explain the negative association of sclerostin with CV risk through its negative relationship with iPTH and/or ALP, as already recognized risk factors for increased morbidity and mortality in CKD patients [50].

There are various reports about the level of serum sclerostin according to the gender of patients with normal kidney function and some of them showed higher levels in female [61] whereas others in male patients [52]. The same difference is reported among CKD patients [40, 52, 62].

Another important question in patients with CKD is whether the higher levels of serum sclerostin are only result of reduced kidney function and what is the contribution of bone and extraskeletal sclerostin production? Recent findings in patients CKD 3-5D revealed that serum sclerostin was associated with bone sclerostin only in patients not treated with glucocorticoids and that female CKD patients had higher median bone sclerostin than males [63]. Moreover, a local production of sclerostin in the tissue of aortic valve near calcification zones in HD patients has been demonstrated [64]. In vitro studies confirmed that the expression of sclerostin is increased during smooth muscle cells calcification [65].

Sclerostin and mortality in CKD?

At best of our knowledge from the studies conducted up to know, the exact role of serum sclerostin in CKD–MBD and in cardiovascular and overall mortality has not been yet elucidated. Most of these studies included patients with advanced and/or terminal CKD. In addition, the use of various assays makes it difficult to compare results of different studies. While, somewhere, sclerostin was found as an independent predictor of mortality among patients on HD [66], other studies (NECOSAD and CONTRAST) showed lower cardiovascular and overall mortality in CKD patients with higher sclerostin levels [8, 19, 26]. Further confusion was brought by in studies demonstrating the lack of possibility of sclerostin to predict long-term cardiovascular mortality in HD patients [55].

In terms of relationship between sclerostin and all-cause mortality, studies showed conflicting results [8, 30, 66]. In recent meta-analysis by Kanbay et al., there was no association between serum sclerostin and all-cause and cardiovascular mortality in patients with CKD [67]. The authors also underlined the small number of studies and their heterogenous character with the need of further clarification of this association.

The question whether serum sclerostin has a protective or deleterious role in CKD–MBD pathophysiology, and therefore in CV risk and overall mortality is still open and needs to be answered. One important step forward should be standardization of assays to compare the results of various studies [68]. Moreover, this would establish clear cut-off values when sclerostin starts to switch from physiological to pathophysiological role, and to possibly define an adequate therapeutic approach.

Conclusions

Sclerostin is a promising biomarker for detection of an early CKD and CKD–MBD, as being elevated from initial stages of CKD. Data from basic research suggest that sclerostin production beyond osteocytes might be important for development of vascular and valvular calcification in CKD patients. However, there is no clinical evidence suggesting that sclerostin increases cardiovascular and/or overall mortality as well as whether it might have a protective role in CKD–MBD. The standardization of assays and the establishment of a clear cut-off values when sclerostin starts to switch from physiological to pathophysiological role have to be another important step. Further research is needed also

to define its relationship with other CKD–MBD biomarkers for future diagnostic and therapeutic strategies.

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