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LETTER TO THE EDITOR

COULD SERUM SCLEROSTIN HELP IN EARLY ASSESSMENT AND TREATMENT OF CHRONIC KIDNEY DISEASE – MINERAL AND BONE DISORDER?

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Dear Sir,

Chronic kidney disease (CKD) is an important health burden worldwide with high cardiovascular (CV) morbidity and mortality of patients [1]. Absence of early signs and symptoms of the disease makes it difficult to be timely diagnosed, instead rather late, with already developed various complications.

Numerous efforts have been made so far in order to find a perfect biomarker to diagnose early CKD and prevent further course of the disease. It has been proposed that chronic kidney disease – mineral and bone disorder (CKD-MBD) develops in fact from the CKD initiation and that main players in this complex pathophysiological mechanism could be excellent candidates for early assessment of CKD. Indeed, CKD-MBD should be perceived as an actual link between CKD and CV risk [2].

Sclerostin is a protein produced by osteocytes in a normal state and plays a role in normal bone metabolism through inhibition of wingless-type mouse mammary tumour virus integration site (Wnt) pathway in osteoblasts reducing the bone formation [3]. It has been shown that sclerostin serum levels are elevated from CKD initiation [4], but the cause is not clear yet. Apart from many other peptides, renal function reduction does not seem to affect sclerostin serum levels since also tubular excretion tends to be increased [5]. Alternatively, it is suggested that increased circulating levels found in CKD may be the effect of the enhanced production by osteocytes [6]. Answering if the sclerostin is dialyzable is still a debatable topic. Sclerostin levels in HD correlated well with Kt/V [7], in contrast with data from CONTRAST - randomized control trial that showed decreased level of sclerostin in HDF depending on the magnitude of the convection volume, but those were unaltered in HD patients. In addition, in PD patients, the total sclerostin elimination in the PD dialysate was 2.5 times higher than that in urine [8].

Sclerostin is associated with CKD-MBD. A sustained evidence shows CKD-MBD influences the Wnt pathway and phosphorus and Fibroblast growth Factor 23 (FGF-23) could additionally modulate sclerostin expression as an important component of the bone-kidney axis represented by FGF23 and its kidney-produced coreceptor Klotho [9].

The absence of sclerostin leads to higher concentrations of an active vitamin D metabolite, likely related with the decrease in FGF-23 concentration and/or due to a direct impact of sclerostin on cyp27B1 expression in proximal tubules. Several observational studies reported significant and independent positive correlation between serum phosphate, FGF23, and sclerostin concentrations and negative relationship with PTH. Hence, sclerostin may be a possible candidate to aggravate PTH resistance in CKD which could cause and/or aggravate adynamic bone disease (ABD) as well [10]. Patients with ABD associated with low PTH usually tends to have severe vascular calcification. Moreover, PTH appears to suppress sclerostin in osteocytes and probably the low sclerostin levels of CKD patients may lead to even greater vascular calcification.

Nevertheless, whether high sclerostin level is compensatory as protective response or sclerostin acts as uremic toxin, is still unclear. Studies on CV risk and mortality showed conflicting results as it has been reported that serum sclerostin is associated with either higher [11] or lower CV mortality [12], or were no association with CV risk and mortality [13]. Moreover, studies conducted so far are mainly done in advanced CKD, and therefore there are not sufficient data to get exact conclusions when potential "CV protective" role of sclerostin turns into a "CV deleterious" role. In addition, the cut-off level of serum sclerostin in this pathophysiological switch needs to be defined. The standardization of assays is another important step that makes results of various studies comparable.

Concerning the CKD-MBD treatment a question is raised whether serum sclerostin levels should be really lowered. It is clear that blocking of sclerostin will increase bone mineral density [14] and help curing renal osteodystrophy, but the concern stays whether it influences CV risk in CKD patients promoting pathological ossification within the walls of blood vessels [15].

Considering all these unanswered questions, further studies on the role of sclerostin in CKD-MBD are more than required intending to get its exact role in CKD-MBD pathophysiological mechanism and possibility to early treat this important burden preventing it's numerous complications. Ultimately, it may be perceived as chance to reduce the number of patients in need of renal replacement therapy.

Conflict of interest statement. None declared.

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