Sclerostin and cardiovascular disease: any prognostic implications?

To the editor We read with interest the results of the retrospective study conducted by Kern et al,[1] who demonstrated that in a total of 205 patients referred for coronary angiography, serum sclerostin levels did not correlate with coronary artery disease severity; however, they correlated positively with high-sensitive C-reactive protein and intact parathormone. Of note, patients with higher body mass index and lower estimated glomerular filtration rate had higher sclerostin levels, despite the fact that they did not differ in terms of other classic cardiovascular risk factors.[1] Sclerostin has been positively and independently associated with markers of subclinical atherosclerosis, such as carotid intima-media thickness, in high risk patients, such as these with concomitant type 2 diabetes mellitus.[2]

Despite these interesting associations, there are limited and contradictory data regarding the prognostic role of serum sclerostin in cardiovascular disease. In their cohort study including 130 subjects, Novo-Rodríguez et al[3] showed that serum sclerostin was an independent predictor of cardiovascular mortality (odds ratio, 1.318; 95% CI, 1.090–1.595; P = 0.004), yielding an area under the curve in the receiver operating characteristic analysis equal to 0.849 (95% CI, 0.758–0.940; P <0.001), after adjustment for baseline characteristics including established cardiovascular risk factors. Interestingly, serum sclerostin was not predictive of noncardiovascular mortality.[3] In their prospective observational study recruiting 98 stable peritoneal dialysis patients, Gong et al[4] demonstrated that high serum sclerostin levels represent an independent predictor of cardiovascular events and cardiovascular mortality after a 6-year follow-up period (hazard ratio, 3.484; 95% CI, 1.134–10.706) in the multivariable Cox regression analysis. Finally, in their prospective observational study enrolling 161 subjects with chronic kidney disease stage 3 to 5, Wang et al[5] showed that lower serum sclerostin levels were an independent predictor of cardiovascular events after adjustment for confounding factors in a Cox regression model (HR, 0.294; 95% CI, 0.151–0.575; P = 0.001) after a median follow-up of 16 months.

Therefore, it would be interesting if Kern et al[1] could provide us with data regarding the outcome of their enrolled nonchronic kidney disease subjects, since the study took place almost a decade before, if such information is available. Future, larger studies will clarify whether serum sclerostin can become a cardiovascular disease prognostic marker, and if yes, in which patient populations.

ARTICLE INFORMATION

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5 Wang XR, Yuan L, Zhang JJ, et al. Serum sclerostin values are associated with abdominal aortic calcification and predict cardiovascular events in patients with chronic kidney disease stages 3-5D. Nephrology (Carlton). 2017; 22: 286-292.

Authors' reply We thank Patoulias et al[1] for their comment on our paper. We are delighted that our study on sclerostin and its association with coronary artery disease was of interest.[2]

Few studies have analyzed possible associations between serum sclerostin levels and atherosclerosis development in populations without advanced chronic kidney disease. Therefore, in our paper, we decided to evaluate the impact of sclerostin concentrations on coronary artery disease advancement in such a population. The inclusion criterium of a serum creatine level of less than 1.2 mg/dl resulted in only 2 subjects with estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, that is, 55 and 58 ml/min/1.73 m^2, and the mean (standard error of the mean [SEM]) eGFR value was 86.5 (1.6) ml/min/1.73 m^2. Although the median serum sclerostin concentration was 133.22 pg/ml (mean [SD] was 261.8 [25.3]), individual concentrations varied. The range of sclerostin concentration was 7.6 to 2000 pg/ml, 60% of subjects had sclerostin in the range from 0 to 200 pg/ml, and 80% of subjects had sclerostin within the range of 0 to 400 pg/ml.

We did not observe any statistically significant differences between mean (SD) sclerostin concentration and coronary artery disease advancement (no obstructive disease, 342.5 [63.6]; 1-vessel disease, 257.6 [45.1]; 2-vessel disease, 238.5 [51.4]; 3-vessel disease, 201.7 [37.8], and left main disease, 264.1 [138.5]). However, those with serum sclerostin levels above median had increased mean (SEM) body mass index (26.9 [0.3] kg/m^2 vs 28.3 [0.5] kg/m^2; P = 0.049) and decreased mean (SEM) eGFR (89.9 [2.2] ml/min/1.73 m^2 vs 83.7 [2.4] ml/min/1.73 m^2; P = 0.01) together with decreased mean (SEM) fibrinogen level (406.9 [7.22] mg/dl vs 390.1 [10.8] mg/dl; P = 0.04).

Patoulias et al[1] cited several papers. However, Gong et al[3] assessed subjects with stage 5 chronic kidney disease treated with peritoneal dialysis, and Wang et al[4] analyzed serum sclerostin values as a predictor of cardiovascular events in patients with eGFR below 60 ml/min/1.73 m^2. These populations were different from the ones we focused on in our research.[3,4]

The study by Novo-Rodriguez et al[5] is quite interesting. They assessed the utility of sclerostin concentrations as a prognostic factor of death, both due to cardiovascular and noncardiovascular reasons. They found increased mean (SD) serum sclerostin concentrations in subjects with cardiovascular diseases, compared with subjects without prevalent cardiovascular disorders (57.96 [25.75] vs 43.61 [18.79] pmol/l; P <0.001). Patients with prevalent cardiovascular diseases, especially with lower extremity artery disease, had the highest mean (SD) sclerostin concentrations compared with subjects without peripheral artery disease (77.01 [26.57] vs 53.33 [23.65] pmol/l; P = 0.01). Interestingly, authors did not observe any significant differences in mean (SD) sclerostin concentrations when they compared subjects with eGFR value above and below 60 ml/min/1.73 m^2 (49.85 [19.94] vs 48.58 [22.78] pmol/l; P = 0.86). These results are somewhat contradictory to ours, but we have to be cautious interpreting them since the mean sclerostin levels were approximately 5- to 7-fold lower than in our study. Also, in the study by Novo-Rodriguez et al,[5] nearly all patients (93.8%) with coronary artery disease had type 2 diabetes (!).

Concluding, in our study, we did not find any direct correlation between sclerostin levels and coronary artery disease progression, but sclerostin levels were associated with intact parathormone, high-sensitivity C-reactive protein, and Klotho protein in subjects without significant kidney function impairment. To address the issue raised by Patoulias et al[1]—indeed, we are preparing a manuscript assessing the impact of baseline sclerostin concentrations on the risk of major adverse cardiovascular events in 8-year follow-up.

ARTICLE INFORMATION

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