Association of serum sclerostin levels with atherosclerosis severity in patients referred for invasive coronary angiography

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Introduction Sclerostin is a soluble glycoprotein secreted by osteocytes and has been identified as a relevant regulator of bone formation and an inhibitor of the Wnt/β-catenin signaling pathway.[1] The Wnt/β-catenin signaling pathway plays a vital role in the regulation of endothelial inflammation, vascular calcification, and mesenchymal stem cell differentiation and, therefore, contributes to atherosclerosis.[2] As a result, it is suspected that sclerostin might play a role in patients with atherosclerosis.[3,4]

Few studies have focused on the pathophysiologic effects of sclerostin on the atherosclerotic process in the population without severe chronic kidney disease (CKD).[5,6] Thus, our study aimed to analyze the profile of serum concentrations as well as correlations between the classic parameters and new indicators of bone turnover in a group of patients referred for coronary angiography.

Methods **Participants and study design** Consecutive patients undergoing coronary angiography between June 29, 2011 and November 17, 2011 who fulfilled the inclusion criteria were enrolled in the study. The criteria were as follows: age ≥40 years and <80 years, eligibility for coronary angiography due to stable coronary artery disease (CAD) or acute coronary syndrome, serum creatinine concentration before the procedure ≤1.2 mg/dl, left ventricular ejection fraction >30% on echocardiography, available data on weight and height, as well as willingness to participate in the study and to sign a written informed consent form. An independent ethics committee of University of Warmia and Mazury in Olsztyn approved the study protocol.

Severity of coronary artery disease Coronary artery disease severity was graded as single-vessel disease (1VD), 2-vessel disease (2VD), 3-vessel disease (3VD), or left main stem disease as well as score ≤22 points (low risk), of 23–32 points (intermediate risk), and ≥32 points (high risk) according to the European Society of Cardiology guidelines.[7] Nonobstructive disease was defined as the absence of stenosis greater than 40% of the vessel diameter.

Biochemical analysis The following biochemical parameters were analyzed: triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin (HbA_{1C}), creatinine, and bone turnover markers (such as the levels of intact parathormone [iPTH]). Estimated glomerular filtration rate was calculated according to the simplified Modification of Diet in Renal Disease formula. Serum sclerostin levels were measured using an enzyme-linked immunosorbent assay (DY1406, R&D SYSTEMS, Minneapolis,

TABLE 1 Sclerostin levels in the study patients depending on coronary artery disease severity

Parameter	Patients (n = 205)	Coronary artery disease severity						SYNTAX score			
		No obstructive disease (n = 49)	1VD (n = 51)	2VD (n = 50)	3VD (n = 43)	LM (n = 12)	*P* value	0–22 (n = 150)	23–32 (n = 35)	>32 (n = 20)	*P* value
Sclerostin, pg/ml, median (IQR)	133.21 (64–276.17)	170.23 (60.38–469.74)	152.94 (89.47–237.33)	123.97 (52.26–220.99)	125.61 (64.41–235.92)	95.06 (55.57–129.24)	0.4	137.66 (64.27–267.54)	125.61 (59.74–331.64)	132.47 (65.32–304.48)	0.94
iPTH, pg/ml	36.1 (2.1)	35.01 (4.5)	38.1 (4.31)	37.8 (5.23)	35.4 (3.58)	28.1 (3.29)	0.93	35.1 (2.42)	39.29 (6.1)	38.1 (5.7)	0.61
Klotho, pg/ml	232.1 (15)	243.7 (34.3)	253.7 (29.9)	225 (32)	222.2 (29.8)	158.6 (32.9)	0.31	241 (18.3)	227.17 (37.6)	174.4 (22.04)	0.24
FGF23, pg/ml	1.37 (0.05)	1.37 (0.09)	1.52 (0.08)	1.17 (0.1)	1.49 (0.1)	1.13 (0.27)	0.06	1.37 (0.05)	1.36 (0.12)	1.36 (0.15)	0.91

Data are presented as mean (SEM) unless otherwise indicated.

Abbreviations: 1VD, single-vessel disease; 2VD, 2-vessel disease; 3VD, 3-vessel disease; iPTH, intact parathormone; FGF23, fibroblast growth factor 23; LM, left main

Minnesota, United States). The limit of sclerostin detection was 41.5 pg/ml. The intact form of the fibroblast growth factor 23 protein (60-6600, Immunotopics, Inc., San Diego, California, United States) was detected at 1.5 pg/ml. The sensitivity of the enzyme-linked immunosorbent assay for the Klotho protein (CSB-E13235h, CUSABIO, Wuhan, China) was at 39 pg/ml. The intra- and interassay variability was less than 10% for all proteins tested.

Statistical analysis The R software, version 3.6.1 for Mac (R Foundation, Vienna, Austria), and GraphPad Prism 6 (GraphPad Software, San Diego, California, United States) were used to analyze the data. The Kolmogorov–Smirnov test was applied to check the normality of continuous variable distribution. The *t* test was used to compare variables between 2 groups if data were normally distributed, and the analysis of variance test, for multiple group comparison. Skewed variables were analyzed with the Mann–Whitney test. Data were presented as number and percentage for qualitative values and as mean (SEM) or median (interquartile range) for quantitative values. Categorical variables expressed as percentages were compared by the χ^2 test or the Fisher exact test, as appropriate. The Pearson correlation was used to assess the association between serum sclerostin levels and other clinical parameters. Differences were considered significant at a *P* value less than 0.05.

Results and discussion In total, we enrolled 205 patients at the mean (SEM) age of 62.9 (0.6) years, and men constituted 70.2% (n = 144) of the study population. The patients were classified into 5 subgroups with: no obstructive disease (23.9%), 1VD (24.9%), 2VD (24.4%), 3VD (20.9%), and left main disease (5.9%). No differences were observed between the groups except for the SYNTAX score value (*P* <0.001), fasting plasma glucose levels (*P* = 0.046), high-density lipoprotein cholesterol levels (*P* <0.01), and potassium concentration (*P* = 0.03) (Supplementary material, *Tables S1* and *S2*).

There were no significant differences in mean serum sclerostin, iPTH, Klotho protein, and fibroblast growth factor 23 levels between the study subgroups depending on CAD severity (TABLE 1).

The median (interquartile range) serum sclerostin level was 133.22 pg/ml (64–276.17 pg/ml). In patients with higher serum sclerostin levels (higher than the median value), we observed a higher mean (SEM) BMI (26.9 [0.3] kg/m^2 vs 28.3 [0.5] kg/m^2; *P* = 0.049), a lower mean (SEM) estimated glomerular filtration rate (89.9 [2.2] ml/min/1.73 m^2 vs 83.7 [2.4] ml/min/1.73 m^2; *P* = 0.01), and lower mean (SEM) fibrinogen levels (406.9 [7.22] mg/dl vs 390.1 [10.8] mg/dl; *P* = 0.04) (Supplementary material, *Table S3* and *Figure S1*).

The most reproducible relationship in the whole study group and in particular subgroups was found between sclerostin and iPTH levels, which was most strongly marked among the patients with a SYNTAX score of 23 to 32 points (r = 0.6671, P <0.001). The correlation for the whole study group was r = 0.513 (P <0.001) (Supplementary material, *Table S3*).

Vascular calcification and remodeling are involved in the development and progression of atherosclerosis. Parathormone provokes vascular dysfunction directly through the activation of the PTH receptor in the vascular wall as well as indirectly via inflammation.[8] Low-grade inflammation contributes to the development of atherosclerosis, and both CRP and fibrinogen levels represent inflammatory markers, linked to atherosclerosis and cardiovascular disease.[9,10]

In our study, sclerostin levels strongly and negatively correlated with serum iPTH levels. Of note, we also found a strong yet positive association between these 2 bone turnover–regulating proteins. This may point to the different nature of the interaction between these hormones in patients with normal renal function and those with advanced CKD. The positive association between sclerostin and serum calcium levels found by Qureshi et al[11] was also observed in one of the subgroups investigated in our study. Interestingly, the cited authors did not observe any relationship between sclerostin and CRP nor interleukin 6 levels, but they found a positive association with tumor necrosis factor α. We showed the positive association between sclerostin and CRP levels in the whole study group and specific subgroups. However, we could not define the relation between sclerostin levels and inflammation, as we did not measure the level of inflammatory cytokines. Thus, this association remains a subject of debate.[12]

Admittedly, our study had several limitations. First, it was an observational, single-center study with a limited number of elderly participants enrolled and, therefore, the possibility of bias cannot be excluded. No formal sample size calculation was performed, and serum creatinine concentration <1.2 mg/dl was the only criterion for not having clinically significant CKD.

Our study suggested that there is no direct relationship between sclerostin levels and CAD severity, but sclerostin levels, to some extent, correlated with hs-CRP, iPTH, and Klotho protein levels.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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REFERENCES

1 Evrard S, Delanaye P, Kamel S, et al. Vascular calcification: from pathophysiology to biomarkers. Clin Chim Acta. 2015; 438: 401-414.

2 Kirkpantur A, Balci M, Turkvatan A, et al. Independent association between serum sclerostin levels and carotid artery atherosclerosis in prevalent haemodialysis patients. Clin Kidney J. 2015; 8: 737-743.

3 Morales-Santana S, Garcia-Fontana B, Garcia-Martin A, et al. Atherosclerotic disease in type 2 diabetes is associated with an increase in sclerostin levels. Diabetes Care. 2013; 36: 1667-1674.

4 Bruzzese A, Lacquaniti A, Cernaro V, et al. Sclerostin levels in uremic patients: a link between bone and vascular disease. Ren Fail. 2016; 38: 759-764.

5 Teng IC, Wang JH, Lee CJ, et al. Serum sclerostin as an independent marker of peripheral artery disease in elderly persons. Int J Clin Exp Pathol. 2018; 11: 2816-2821.

6 He W, Li C, Chen Q, et al. Serum sclerostin and adverse outcomes in elderly patients with stable coronary artery disease undergoing percutaneous coronary intervention. Aging Clin Exp Res. 2020; 32: 2065-2072.

7 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40: 87-165.

8 Hagstrom E, Michaelsson K, Melhus H, et al. Plasma-parathyroid hormone is associated with subclinical and clinical atherosclerotic disease in 2 community-based cohorts. Arterioscler Thromb Vasc Biol. 2014; 34: 1567-1573.

9 Albert MA, Ridker PM. C-reactive protein as a risk predictor: do race/ethnicity and gender make a difference? Circulation. 2006; 114: e67-e74.

10 Batko K, Krzanowski M, Pietrzycka A, et al. Interplay of nitric oxide metabolites and markers of endothelial injury, inflammation, and vascular disease in the spectrum of advanced chronic kidney disease. Kardiol Pol. 2020; 78: 51-58.

11 Qureshi AR, Olauson H, Witasp A, et al. Increased circulating sclerostin levels in end-stage renal disease predict biopsy-verified vascular medial calcification and coronary artery calcification. Kidney Int. 2015; 88: 1356-1364.

12 Donham C, Manilay JO. The effects of sclerostin on the immune system. Curr Osteoporos Rep. 2020; 18: 32-37.