ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Relationship Between Sclerostin Levels and Coronary Artery Calcification and Plaque Composition

Sklerostin Seviyeleri ile Koroner Arter Kalsifikasyonu ve Plak Yapısı Arasındaki İlişki

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: The primary function of sclerostin is the regulation of bone metabolism. Research investigating the cardiovascular effects of sclerostin had conflicting results. We aimed to study serum sclerostin levels in coronary artery plaque types.

Methods: Coronary calcium scores of 175 patients were evaluated. Patients with normal coronary arteries and calcium score of greater than zero constituted control (n=47) and study groups (n=83), respectively. Patients' plaques were further categorized as non-calcified plaque, calcified plaque, or mixed plaque (n=45, n=40, and n=43, respectively).

Results: The study group had increased serum sclerostin levels than that of controls. Moreover, sclerostin levels were significantly higher in patients with calcified or mixed plaques compared to those without plaque or non-calcified plaque (median 248.5, 60.7-790.4) pg/mL and 1085.8 (185.8-3902.2) pg/mL versus 68.7 (34.0-141.3) pg/mL, and 67.7 (48.6-94.9) pg/mL, $P < 0.001$, respectively). Sclerostin showed a high correlation with coronary calcium scores ($r=0.95$, $P < 0.001$). Serum sclerostin concentration of 106.27 pg/mL had 97.5% sensitivity and 67.4% specificity for the prediction of calcific plaque, whereas the level of 308.55 pg/mL had 95.3% sensitivity and 90.9% specificity for the prediction of mixed plaque. Coronary calcium scores, serum sclerostin, and C-reactive protein levels were significant predictors of 1-year major adverse cardiac events.

Conclusions: Increased serum sclerostin level is a marker of coronary atherosclerosis burden and has a value for the prediction of 1-year major adverse cardiac events.

Keywords: Coronary calcification, coronary computed tomography angiography, sclerostin

ÖZET

Amaç: Sklerostin'in temel fonksiyonu kemik metabolizmasının regulasyonudur. Sklerostin'in kardiyovasküler etkilerini inceleyen araştırmalar çelişkili sonuçlar vermiştir. Bu çalışmanın amacı farklı koroner arter plak tiplerinde serum sklerostin seviyelerinin araştırılmasıdır.

Yöntem: Yüz yetmiş beş hastanın koroner kalsiyum skoru (KKS) değerlendirildi. Normal koroner artere sahip olan hastalar (n=47) ve KKS sıfırdan büyük (n=83) olan hastalar sırası ile kontrol ve çalışma grubunu oluşturdu. Koroner arter plakları olan hastalar kalsifiye olmayan plak, kalsifiye plak ve mikst plak olmak üzere üç gruba ayrıldı (sırası ile, n=45, n=40, n=43).

Bulgular: Çalışma grubunun sklerostin seviyeleri kontrol grubuna göre daha yüksek saptandı. Ayrıca, sklerostin seviyeleri kalsifiye veya mikst plağı olan hastalarda plak olmayan yada kalsifiye olmayan plağı olan anlamlı olarak daha yüksekti (sırası ile, 248.5, 60.7-790.4) pg/mL ve 1085.8 (185.8-3902.2) pg/mL karşın 68.7 (34.0-141.3) pg/mL, ve 67.7 (48.6-94.9) pg/mL, $P<0,001$,). Sklerostin KKS ile yüksek derecede korrelasyon gösterdi ($r=0.95$, $P<0,001$). 106.27 pg/ml serum sklerostin değeri kalsifik palğı öngördürmede %97.5 duyarlılık ve %67.4 özgüllüğe sahip idi. Buna karşın 308.55 pg/ml serum sklerostin seviyesi mikst plağı öngördürmede %95.3 duyarlılık ve %90.9 özgüllüğe sahip idi. KKS, serum sklerostin ve C-reaktif protein seviyeleri bir yıllık majör kardiyak olayların önemli öngördürücüleri olarak bulundu.

Sonuç: Artmış serum sklerostin seviyesi koroner ateroskleroz yükünün bir göstergesidir ve bir yıllık majör kardiyak olayların öngördürücüsü olarak değer taşımaktadır.

Anahtar Kelimeler: Koroner bilgisayarlı tomografik anjiyografi, sklerostin, koroner kalsifikasyon

Yasin Yüksel[1]
Cennet Yıldız[2]
İbrahim Taşkın Rakıcı[1]

[1]*Department of Cardiology, Istanbul Training and Research Hospital, Istanbul, Türkiye*
[2]*Department of Cardiology, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Türkiye*

Corresponding author:
Cennet Yıldız
✉ cennet_yildiz@live.com

Received: January 4, 2023
Accepted: January 10, 2023

Cite this article as: Yüksel Y, Yıldız C, Taşkın Rakıcı İ. Relationship between sclerostin levels and coronary artery calcification and plaque composition. *Turk Kardiyol Dern Ars.* 2023;51(4):266-273.

DOI:10.5543/tkda.2023.61595

The formation of atherosclerosis is a long-lasting and multifactorial process which is actively controlled by numerous pathways.[1] Recently, it has been recognized that the bone–vascular axis, such as Wnt/β-catenin pathway, engaged in several endocrine, metabolic, and inflammatory processes.[2,3] There is cumulative evidence indicating the contribution of Wnt signaling activity in atheropathogenesis. It is involved in endothelial function, vascular smooth muscle cells proliferation/migration, and intimal hyperplasia.[4]

The osteocytes produce sclerostin, which inhibits the Wnt pathway. Inhibition of sclerostin activity is associated with induction of bone mineralization and decreased bone resorption, with resultant increased bone formation and decreased risk of fracture.[5] Sclerostin is also an emerging marker for vascular disease, and the evidence supports its role in vascular physiopathology.[6] Serum sclerostin levels rise in elderly, metabolic bone diseases, diabetes mellitus (DM), chronic kidney disease (CKD), and postmenopausal women.[7-11]

Invasive coronary angiography (ICA) is still the gold standard method for imaging coronary arteries. However, recent advances in coronary computed tomography angiography (CCTA) technology have enabled us to image the coronary arteries non-invasively. Coronary artery calcifications (CAC), a common pathology encountered in atherosclerotic arteries, have been found to be associated with the burden of coronary artery atherosclerosis and detected in acute coronary syndrome or sudden cardiac death patients.[12,13] The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated higher coronary artery calcification scores, which signifies greater atherosclerotic cardiovascular disease risk, regardless of age, sex, and ethnicity.[14] Subgroup analysis of the MESA study showed that increased plaque calcium density reflects plaque stabilization and indicates a lower risk of major cardiovascular adverse events.[15]

Atherosclerotic lesions can be calcified, non-calcified, and mixed.[16] Calcium content in plaque is affected by age, ethnicity, and gender.[17] Aggressive medical treatment (particularly statins) and lifestyle changes have been shown to slow the progression of coronary atherosclerosis and change the adverse plaque characteristics.[18,19] It has been shown that statin treatment has been associated with higher levels of atherosclerotic calcification, indicating plaque stabilization.[9] There are limited data on the relationship between serum sclerostin levels and coronary atherosclerosis detected by CCTA. We aimed to investigate the relation of serum sclerostin levels with coronary artery calcium score values and evaluate whether it differs with coronary artery plaque types.

ABBREVIATIONS

CABG	Coronary artery bypass graft
CAC	Coronary artery calcifications
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CT	Computed tomography
HRP	Hoseradish peroxidase
ICA	Invasive coronary angiography
MACE	Major adverse cardiac events
MESA	The Multi-Ethnic Study of Atherosclerosis
NCP	Non-calcified plaque
PTCA	Percutaneous coronary angioplasty

Materials and Methods

Study Population

This cross-sectional study was undertaken in the cardiology clinic of a tertiary center. Ethical committee approval was received from the Ethics Committee of Istanbul Training and Research Hospital University (Approval No: 1788, Date: 12.04.2019). The written informed consent was taken from all of the participants included. One hundred seventy-five consecutive patients undergoing CCTA enrolled. Patients were divided into 2 groups according to their findings on CCTA. Patients with normal coronary arteries and calcium score of greater than zero constituted control (n=47) and study group (n=83), respectively. Patients were further analyzed according to their plaque types. Coronary plaque was not detected in 47 patients; 45 patients had non-calcified plaque (NCP), 40 calcified plaques, and 43 mixed plaques. The criteria for exclusion were as follows: having percutaneous coronary angioplasty (PTCA), stent, or coronary artery bypass graft (CABG) operation for coronary artery disease, presence of acute infection, systemic, inflammatory, or rheumatic disease, CKD, ankylosing spondylitis, prolonged rest or immobilization, spinal cord injury or any acute fracture, hypercortisolism, multiple myeloma, and parathyroid dysfunction. Chronic kidney disease was described as a glomerular filtration of less than 60 mL/min per 1.73 m^2 or urinary albumin to creatinine ratio of greater than 30 mg/g. Major adverse cardiac events (MACE) were described as death, myocardial infarction, PTCA, or CABG operation at 1-year follow-up.

Clinical Evaluation and Anthropometric Measurement

Patients with HbA1c > 6.5 g/dL or using antidiabetic therapy (insulin or oral) were considered as having DM. Dyslipidemia was defined as fasting total cholesterol > 200 mg/dL or low-density lipoprotein cholesterol > 130 mg/dL or lipid-lowering chronic use of drugs. An ex-smoker is defined as a former smoker but not one for the past month. Body mass index was calculated as the weight (kg)/height (m) squared (kg/m^2).

Image Analysis

Coronary computed tomography angiography scans of the cases were performed by connecting ECG on 64-slice computed tomography (CT) (Aquilion 64; Toshiba Medical System Corp., Otawara-shi, Japan), and 128-slice CT devices (Philips Ingenuity, Amsterdam, Holland) were used. Images were obtained with a pulse rate of 60-70 per minute, without intravenous contrast and with contrast, at 0.5 mm slice thickness. Those with a heart rate above 70 minutes and those with arrhythmia were not included in the study. Cardiac CT images were examined at the workstation by an experienced radiologist. Plates with a density of 130 Hounsfield Units (HU) and above were automatically marked by the program, and calcium score measurements were made for each vessel. For the quantification of CAC, the Agatston scoring system was used. In this system, calcification was defined as hyperattenuated areas of at least 1 mm^2 with a density value of greater than 130 HU. Calcified areas were multiplied by a factor according to the value of maximum plaque attenuation in order to find the weighted sum of the lesions. For the evaluation

of patients, original slice thickness and interval protocols were used for noise reduction. Plates were confirmed with intravenous contrast maximum intensity projection and multiplanar reformation images. The type of coronary plaque was described as follows: If a plaque had calcified tissue greater or less than 50% of the plaque area, then these plaques were classified as calcified and mixed plaques, respectively. If a plaque had no calcified tissue, then this plaque was classified as NCP.[20] Coronary Artery Disease-Reporting and Data System (CAD-RADS) classification of the lesions was made as follows: (CAD-RADS 0: 0%, CAD-RADS 1: 1%-24%, CAD-RADS 2: 25%-49%, CAD-RADS 3: 50%-69%, CAD-RADS 4: 70%-99% or Left main > 50% or 3-vessel disease, 70%-99%, CAD-RADS 5: 100%).[21]

Laboratory Measurements

After 12 hours of fasting in the sitting position, the blood samples were collected in tubes containing trisodium citrate (0.109 µM). The blood was double centrifuged for 15 minutes at 2500 µg and the obtained supernatant (platelet-poor plasma) was stored at –80°C within 2 hours (less than 5 months) after collection. Frozen samples were thawed and vortexed for 5 minutes in a 37°C water bath before assay. Serum sclerostin level was measured with the relevant kit (Catalog No: E-EL-H1544, Elabscience Inc.: Houston, Texas, USA). Briefly, samples and standards were put into anti-human monoclonal antibody-coated wells, after which added biotin made an immune complex with streptavidin-Hoseradish peroxidase (HRP). The complex was washed to remove the uncombined enzyme. The color of the solution turned blue with the addition of chromogen solutions A and B. In order to stop the reaction, acid was added to the plates and the color becomes yellow. The automated plate reader (Thermo Scientific Microplate Reader, Waltham, Massachusetts, USA) read the optical density of the preparation at 450 nm. The detection range and sensitivity of kits for sclerostin were 62.50-4000 pg/mL and 37.50 pg/mL, respectively. All the remaining biochemical assessments were measured by AU 2700 (Beckman Coulter Inc., Brea, California, ABD SYSMEX: Mundelein Illinois USA) and Sysmex XE 5000 (Sysmex Medical Int.) system.

Statistical Analysis

The demographic characteristics of the subjects and the collected data were entered in the Statistical Package for the Social Sciences version 23 software. Qualitative variables were characterized using mean and percentage values. Categorical variables were expressed using frequency and percentage, and numerical variables were expressed using mean ± standard deviation or median interquartile range if they were normally or non-normally distributed, respectively. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics. Comparison of patients who had normal coronary arteries and calcified plaques was done by Mann–Whitney *U*-test, independent samples *t*-test, or chi-square test. Comparisons of the patients with different plaque types were performed with one-way analysis of variance or Kruskal–Wallis test. Quade's non-parametric analysis of covariance was conducted in order to examine the differences between the study and control groups after controlling age, gender, diabetes, hypertension, and creatinine levels. Pearson correlation test was used to evaluate the association between calcium score and sclerostin. Receiver operating characteristic (ROC) curve analysis was conducted to find values of sclerostin for the prediction of calcified and mixed plaques. Univariate logistic regression analysis was used in order to find the parameters that had predictive value for MACE. A 2-tailed *P*-value < .05 was considered statistically significant.

Table 1. Clinical and Biochemical Variables of 2 Groups

	Control Group (n=47)	Study Group (n=83)	*P*
Age (years)	52 (42.0-56)	58 (51-63)	**<0.001**
BMI (kg/m^2)	27.1 (25.6-29.7)	28.4 (26.1-32)	0.072
HgA1c (%)	5.5 (5.2-6.1)	5.7 (5.4-6.8)	**0.035**
Creatinine (mg/dL)	0.7 (0.6-0.8)	0.8 (0.7-0.8)	**<0.001**
GFR (mL/min/1.73 m^2)	105 (98-112)	94 (86-101)	**<0.001**
LDL-C (mg/dL)	141 ± 42.7	139.1 ± 40.2	0.873
Triglyceride (mg/dL)	138 (91-174)	142 (108-189)	0.197
HDL-C (mg/dL)	50 (39-60)	46 (39-55)	0.333
Albumin (g/dL)	4.4 ± 0.4	4.4 ± 0.4	0.477
C-reactive protein (mg/L)	3.2 (1.9-6.3)	2.7 (1.6-5.2)	0.558
Hemoglobin (g/dL)	13.9 ± 1.6	14.4 ± 1.3	0.071
Platelet (10^3/µL)	268.9 ± 60.3	240.96 ± 71.60	**0.032**
Sclerostin (pg/mL)	68.7 (58.5-78.5)	428.5 (248.5-1098.5)	**<0.001**

BMI, body mass index; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
P value of <0.05 was significant.

Results

Patients with calcified plaques were significantly older, more likely to be male, and had increased creatinine and sclerostin levels (Table 1).

After controlling age, gender, diabetes, hypertension, and creatinine levels, the sclerostin level was still found to be higher in the study group ($F=133.167$, $P < 0.001$). Prevalence of DM, hypertension, dyslipidemia and the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, B-blocker, Ca-channel blocker, statin, acetylsalicylic acid, clopidogrel, oral anticoagulant, and antidiabetic medication were found to be higher in the study group than that of the control group (Table 2).

Patients with calcified or mixed plaque had higher serum sclerostin levels compared to those with no plaque or NCP 248.5 (177.6-389.7) pg/mL and 1085.8 (592.2-3026.7) pg/mL versus 68.7 (58.5-78.5) pg/mL, and 67.7 (62.2-75) pg/mL, $P < 0.001$, respectively). Patients with no plaque and NCP had no difference in serum sclerostin levels (Figure 1).

Patients with NCP had

a higher number of CAD-RADS 1 lesions, patients with calcified plaques had a higher number of CAD-RADS 2 lesions, and patients with mixed plaques had a higher number of CAD-RADS 3 and 4 lesions. Table 3 shows the clinical features of the patients who had no plaque, NCP, calcified plaque, and mixed

Table 2. Comparison of Categorical Variables of 2 groups

(n, %)	Control Group	Study Group	*P*
Gender			**0.002**
Male	19 (40.4)	57(68.7)	
Female	28 (59.6)	26(31.3)	
Smoking	20 (42.6)	51 (61.4)	**0.038**
Diabetes mellitus	8 (17.0)	31 (37.3)	**0.012**
Hypertension	21 (44.7)	67 (80.7)	**<0.001**
Dyslipidemia	10 (21.3)	62 (74.7)	**<0.001**
ACEI/ARB	17 (36.2)	54 (65.1)	**0.001**
B-blocker	13 (27.7)	53 (63.9)	**<0.001**
Ca-channel blocker	5 (10.6)	29 (34.9)	**0.001**
Diuretic	10 (21.3)	28 (33.7)	0.128
Statin	10 (21.3)	62 (74.7)	**<0.001**
Acetylsalicylic acid	7 (14.9)	47(56.6)	**<0.001**
Clopidogrel	0 (0)	10 (12.0)	**0.009**
Oral anticoagulant	2 (4.2)	4 (4.9)	0.709
Antidiabetic use	8 (17)	30 (36.6)	**0.016**

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
P value of <0.05 was significant.

plaque. Patients who had mixed plaques had the highest rate of MACE.

We found a high correlation between the sclerostin levels and coronary calcium scores (CCS) ($r=0.953$, $P < 0.001$) (Figure 2)

Serum sclerostin levels also showed a high correlation with CAD-RADS categories ($r=0.700$, $P < 0.001$). Serum sclerostin level of 106.27 pg/mL had 97.5% sensitivity and 67.4% specificity for prediction of calcific plaque (Area under the curve [AUC]: 0.689, $P < 0.001$, 95% CI: 0.611-0.768), whereas level of 308.55 pg/mL had 95.3% sensitivity 90.9% specificity for the prediction of mixed plaque (AUC: 0.979, $P < 0.001$, 95% CI: 0.962-0.996) (Figures 3 and 4, respectively). Univariate logistic regression analysis showed that C-reactive protein, sclerostin levels, and CCS were the predictors of MACE (Table 3).

Discussion

In the present study, serum sclerostin levels were found to be higher in patients with coronary artery plaques and showed a positive correlation with CCS. In addition, patients with calcified plaques and mixed plaques had higher sclerostin levels than those with no plaque or NCP. Similarly, in another study, subjects with coronary artery disease (CAD) who underwent CABG operation were reported to have higher levels of sclerostin compared with controls, regardless of diabetes status.[22] In addition, sclerostin levels were associated with coronary tortuosity in patients who underwent ICA.[7] The relationship between aortic or carotid plaques and serum sclerostin levels has also been noted in various studies.[23,24] However, not all the studies used CT imaging for the assessment of vascular calcifications; specifically, some of them used lumbar spine x-ray imaging for evaluation of aortic calcification.[9,25] Kuipers et al[26] studied serum sclerostin levels in 191 Afro-Carribean men and sought to determine whether an association exists between serum sclerostin levels and coronary and aortic artery calcifications. In their study, the presence of 1 standard deviation greater sclerostin level was associated with 1.61-fold risk of having coronary artery calcification. However, coronary arterial plaque composition and its relation with sclerostin levels were not assessed. In addition, they did not find any association between serum sclerostin levels and aortic artery calcification, suggesting different mechanisms of action in different vascular beds. Another study found increased levels of circulating sclerostin in the serum of patients who had epigastric arterial calcification.[27] In our study serum sclerostin levels were found to be the highest levels in the mixed plaque group. Coronary artery calcifications represent soft tissue calcification areas surrounding the coronary atherosclerotic plaque. Several studies have shown that increased plaque calcification represents

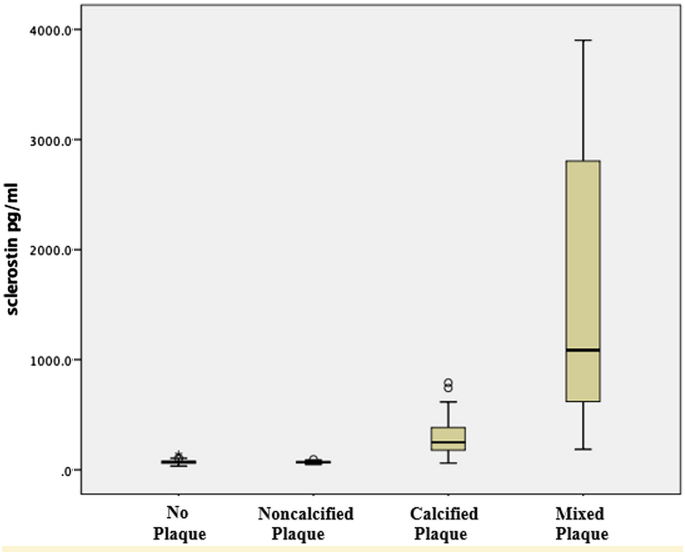

Figure 1. Serum sclerostin levels according to plaque types.

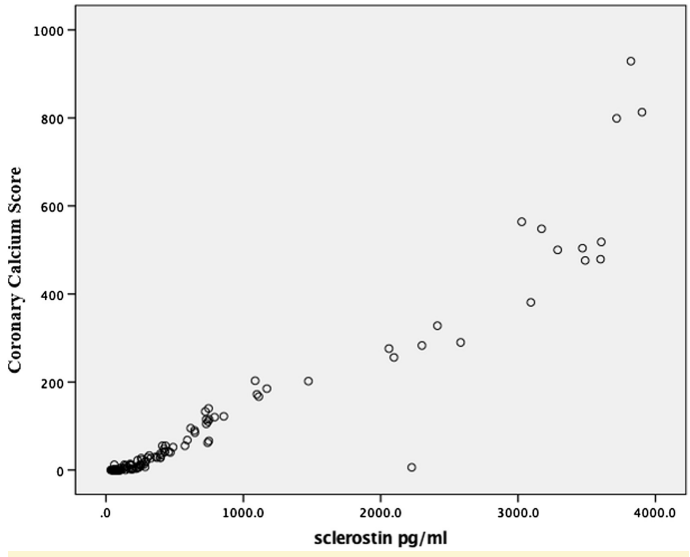

Figure 2. Correlation of sclerostin with coronary calcium score.

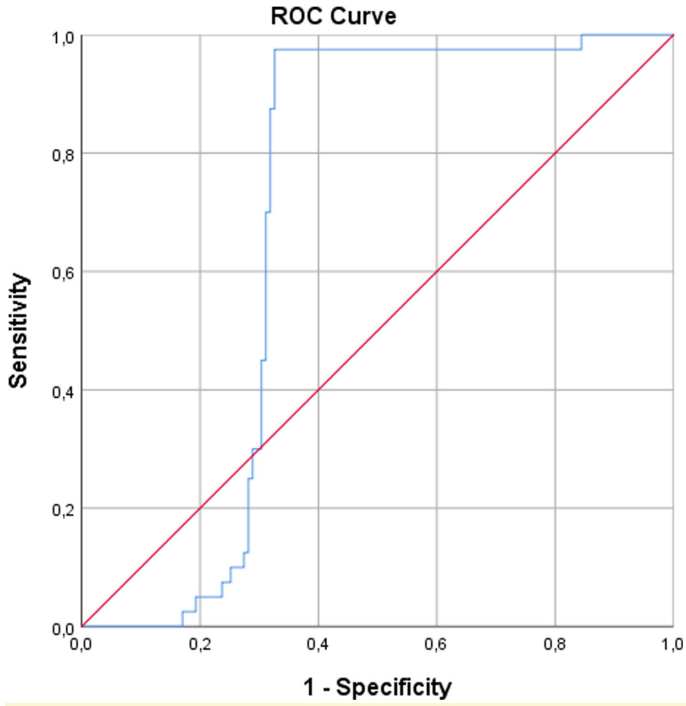

Figure 3. Receiver Operating Characteristic (ROC) curve analysis of sclerostin for prediction of calcified plaque.

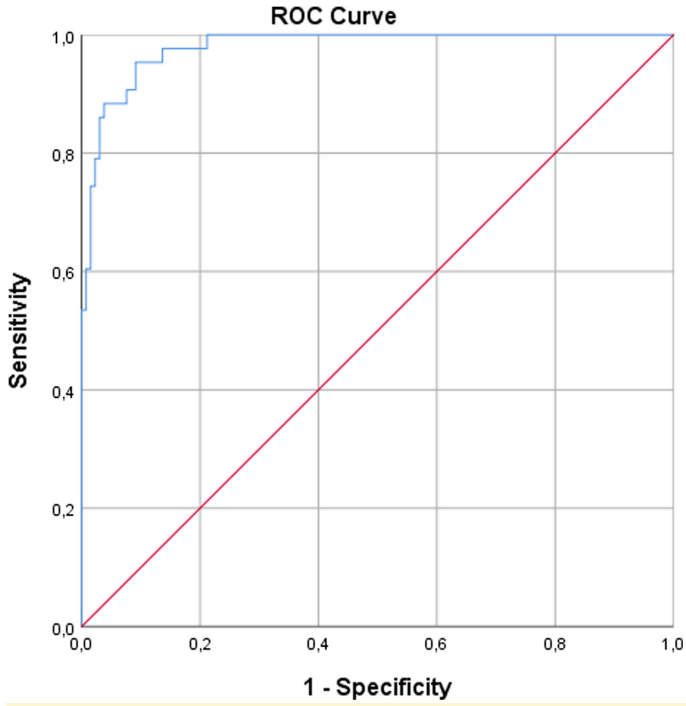

Figure 4. ROC curve analysis of sclerostin for prediction of mixed plaque.

plaque stabilization and decreased calcification is related to the presence of acute coronary syndrome.[15] Despite these findings, increased amounts of CAC have been shown to have prognostic value for future cardiovascular events.[28] Similar to our findings, previous reports demonstrated that CAC were related to heterogeneous coronary plaque, more specifically increased amount of mixed plaque burden.[29]

Reports on the relationship between sclerostin and mortality were highly controversial. After 18 months of follow-up of 673 dialysis patients, the results of the Netherlands Cooperative Study on the Adequacy of Dialysis study showed that the higher the sclerostin level, the lower the risk of cardiovascular death and all-cause mortality.[30] Low levels of sclerostin predicted worse outcomes in elderly patients who underwent percutaneous coronary intervention for stable CAD.[8] Another study found no significant association between the number of occlusive vessels on coronary angiography and serum sclerostin level.[31] Higher incidence of serious cardiovascular events with sclerostin inhibition (romosuzumab) suggested that sclerostin might have a vasoprotective aspect.[32] In the study by Ge et al.[33] sclerostin levels were found to be increased in maintenance dialysis patients with CAC, but it did not have any prognostic value for 5-year survival outcomes. Contrary to this, Gonçalves et al[11] found that the high basal level of serum sclerostin was associated with worse survival in 91 hemodialysis patients.[11] Kanbay et al[34] examined 173 nondialyzed CRD patients and 47 control patients and found that higher sclerostin level was associated with fatal and nonfatal cardiovascular events. A meta-analysis of observational studies demonstrated that circulating sclerostin level was an independent risk factor of all-cause and cardiovascular mortality.[35] In the present study, sclerostin and CCS were the significant predictors of 1-year MACE. Sclerostin might reflect the severity of coronary atherosclerotic burden and hence might have prognostic value in CAD patients.

Previous studies reported that serum sclerostin levels increased with age in both men and women indicating the age-related decrease in bone formation.[36] Studies investigating the gender differences in sclerostin levels revealed conflicting results. Mödder et al[36] stated that serum sclerostin levels were higher in men than women at any age. They explained that this situation might be the reflection of larger skeletal mass in men than in women. On the contrary to this, Catalano et al[37] reported higher sclerostin levels in type 1 diabetic women. In our study, study group patients were older and the percentage of male patients in the study group was higher compared to controls. However, sclerostin levels continued to be higher in study patients after controlling risk factors such as age, gender, diabetes, hypertension, and creatinine levels.

Sclerostin is primarily produced in osteocytes, increases osteoclastic activity, and decreases osteoblastic activity. It exhibits inhibitory actions on canonical Wnt activity that is involved in atheropathogenesis such as lipid deposition, plaque formation, monocyte differentiation, and progression of vascular calcification.[4] Intuitively, the association of serum sclerostin and vascular calcifications may seem contradictory. However, studies have shown that higher sclerostin levels were correlated with increased bone mineralization and vascular arterial calcifications, suggesting a possible physiological adaptation to vascular calcification.[38] In correlation with this, in this study, the sclerostin

Table 3. Analysis of Patients According to Their Plaque Types

Characteristics	No Plaque (n = 47)	Non-Calcified Plaque (n = 45)	Calcified Plaque (n = 40)	Mixed Plaque (n = 43)	*P*
Age (years)	49.7 ± 7.8	49.5 ± 7.3	55.3 ± 9.8	57.5 ± 7.1	**<0.001**
Male gender, n (%)	19 (40.4%)	25 (55.6%)	27 (67.5%)	30 (69.8%)	0.02
BMI (kg/m^2)	27.7 ± 3.1	28.4 ± 4.8	28.8 ± 4.3	29.9 ± 4.2	0.26
Smoker, n (%)	20 (42.6%)	30 (66.7%)	23 (57.5%)	28 (65.1%)	0.08
Hypertension, n (%)	21 (44.7%)	29 (64.4%)	31 (77.5%)	36 (83.7%)	**<0.001**
Dyslipidemia, n (%)	10 (21.3%)	19 (42.2%)	29 (72.5%)	33 (76.7%)	**<0.001**
Diabetes mellitus, n (%)	8 (17.0%)	5 (11.1%)	13 (32.5%)	17 (40.5%)	**0.01**
Hemoglobin (g/dL)	13.9 ± 1.6	14.2 ± 1.7	14.4 ± 1.2	14.5 ± 1.4	0.441
Platelet (10^3/µL)	268.9 ± 60.3	237 ± 59	232 ± 63	249 ± 79	**0.045**
Creatinine (mg/dL)	0.73 ± 0.18	0.78 ± 0.21	0.80 ± 0.18	0.89 ± 0.36	**0.014**
GFR (mL/min/1.73 m^2)	102 ± 13	101 ± 22	95 ± 14	89 ± 16	**0.001**
LDL-C (mg/dL)	141 ± 42.7	135 ± 43	140 ± 36	139 ± 44	0.875
HDL-C (mg/dL)	51.1 ± 13.1	51.0 ± 13.0	48.0 ± 12.0	49.5 ± 12.3	0.626
Triglycerides (mg/dL)	138 (91-174)	123 (90-181)	159 (111.7-209)	134 (103-182)	0.13
HbA1c (%)	6.0 ± 1.6	5.7 ± 1.0	6.0 ± 1.1	6.8 ± 2.4	**0.012**
Albumin (g/dL)	4.4 ± 0.4	4.31 ± 0,31	4.40 ± 0.38	4.46 ± 0.39	0.524
C-reactive protein (mg/L)	3.2 (1.9-6.3)	2.9 (1.3-4.5)	2.6 (1.8-5.2)	3.1 (1.4-6.1)	0.93
Sclerostin (pg/mL)	68.7 (58.5-78.5)	67.7 (62.2-75)	248.5 (177.6-389.7)	1085.8 (592.2-3026.7)	**<0.001**
Coronary calcium score	-	-	23.83 ± 28.2	240.49 ± 238.4	**<0.001**
CAD-RADS category					**<0.001**
0	47 (100)	0 (0)	0 (0)	0 (0)	
1	0 (0)	32 (71.2)	20 (50)	4 (9.3)	
2	0 (0)	13 (28.9)	15 (37.5)	12 (27.9)	
3	0 (0)	0 (0)	5 (12.5)	11 (25.6)	
4	0 (0)	0 (0)	0 (0)	15 (34.9)	
5	0 (0)	0 (0)	0 (0)	1 (2.3)	
Drug use, n (%)					
ACEI/ARB	17 (36.2%)	24 (53.3%)	27 (67.5%)	27 (62.8%)	**0.016**
Statin	10 (21.3%)	19 (42.2%)	29 (72.5%)	33 (76.7%)	**<0.001**
Antidiabetic	8 (17%)	5 (11.1%)	13 (32.5%)	17 (40.5%)	**0.004**
MACE	0 (0)	0 (0)	4 (10)	14 (32.5)	**<0.001**

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD-RADS, Coronary Artery Disease-Reporting and Data System; GFR, glomerular filtration rate; HDL-C; high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol, MACE, major adverse cardiac events.
P value of <0.05 was significant.

concentrations were correlated with calcium scores (r=0.90, $P < 0.001$) in the CCTA of patients.

The fact that sclerostin levels were found to be similar to those without plaque in NCP patients suggests that sclerostin levels are effective on coronary artery calcification rather than coronary atherosclerosis. The CCTA has become an important imaging modality for both risk stratification and diagnosing coronary artery stenosis in patients. It is now well known that cardiovascular mortality is lower and the overall prognosis is better in the absence of coronary calcification.[39] Cardiovascular risk increases proportionally with CCS and is highest when CCS > 400 (Agatston scores). More than 15% annual progression of CCS increases the risk of myocardial infarction.[36]

The treatment and clinical consequences of reducing the calcium load on coronary and vascular plaques are not definitely known. More comprehensive studies are needed on this subject.

Limitations

The present study has some limitations. First, the size of our study was relatively small. Second, the prognostic value of serum sclerostin level was not evaluated. Although we minimized the factors that may affect serum sclerostin levels in our study, some

conditions (age, gender, DM, etc.) may affect sclerostin levels. All patients did not undergo coronary angiography, so we could not know the definite coronary stenosis level. However, most patients with coronary plaques were evaluated with a treadmill stress test or scintigraphy. Another limitation was a lack of multivariate analysis to show an independent association between sclerostin level and CAC score.

Conclusion

A high serum sclerostin level can be a strong indicator of CAC and CAD. However, a normal serum sclerostin level does not exclude the presence of CAD. Serum sclerostin level correlates with CCS, independent of plaque composition. Moreover, serum sclerostin had predictive value for 1-year MACE. Our study provides additional literature on the vascular effect of sclerostin.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Istanbul Training and Research Hospital University (Approval No: 1788, Date: 12.04.2019).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.Y., C.Y., I.T.R.; Design – Y.Y., I.T.R.; Supervision – Y.Y., C.Y., I.T.R.; Funding – Y.Y.; Materials – Y.Y., I.T.R.; Analysis and/or Interpretation – C.Y., I.T.R.; Literature Review – Y.Y., C.Y.; Writing – Y.Y., C.Y.; Critical Review – Y.Y., C.Y., I.T.R.

Declaration of Interests: None.

Funding: We did not receive any specific grant from any funding agency during conduction of the study.

References

1. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, et al. Pathophysiology of atherosclerosis. *Int J Mol Sci*. 2022;23(6):3346. [CrossRef]
2. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. *Nat Rev Endocrinol*. 2012;8(9):529-543. [CrossRef]
3. Reis M, Liebner S. Wnt signaling in the vasculature. *Exp Cell Res*. 2013;319(9):1317-1323. [CrossRef]
4. Marinou K, Christodoulides C, Antoniades C, Koutsilieris M. Wnt signaling in cardiovascular physiology. *Trends Endocrinol Metab*. 2012;23(12):628-636. [CrossRef]
5. McClung MR. Sclerostin antibodies in osteoporosis: latest evidence and therapeutic potential. *Ther Adv Musculoskelet Dis*. 2017;9(10):263-270. [CrossRef]
6. Catalano A, Bellone F, Morabito N, Corica F. Sclerostin and vascular pathophysiology. *Int J Mol Sci*. 2020;21(13):4779. [CrossRef]
7. Ibrahim IM, Farag EM, Tabl MAE, Abdelaziz M. Relationship between sclerostin and coronary tortuosity in postmenopausal females with non-obstructive coronary artery disease. *Int J Cardiol*. 2021;322:29-33. [CrossRef]
8. He W, Li, 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(10):2065-2072. [CrossRef]
9. Morales-Santana S, García-Fontana B, García-Martín A, et al. Atherosclerotic disease in type 2 diabetes is associated with an increase in sclerostin levels. *Diabetes Care*. 2013;36(6):1667-1674. [CrossRef]
10. Figurek A, Spasovski G. Is serum sclerostin a marker of atherosclerosis in patients with chronic kidney disease-mineral and bone disorder? *Int Urol Nephrol*. 2018;50(10):1863-1870. [CrossRef]
11. Gonçalves FL, Elias RM, dos Reis LM, et al. Serum sclerostin is an independent predictor of mortality in hemodialysis patients. *BMC Nephrol*. 2014;15:190. [CrossRef]
12. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association expert consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol*. 2000;36(1):326-340. [CrossRef]
13. Pohle K, Ropers D, Mäffert R, et al. Coronary calcifications in young patients with first, unheralded myocardial infarction: a risk factor matched analysis by electron beam tomography. *Heart*. 2003;89(6):625-628. [CrossRef]
14. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018;39(25):2401-2408. [CrossRef]
15. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA*. 2014;311(3):271-278. [CrossRef]
16. Davies MJ. The composition of coronary-artery plaques. *N Engl J Med*. 1997;336(18):1312-1314. [CrossRef]
17. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the multi-ethnic study of atherosclerosis (MESA). *Circulation*. 2006;113(1):30-37. [CrossRef]
18. Goh VK, Lau CP, Mohlenkamp S, Rumberger JA, Achenbach S, Budoff MJ. Outcome of coronary plaque burden: a 10-year follow-up of aggressive medical management. *Cardiovasc Ultrasound*. 2010;8:5. [CrossRef]
19. Lee SE, Chang HJ, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. *JACC Cardiovasc Imaging*. 2018;11(10):1475-1484. [CrossRef]
20. Narula J, Chandrashekhar Y, Ahmadi A, et al. SCCT 2021 expert consensus document on coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr*. 2021;15(3):192-217. [CrossRef]
21. Cury RC, Abbara S, Achenbach S, et al. CAD-RADS(TM) coronary artery disease - reporting and data system. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. *J Cardiovasc Comput Tomogr*. 2016;10(4):269-281. [CrossRef]
22. Kim KM, Lim S, Moon JH, et al. Lower uncarboxylated osteocalcin and higher sclerostin levels are significantly associated with coronary artery disease. *Bone*. 2016;83:178-183. [CrossRef] [published correction appears in *Bone*. 2016 December;93:235. (https://doi.org/10.1016/j.bone.2016.02.003)].
23. Zhao B, Chen A, Wang H, et al. The relationship between sclerostin and carotid artery atherosclerosis in patients with stage 3-5 chronic kidney disease. *Int Urol Nephrol*. 2020;52(7):1329-1336. Published online. [CrossRef]
24. Elarbagy AR, Yassein YS, Emara MM, et al. Study of serum sclerostin levels and its role in vascular calcification in patients with chronic kidney disease. *Egypt J Intern Med* . 2019;31:13-821.
25. Hampson G, Edwards S, Conroy S, Blake GM, Fogelman I, Frost ML. The relationship between inhibitors of the Wnt signaling pathway (Dickkopf-1(DKK1) and sclerostin), bone mineral density, vascular calcification and arterial stiffness in postmenopausal women. *Bone*. 2013;56(1):42-47. [CrossRef]
26. Kuipers AL, Miljkovic I, Carr JJ, et al. Association of circulating sclerostin with vascular calcification in Afro-Caribbean men. *Atherosclerosis*. 2015;239(1):218-223. [CrossRef]
27. 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(6):1356-1364. [CrossRef]
28. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358(13):1336-1345. [CrossRef]

29. Nasir K, Rivera JJ, Yoon YE, et al. Variation in atherosclerotic plaque composition according to increasing coronary artery calcium scores on computed tomography angiographyInt. *Int J Cardiovasc Imaging*. 2010;26(8):923-932. [CrossRef]
30. Drechsler C, Evenepoel P, Vervloet MG, et al. High levels of circulating sclerostin are associated with better cardiovascular survival in incident dialysis patients: results from the NECOSAD study. *Nephrol Dial Transplant*. 2015;30(2):288-293. [CrossRef]
31. Kern A, Stompór T, Kiewisz J, et al. Association of serum sclerostin levels with atherosclerosis severity in patients referred for invasive coronary angiography. *Kardiol Pol*. 2020;78(12):1271-1273. [CrossRef]
32. Langdahl BL, Hofbauer LC, Forfar JC. Cardiovascular safety and sclerostin inhibition. *J Clin Endocrinol Metab*. 2021;106(7):1845-1853. [CrossRef]
33. Ge Y, Wu B, Yu X, et al. Association of serum sclerostin level, coronary artery calcification, and patient outcomes in maintenance dialysis patients. *Blood Purif*. 2022;51(3):260-269. [CrossRef]
34. Kanbay M, Siriopol D, Saglam M, et al. Serum sclerostin and adverse outcomes in nondialyzed chronic kidney disease patients. *J Clin Endocrinol Metab*. 2014;99(10):E1854-E1861. [CrossRef]
35. Kanbay M, Solak Y, Siriopol D, et al. Sclerostin, cardiovascular disease and mortality: a systemic review and meta-analysis. *Int Urol Nephrol*. 2016;48(12):2029-2042. [CrossRef]
36. Mödder UI, Hoey KA, Amin S, et al. Relation of age, gender, and bone mass to circulating sclerostin levels in women and men. *J Bone Miner Res*. 2011;26(2):373-379. [CrossRef]
37. Catalano A, Pintaudi B, Morabito N, et al. Gender differences in sclerostin and clinical characteristics in type 1 diabetes mellitus. *Eur J Endocrinol*. 2014;171(3):293-300. [CrossRef]
38. Zeng C, Guo C, Cai J, Tang C, Dong Z. Serum sclerostin in vascular calcification and clinical outcome in chronic kidney disease. *Diab Vasc Dis Res*. 2018;15(2):99-105. [CrossRef]
39. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging*. 2009;2(6):675-688. [CrossRef]