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Original article

SCLEROSTIN TO PREDICT CORONARY ARTERY DISEASE SEVERITY

MELTEM ALTINSOY[1], MUHAMMED BORA DEMIRCELIK[2]

[1]Cardiology Deparment, Ankara Etlik City Hospital, Ankara,Turkey, [2]Cardiology Deparment, Medipol University, Istanbul, Turkey

Postal address Meltem Altinsoy, Ankara Etlik City Hospital, Varlik Mahallesi, Halil Sezai Erkut Caddesi, No:5 Postal Code: 06170, Yenimahalle, Ankara, Turkey
E-mail: meltemaltinsoy@hotmail.com
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Abstract

Introduction: Sclerostin is an extracellular inhibitor of the canonical Wnt/β-catenin signaling pathway. However, the relationship between sclerostin levels in patients with coronary artery disease (CAD) and the severity of their condition remains unclear. This investigation aimed to determine if a specific sclerostin cutoff value correlates with the degree of CAD.

Materials and methods: We consecutively enrolled 290 patients who underwent investigation at a catheterization laboratory. The study population comprised a control group of 140 patients with normal coronary arteries and a CAD group of 150 patients with angiographically confirmed coronary lesion(s). The severity of CAD was assessed using Gensini and SYNTAX scores.

Results: Patients with CAD exhibited significantly higher sclerostin levels compared to control group ($p<0.01$). Univariate linear regression analysis demonstrated that sclerostin levels were significantly correlated with and independently predicted both the Gensini score ($b = 0.040$, 95% CI: 0.014–0.066, $p=0.03$) and the SYNTAX score ($b = 0.025$, 95% CI: 0.015–0.035, $p<0.01$). At a cutoff level of >235 pg/mL, sclerostin showed a specificity of 82.5% and a sensitivity of 60%. Sclerostin had the largest area under the receiver operating characteristic (ROC) curve (0.769 ± 0.053, $p<0.01$). In a population with a 10% CAD prevalence, the positive and negative predictive values of sclerostin were calculated as 27.8% and 94.86%, respectively.

Discussion: Plasma sclerostin levels are elevated in patients with CAD and correlate with the severity of the disease. These findings suggest that sclerostin may have potential as a biochemical marker for the diagnosis or risk stratification of CAD.

Key words: sclerostin, coronary artery disease, Gensini score, SYNTAX score

Resumen

Esclerostina para predecir la gravedad de la enfermedad arterial coronaria

Introducción: La esclerostina es un inhibidor extracelular de la vía de señalización Wnt/β-catenina. Su relación con la gravedad de la enfermedad arterial coronaria (EAC) no está claramente establecida. Este estudio evaluó si un valor de corte específico de esclerostina se asocia con la severidad de la EAC.

Materiales y métodos: Se incluyeron 290 pacientes sometidos a cinecoronariografía: 140 con coronarias normales (grupo control) y 150 con lesiones coronarias angiográficamente confirmadas (grupo EAC). La gravedad de la EAC se valoró mediante los puntajes de Gensini y SYNTAX.

Resultados: Los pacientes con EAC presentaron niveles significativamente más altos de esclerostina que el grupo control ($p<0.01$). En el análisis de regresión lineal univariante, los niveles de esclerostina se correlacionaron y predijeron de forma independiente tanto la puntuación de Gensini ($\beta = 0.040$; IC 95%: 0.014–0.066; $p=0.03$) como la SYNTAX ($\beta = 0.025$; IC 95%: 0.015–0.035;

p<0.01). Con un valor de corte >235 pg/mL, la esclerostina mostró una especificidad del 82.5% y una sensibilidad del 60%. Fue el marcador con mayor área bajo la curva ROC (0.769 ± 0.053; p<0.01). En una población con 10% de prevalencia de EAC, el valor predictivo positivo fue de 27.8% y el negativo de 94.86%.

Discusión: La esclerostina se encuentra elevada en pacientes con EAC y se correlaciona con la gravedad de la enfermedad. Puede representar un biomarcador útil para el diagnóstico o la estratificación del riesgo en la EAC.

Palabras clave: esclerostina, enfermedad de las arterias coronarias, puntaje de Gensini, SINTAX

KEY POINTS
Current knowledge

- Sclerostin, produced by osteocytes, regulates bone turnover and is linked to vascular calcification in animal models, with human studies showing associations between elevated sclerostin levels and arterial stiffness and atherosclerosis severity, particularly in patients with type 2 diabetes mellitus and chronic kidney disease.

Contribution of the article to current knowledge

- Higher sclerostin levels correlate independently with the degree and complexity of coronary atherosclerosis, with elevated sclerostin levels predicting higher SXscores and Gensini score, which are widely recognized as prognostic indicators for patients with coronary artery disease.

Coronary artery disease (CAD), characterized by narrowing or obstruction of the coronary arteries, remains a leading cause of global morbidity and mortality. Emerging evidence indicates that atherosclerosis is a dynamic and actively regulated process[1]. One key regulatory mechanism is the bone-vascular axis, which involves endocrine and metabolic pathways such as Wnt/β-catenin signaling[2]. This pathway plays a critical role in endothelial inflammation, vascular calcification, and mesenchymal stem cell differentiation, thereby contributing to atherogenesis. Following myocardial infarction, Wnt/β-catenin signaling is activated and modulates the early inflammatory response, which is essential for post-infarction tissue repair[3]. Activated Wnt signaling promotes immune cell recruitment to the infarcted myocardium, particularly neutrophils and macrophages, facilitating clearance of necrotic tissue. This initiates a reparative phase characterized by fibrosis, during which cardiac fibroblasts differentiate into myofibroblasts—key mediators of scar formation[4]. These cells synthesize extracellular matrix proteins such as collagen, which reinforce myocardial structural integrity. However, excessive fibrosis may impair cardiac function, highlighting the importance of tightly regulated Wnt signaling[5].

Sclerostin, a glycoprotein encoded by the *SOST* gene on chromosome 17q12–q21, is primarily secreted by osteocytes and acts as a Wnt/β-catenin pathway inhibitor[6]. Beyond bone, sclerostin is also expressed in vascular tissues, especially in areas of vascular calcification[7]. Given its inhibitory role in Wnt signaling, sclerostin may exert protective effects against atherogenesis. While sclerostin inhibition has shown efficacy in osteoporosis treatment (e.g., blosozumab, romosozumab), concerns about cardiovascular safety have emerged[8]. Although initial trials indicated no significant cardiovascular risk, a later study comparing romosozumab to alendronate reported a potential increase in myocardial infarction and stroke risk[9,10].

Furthermore, Mendelian randomization studies have demonstrated an association between low sclerostin levels and increased risk of coronary artery disease (CAD) and myocardial infarction[11]. Angiographic scoring systems such as SYNTAX and Gensini are commonly used to assess the extent and severity of CAD, guiding treatment decisions. While these tools are valuable, recent interest has grown in non-invasive, cost-effective methods for CAD assessment.

In this context, our study aimed to evaluate the association between serum sclerostin levels and the presence and severity of coronary lesions –quantified using the SYNTAX and Gensini score– in a consecutive cohort of patients under-

going coronary angiography. This investigation may support the clinical utility of sclerostin as a potential noninvasive biomarker for CAD.

Materials and methods

Patient Selection

A total of 290 consecutive patients who underwent evaluation in the Cardiology Department's catheterization laboratory between October 1, 2014, and June 6, 2015, were enrolled. Patients with normal coronary arteries on angiography (n = 140) were assigned to the control group, while those with angiographically confirmed coronary artery disease (CAD) (n = 150) were included in the CAD group. The CAD group comprised 99 males, and the control group 68 males. The overall mean age was 58.5 ± 22 years.

Exclusion criteria were: moderate-to-severe valvular heart disease, valvular calcification on echocardiography, cardiomyopathy, acute heart failure, serum creatinine >1.4 mg/dL, liver failure (transaminases >3× upper limit), previous coronary artery bypass grafting, age <18 years, and history of malignancy. All participants provided written informed consent. The study protocol was approved by the Ethics Committee (Approval No: TOUEK 12-01-2015-139).

Laboratory analysis

Peripheral venous blood (15 mL) was collected into EDTA tubes prior to coronary angiography. Samples were centrifuged at 4000 rpm for 15 minutes within 30 minutes of collection. Plasma was stored at –80°C and analyzed for sclerostin levels at the end of the study using the DSST00 Human SOST/Sclerostin Quantikine ELISA Kit (R&D Systems, Minneapolis, MN). ELISA plates were processed with the BioTek ELX50/8 washer and ELX808 reader (BioTek Instruments, Winooski, VT) in the Medical Biochemistry Department.

Fasting glucose was measured via capillary sampling at bedside. Serum levels of total cholesterol, LDL, HDL, triglycerides, urea, creatinine, AST, and ALT were measured after 10 hours of fasting using Cobas 501 analyzer (Roche Diagnostics, Switzerland) with Cobas c kits. GFR was calculated using the MDRD formula. Complete blood count parameters (WBC, hemoglobin, hematocrit, platelets) were analyzed using the Coulter LH 780 analyzer (Beckman Coulter Inc., USA).

Angiographic assessment

The Gensini score was used to quantify the severity of coronary atherosclerosis based on angiographic findings[12]. The SYNTAX score (SXscore) was applied to evaluate lesion complexity and coronary anatomy[13]. Higher SXscores are associated with more extensive disease and poorer outcomes, particularly in acute coronary syndrome (ACS) patients[14,15]. Both scores reflect the extent of coronary involvement and are influenced by pathophysiological mechanisms such as inflammation, thrombogenicity, and endothelial dysfunction[16,17].

SYNTAX Score

Diagnostic coronary angiography (CAG) was performed using standard protocols (Siemens Axiom Artis zee 2011; Siemens Healthcare, Erlangen, Germany), via femoral access with a 6-French guiding catheter (Launcher; Medtronic, Minneapolis, MN, USA). Multivessel disease (MVD) was defined as >50% stenosis in at least three major coronary arteries. The preprocedural SYNTAX (SX) score was calculated for each patient by two independent interventional cardiologists. Each lesion causing ≥50% luminal stenosis in vessels ≥1.5 mm was scored using the online SYNTAX score calculator (http://www.syntaxscore.com), and the total score was obtained by summing individual lesion scores[13]. Patients were stratified into three categories based on their total SXscore: low (≤22), intermediate (23–32), and high (≥33).

Gensini Score

The severity of coronary artery disease was also assessed using the Gensini scoring system. Lesions were assigned scores based on the degree of luminal narrowing: 25% = 1, 50% = 2, 75% = 4, 90% = 8, 99% = 16, and total occlusion = 32. These scores were then multiplied by a weighting factor reflecting the functional significance of the myocardial territory supplied by the affected vessel.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test assessed the normality of data distribution. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using two-tailed Student's t-test. Non-normally distributed variables were presented as median (interquartile range) and analyzed using the Mann-Whitney U test. Correlations between continuous variables were assessed using Pearson or Spearman correlation tests, depending on data distribution.

Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of candidate biomarkers in distinguishing CAD from non-CAD patients. Univariate linear regression was performed

to evaluate the association between individual variables and both the Gensini and SYNTAX (SX) scores. Results are presented as β coefficients with corresponding 95% confidence intervals (CIs) to indicate the strength and direction of associations.

The Youden index, a composite measure defined as *sensitivity + specificity – 1* (or *sensitivity – false positive rate*), was calculated to identify the optimal diagnostic cut-off point. This index ranges from 0 to 1, where higher values indicate better discriminative ability[18]. Importantly, unlike accuracy, the Youden index is independent of disease prevalence. A p-value <0.05 was considered statistically significant in all tests.

Results

Baseline characteristics and laboratory parameters

Table 1 presents the demographic and laboratory characteristics of the study population. The CAD group had a higher proportion of males and individuals with diabetes compared to the control group. Serum levels of creatinine, triglycerides (TG), glomerular filtration rate (GFR), and sclerostin were significantly elevated in the CAD group, while HDL levels were significantly lower. The mean serum sclerostin concentration was significantly higher in the CAD group than in the control group ($p < 0.01$). Similarly, TG, glucose, and creatinine levels were higher in the CAD group, while HDL and GFR values were lower. No significant differences were observed for other laboratory parameters between the two groups.

Regression and correlation analyses

Univariate linear regression analysis revealed that serum sclerostin was independently associated with both Gensini ($\beta = 0.040$; 95% CI: 0.014-0.066; $p = 0.03$) and SYNTAX scores ($\beta = 0.025$; 95% CI: 0.015–0.035; $p < 0.01$), as shown in Tables 2 and 3. Both systolic and diastolic blood pressures were also found to be independent predictors of Gensini ($\beta = 2.881$ and 2.972; $p < 0.001$) and SYNTAX scores ($\beta = 1.338$ and 1.448; $p < 0.001$).

Table 1 | Demographic characteristics and laboratory parameters in coronary artery disease (CAD) and control groups

Parameters	CAD group (n=150)	Control group (n=140)	p
Age, years	61.4 ± 12.7	56.0 ± 12.9	**0.03**
Male sex, (%)	99 (66)	68 (48.5)	**0.02**
Diabetes mellitus, (%)	64 (43)	7 (5)	**<0.01**
Hypertension, (%)	70 (46.6)	59 (42.1)	0.45
Sclerostin, pg/mL	462.8 ± 60.1	161.0 ± 10.3	**<0.01**
Hgb, g/dL	14.0 ± 1.5	13.5 ± 1.7	0.25
Hct, (%)	43.0 ± 4.3	41.3 ± 5.4	0.16
Plt (x1000/uL)	256.0 ± 105	243.28 ± 66.8	0.97
Wbc (x1000/uL)	8.70 ± 2.5	7.71 ± 2.4	0.06
LDL, mg/dL	126.3 ± 34.7	115.2 ± 33.9	0.15
HDL, mg/dL	41.5 ± 12.1	46.9 ± 15	**0.03**
TG, mg/dL	155 ± 58.6	137 ± 82.2	**0.04**
AST, U/L	21.5 ± 12.2	17.8 ± 5.6	0.45
ALT, U/L	25.4 ± 19.4	25.7 ± 21	0.81
Glucose, mg/dL	129.3 ± 47.6	102.9 ± 26.8	**<0.01**
Urea, mg/dL	34.5 ± 10.8	32.0 ± 7.2	0.40
Creatinine, mg/dL	0.95 ± 0.2	0.81 ± 0.1	**<0.01**
GFR, mL/m/1.73 m^2	83.0 ± 17.8	90.6 ± 17.3	**0.04**

ALT: alanine transaminase; AST: aspartate transaminase; Htc: hematocrit; Hgb: hemoglobulin; GFR: glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein; Plt: platelets; TG: triglyceride; Wbc: white blood cells

Correlation analysis demonstrated a statistically significant positive correlation between sclerostin and SYNTAX score (r = 0.361, p < 0.01) and between sclerostin and Gensini score (r = 0.337, p < 0.01). Additionally, a positive correlation was observed between the Gensini and SYNTAX scores themselves (r = 0.358, p < 0.01), as detailed in Table 4.

Table 2 | Univariate linear regression analysis of the factors correlated to Gensini Score in patients with coronary artery disease

Variables	β	95% confidence interval	p-value
Sclerostin, pg/mL	0.040	0.014-0.066	**0.003**
High density lipoprotein cholesterol(mg/dL)	-0.582	-1.338-0.173	0.129
Systolic blood pressure(mmHg)	2.881	2.280-3.482	**<0.001**
Diastolic blood pressure(mmHg)	2.972	2.249-3.069	**<0.001**
Blood urea nitrogen(mg/dL)	0.873	-0.250-1.996	0.126
Age(years)	0.755	-0.187-1.697	0.115
Glomerular filtration rate(mL/min)	-0.779	-1.344- -0.215	**0.007**

ALT: alanine transaminase; AST: aspartate transaminase; Htc: hematocrit; Hgb: hemoglobulin; GFR: glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein; Plt: platelets; TG: triglyceride; Wbc: white blood cells

Table 3 | Univariate linear regression analysis of the factors correlated to Syntax score in patients with coronary artery disease

Variables	β	95% confidence interval	p-value
Sclerostin, pg/mL	0.025	0.015-0.035	**<0.001**
High density lipoprotein cholesterol(mg/dL)	-0.293	-0.612-0.026	0.071
Systolic blood pressure(mmHg)	1.338	1.114-1.561	**<0.001**
Diastolic blood pressure(mmHg)	1.448	1.188-1.709	**<0.001**
Blood urea nitrogen(mg/dL)	0.200	-0.282-0.682	0.411
Age(years)	0.323	-0.076-0.723	0.111
Glomerular filtration rate(mL/min)	-0.286	-0.529 - -0.044	**0.021**

**p <0.05 was considered statistically significant*

Table 4 | The correlation of sclerostin level with Gensini score and SYNTAX score and the correlation between Gensini score and SYNTAX score

Variables	Gensini score		SYNTAX score	
	Correlation (r)	p	Correlation (r)	p
Sclerostin, pg/mL	0.337	<0.001	0.361	<0.001
Parameter			**Gensini Score**	
	Correlation (r)	p		
SYNTAX Score	0.358	<0.001		

Diagnostic performance of biomarkers

The diagnostic efficacy of sclerostin, HDL, LDL, creatinine, GFR, and glucose in identifying CAD was evaluated using ROC curve analysis (Figure 1). Sclerostin demonstrated the highest area under the curve (AUC = 0.769), indicating superior discriminatory ability compared to the other biomarkers. The optimal cut-off value for sclerostin, determined using the Youden index, was 235.4 pg/mL, corresponding to a sensitivity of 60% and specificity of 82.05% (Figure 2).

Assuming a disease prevalence of 10%, as adopted from prior literature[19], the positive predictive value (PPV) and negative predictive value (NPV) of sclerostin were 27.08% and 94.86%, respectively.

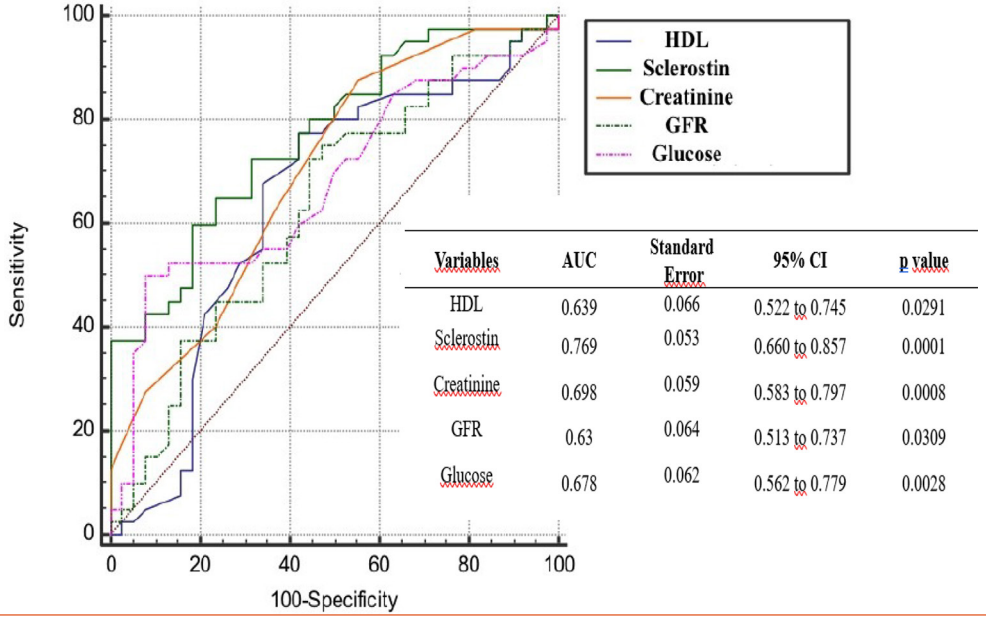
As shown in Table 5, creatinine had the highest sensitivity (87.5%), while glucose had the highest specificity (92.31%) among the tested variables. The PPV of glucose was 41.94%, and the NPV of creatinine was 96.98%. Table 6 presents PPV and NPV values for various prevalence levels, further illustrating how diagnostic performance changes under different epidemiological conditions.

Discussion

The main finding of our study is that serum sclerostin levels at admission are independently associated with the extent and complexity of coronary atherosclerosis. Elevated sclerostin levels were predictive of higher SYNTAX scores. In patients with acute coronary syndromes (ACS), the SYNTAX score is a well-established independent prognostic marker[14,15].

Sclerostin is a glycoprotein primarily secreted by osteocytes and encoded by the *SOST* gene (implicated in sclerosteosis and Van Buchem disease). It acts as an endogenous inhibitor of the Wnt signaling pathway, regulating bone turnover and suppressing osteoblastic activity[20]. Animal studies in models of vascular calcification have demonstrated upregulation of sclerostin in vascular tissues associated with increased calcification. This suggests a potential link between Wnt signaling and vascular calcification. Supporting this, sclerostin expression has been observed in human dialysis fistulas and calcified aortic valves, particularly in patients with end-stage renal disease and type 2 diabetes mellitus, aligning with the animal model findings[21].

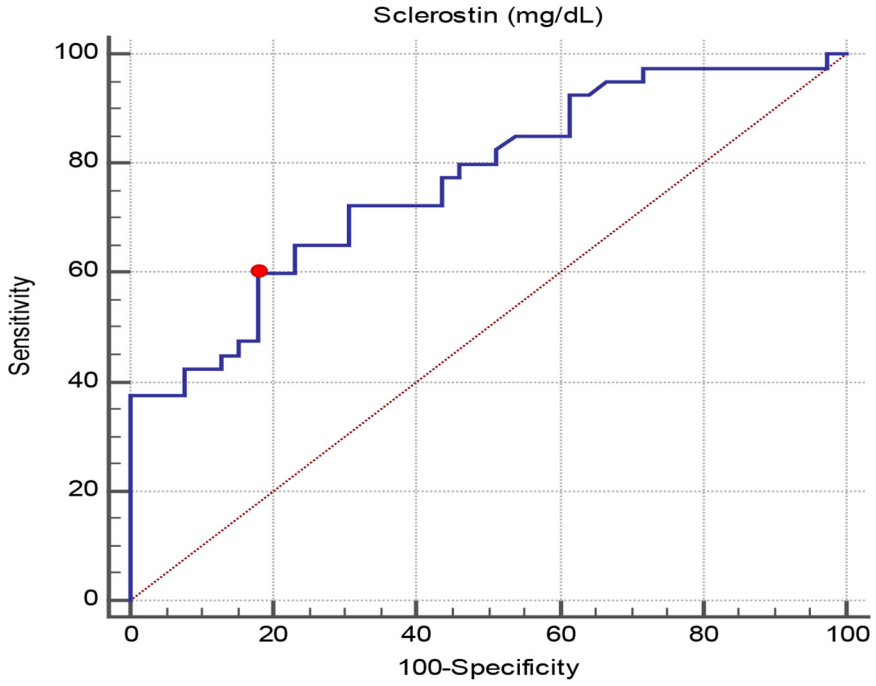
Figure 1 | ROC curves for the prediction of coronary artery disease



Variables	AUC	Standard Error	95% CI	p value
HDL	0.639	0.066	0.522 to 0.745	0.0291
Sclerostin	0.769	0.053	0.660 to 0.857	0.0001
Creatinine	0.698	0.059	0.583 to 0.797	0.0008
GFR	0.63	0.064	0.513 to 0.737	0.0309
Glucose	0.678	0.062	0.562 to 0.779	0.0028

GFR: glomerular filtration rate; HDL: high density lipoprotein

Figure 2 | ROC curve for the usefulness of serum sclerostin level estimating coronary artery disease severity



Associated criterion	>235.451
Sensitivity	60%
Specificity	82.05%

ROC: receiver operating curve

Area under the curve (AUC)	*0.769*
Standard Error	*0.0526*
95% Confidence interval	*0.659 to 0.856*
z statistic	*5.093*
Significance level P (Area=0.5)	*0.0001*

Table 5 | Sensitivity and specificity of sclerostin. High density lipoprotein, creatinine, glomerular filtration rate and glucose. Predictive values were adjusted for a 10% prevalence of coronary artery disease

Variables	Youden Index	Cut-off level	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Sclerostin (pg/mL)	0.4205	>235.45	60	82.05	27.08	94.86
HDL (mg/dL)	0.3647	≤44	77.5	58.97	17.35	95.93
Creatinine (mg/dL)	0.3224	>0.7	87.5	44.74	14.96	96.98
GFR (mL/dk)	0.2891	≤95.07	72.5	56.41	15.59	94.86
Glucose (mg/dL)	0.4231	>110	50	92.31	41.94	94.32

GFR: glomerular filtration rate; HDL: high density lipoprotein

Variability in previous study results may be attributed to differences in sampling methods (e.g., arteriovenous fistula vs. peripheral venous sampling), fasting status at the time of collection, assay techniques, and heterogeneity of the study populations. Several studies reporting a

Table 6 | Positive and negative predictive values for different disease prevalences

Parameters	Disease Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)
Sclerostin(pg/mL)	10	27.08	94.86
	20	45.52	89.13
	30	58.89	82.72
	40	69.03	75.47
	50	76.97	67.22
HDL (mg/dL)			
	10	17.35	95.93
	20	32.07	91.29
	30	44.74	85.95
	40	55.74	79.72
	50	65.38	72.38

HDL: high density lipoprotein

positive association between sclerostin levels and atherosclerosis severity included patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD). In our study, these patient groups were explicitly excluded to eliminate the confounding effects of impaired renal clearance. Given its molecular weight, sclerostin is primarily eliminated via the kidneys; thus, reduced renal function may result in accumulation of circulating sclerostin.

There is ongoing debate regarding the cardiovascular safety of sclerostin inhibitors. Although most clinical trials were not primarily designed to assess cardiovascular outcomes, some studies have raised significant safety concerns, reporting increased risks of myocardial infarction and stroke [22,23] .In contrast, other studies have observed a low incidence of cerebrovascular and ischemic cardiovascular events, suggesting a more favorable safety profile[24].When interpreting these findings, it is important to consider differences in study populations. Many clinical trials were conducted primarily in postmenopausal women without a history of cardiovascular disease, with men underrepresented in most cohorts. Genetic studies in humans suggest that variants leading to reduced arterial sclerostin expression are associated with an increased risk of cardiovascular events. In contrast, biomarker-based studies have reported that elevated circulating sclerostin levels are linked to the presence and diagnosis of various cardiovascular diseases, positioning sclerostin as a potential disease marker.This apparent contradiction may reflect reverse causality—that is, increased sclerostin levels may result from underlying cardiovascular disease rather than acting as a causal factor.A recent study investigating the relationship between sclerostin, periostin, and major vascular risk scores reported a positive correlation between serum levels of both markers and the SCORE2-Diabetes algorithm. As this tool identifies patients with type 2 diabetes at high or very high cardiovascular risk, elevated circulating sclerostin levels were noted in those at increased risk[25].In line with these findings, we observed higher sclerostin concentrations (>234 pg/mL) in patients with elevated SYNTAX and Gensini scores, compared to those with lower sclerostin levels (≤234 pg/mL). However, unlike the previous study, we did not find a correlation between sclerostin levels and either age or eGFR. Possible explanations include our broader age distribution and the exclusion of patients with chronic kidney disease, which may have minimized confounding by renal function.

Our findings demonstrate that higher admission sclerostin levels are associated with the extent and complexity of coronary atherosclerosis. However, the precise mechanisms linking inflammation, vascular calcification, and atherogenesis remain incompletely understood. Ath-

erosclerosis is known to involve several localized inflammatory processes, including endothelial dysfunction, leukocyte recruitment, extracellular matrix degradation, and platelet activation, all of which contribute to disease progression[26]. Sclerostin may play a critical role at multiple stages of atherosclerotic progression. In a study involving Egyptian female patients with type 2 diabetes, sclerostin levels were significantly higher in those with atherosclerosis compared to both diabetic patients without atherosclerosis and healthy controls[27]. Similarly, another study reported that each picomole per liter increase in serum sclerostin was associated with a 4% increase in the risk of atherosclerotic disease, particularly among individuals with type 2 diabetes and coexisting atherosclerosis[28].These findings align with our study, in which 43% of patients had type 2 diabetes mellitus (T2DM). Hyperglycemia contributes to vascular complications through the formation of advanced oxidation protein products, which promote vascular calcification by inducing osteoblastic trans-differentiation of vascular smooth muscle cells. This mechanism may partly explain the upregulation of sclerostin observed in patients with T2DM. Moreover, plasma sclerostin levels have been identified as independent predictors of atherosclerotic heart disease in individuals with T2DM. Notably, conventional CAD risk factors –including age, sex, BMI, hypertension, dyslipidemia, creatinine, homocysteine, HbA1c, and carotid intima-media thickness– were not found to be independently predictive in these studies[29,30].

The primary limitation of our study is the relatively small sample size and the lack of long-term follow-up, which restricts conclusions regarding causality and prognosis. Secondly, sclerostin levels were measured only once, and longitudinal data are lacking. It remains unclear whether sclerostin concentrations vary over time, particularly in response to disease progression or therapeutic intervention. Finally, as sclerostin levels can be influenced by multiple comorbid conditions, elevated levels may act as a non-specific marker rather than a direct causal factor in atherosclerosis.

Reliable predictive biomarkers are critical for the early detection, monitoring, and prevention of atherosclerosis. Our findings demonstrate that serum sclerostin levels are elevated in patients with both severe and extensive coronary artery disease (CAD). These results suggest a potential role for sclerostin in the progression of atherosclerosis. Conversely, lower sclerostin levels may be associated with atherosclerotic regression. However, further large-scale, prospective studies are warranted to clarify whether sclerostin plays a causal role in the pathophysiology of atherosclerosis or serves primarily as a surrogate marker.

Conflict of interest: None to declare

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