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Correlation between the serum lumican level and the severity of coronary artery disease

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Abstract. – OBJECTIVE: Several studies have previously shown that some small leucine-rich proteoglycans (SLRPs) are associated with atherosclerotic plaque. We aim to investigate the relationship between circulating lumican levels and the severity of coronary artery disease (CAD).

PATIENTS AND METHODS: This study included 255 consecutive patients who underwent coronary angiography for stable angina pectoris. All demographic and clinical data were collected prospectively. The severity of CAD was assessed based on the Gensini score and a value >40 was defined as advanced CAD.

RESULTS: Eighty-eight patients were in the advanced CAD group; these are older and the frequency of diabetes mellitus, cerebrovascular accidents, reduced ejection fraction (EF), left atrium diameter was higher. Serum lumican levels were found as higher in advanced CAD group (0.4 ng/ml *vs.* 0.6 ng/ml, respectively, *p*<0.001). When the Gensini score increased, a statistically significant increase was observed in lumican levels with a good correlation (r=0.556 and *p*<0.001). In multivariate analysis, diabetes mellitus, EF and lumican were predictive for advanced CAD. Lumican level predicts CAD seriousness with a sensitivity rate of 64%, specificity rate of 65%.

CONCLUSIONS: In this study, we reveal a relationship between serum lumican levels and CAD severity. More research is warranted to determine the mechanism and prognostic values of lumican in the atherosclerosis.

Key Words:
Lumican, Coronary artery disease, Gensini score.

Introduction

Atherosclerosis is the most common underlying pathology of coronary artery disease (CAD), peripheral artery disease, and cerebrovascular disease[1]. Atherosclerotic plaques are composed of lipids, inflammatory cells, smooth muscle cells, apoptotic cells, calcium, and extracellular matrix (ECM)[2,3]. The ECM of atherosclerotic plaques includes different proteins and glycoproteins, the most abundant being collagen, elastin, and proteoglycans[4]. The structure, composition, and turnover of the ECM, as well as cell-matrix interactions, are crucial in the development of atherosclerotic plaque. During the proliferation of an atherosclerotic lesion, a continuous remodeling of the extracellular matrix occurs, characterized by varying degrees of biosynthesis and degradation[5]. The content of proteoglycans is low in the ECM of vascular tissue but increases significantly in all phases of vascular disease[6].

Lumican is an ECM protein and belongs to a family of proteins called small leucine-rich proteoglycans (SLRPs), which consist of a core protein with leucine-rich repeats and one or more linked glycosaminoglycan chains[7]. Members of this family play an important role in cell migration and proliferation during embryonic development, tissue repair, and tumor growth[8]. Lumican levels have previously been reported to increase in various inflammatory-like conditions such as keratitis[9], inflammatory colitis[10], pancreatitis[11], and non-alcoholic fatty liver disease[12]. Recent research has suggested that some SLRPs play a role in the development of atherosclerosis[13]; similarly, lumican was found to be expressed in human coronary atherosclerotic tissue and carotid plaques[8]. However, the relationship between serum lumican levels and the severity of coronary artery disease has not been studied to date. In this study, we aim to examine the relationship between serum lumican levels and the severity of coronary artery disease in a group of patients who underwent coronary angiography for stable angina pectoris.

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Patients and Methods

Study Population and Data Collection

This prospective, cross-sectional study includes 255 patients who underwent coronary angiography for stable angina pectoris between February 2020 and March 2021. Stable angina was defined as typical discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. CAD was defined as at least 50% diameter stenosis in one or more major epicardial coronary artery, and the severity of CAD was assessed based on the Gensini score[14]. The age, sex, and body mass index (BMI) of each patient were recorded in addition to details of any of the following CAD risk factors: hypertension (HT) (self-reported blood pressure >140/90 mm Hg or use of an antihypertensive drug); diabetes mellitus (DM) (self-reported fasting glucose >126 mg/dL or use of oral hypoglycemic agents or insulin); dyslipidemia (self-reported low-density lipoprotein >130 mg/dL or total cholesterol >200 mg/dL); and smoking (within one year). All demographic and clinical data were collected prospectively. The exclusion criteria for this study were: active infection, glomerular filtration rate <60 mL/min (GFR) (Cockcroft-Gault formula), acute coronary syndrome, congestive heart failure, severe valvular disease, advanced hepatic disease, and systemic inflammatory or autoimmune disease. All patients provided their informed consent to participate in the present study, which was approved by the Local Ethics Committee.

Blood Samples

Fasting peripheral blood samples were drawn for the measurement of blood glucose, urea, creatinine, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and plasma triglycerides. After the samples were centrifuged at 4°C for 15 min, the serum samples were separated and stored at -80°C. Serum lumican levels were determined using a commercially available Enzyme-Linked Immunosorbent Assay kit by Elabscience (CSB-E09797h, Cusabio Biotech Co., Ltd., Wuhan, China).

Coronary Angiography and Gensini Score

Coronary angiography was performed by two experienced interventional cardiologists who had no knowledge of the study or the patient group designation. The coronary arteries were visualized in the left and right oblique planes using cranial and caudal angulation. Gensini scores were used to evaluate the grading and complexity of CAD. A Gensini score is a point scale that is based on the number of stenotic coronary artery segments, including the degree of luminal narrowing and the localization of the stenosis. Thus, the Gensini score is calculated as a sum of stenosis scores and functional significance scores, as calculated for each segment of the coronary artery tree. The stenosis score expresses the percentage reduction in the diameter of the coronary artery lumen; a score from 1 to 32 was assigned, where 32 represents complete occlusion. The functional significance score illustrates the regional importance of the lesion's position as a value from 0.5 to 5. An overall Gensini score greater than 40 was defined as advanced CAD[15].

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 19.0 for Windows (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as percentages. The Chi-squared test was used to assess differences in categorical variables between groups. The relationships among parameters were assessed using Pearson's or Spearman's correlation analysis, according to the normality of the data. Student's *t*-test or the Mann-Whitney U tests were used to compare unpaired samples as required. Univariate and multivariate logistic regression analyses were used to identify independent variables of advanced coronary artery disease. Independent variables in univariate analysis were age, DM, GFR, HbA1C, LVEF, and lumican levels. After performing univariate analysis, statistically significant variables were included in the multivariate logistic regression analysis using the stepwise method. The results of univariate and multivariate regression analyses were presented as odds ratios with a 95% CI. For the laboratory parameter of lumican receiver operating characteristic (ROC), curves were obtained and the optimal values with the greatest total sensitivity and specificity in the prediction of advanced coronary artery disease were selected. Significance was assumed at a two-sided p-value of <0.05.

Results

A total of 255 patients were enrolled in the study prospectively. The patients were divided into two

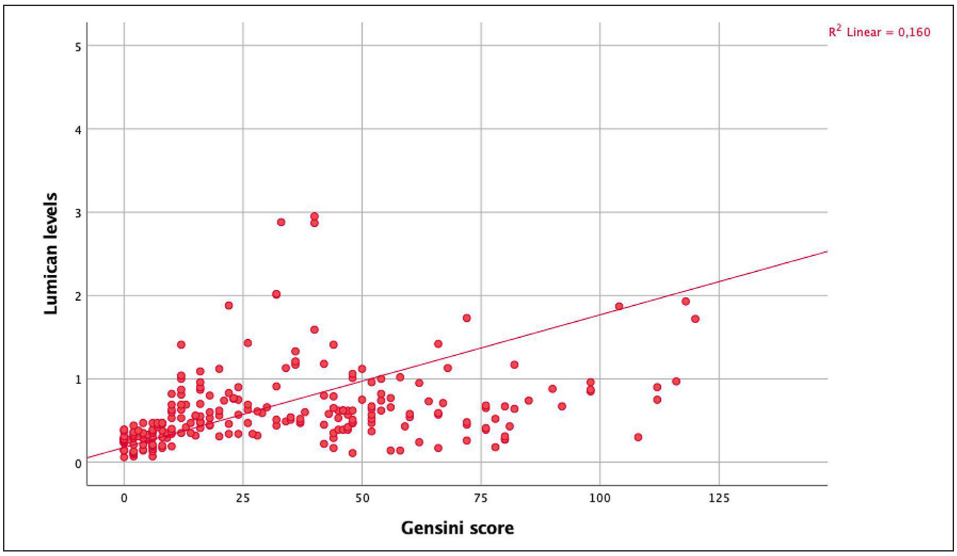

Figure 1. Spearman's correlation analysis of Gensini score and lumican levels.

groups according to their Gensini score, with 88 patients in the advanced CAD group. The demographic, laboratory, and clinical characteristics of the patients according to the Gensini score are summarized in Table I. The mean age of 167 patients with a Gensini score of <40 was 60.4 ± 9.4 years and the mean age of 88 patients with a score> 40 was 62.9 ± 9.5 years. No significant differences were found between the groups regarding gender, BMI, hypertension, hyperlipidemia, pulmonary arterial hypertension, chronic obstructive pulmonary disease, smoking status, family history, or medications [antiplatelet, statin, beta-blocker, Ca channel blocker, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), insulin or oral antidiabetic drugs]. In the advanced CAD group, the frequency of diabetes mellitus, cerebrovascular accident, the incidence of reduced left ventricular systolic function, and left atrium diameter were typically higher. In laboratory parameters, glucose, and HbA1c were higher in the advanced group; total cholesterol, C reactive protein (CRP), low density lipoprotein (LDL), and uric acid levels were similar between the two groups.

Serum lumican levels were found to be higher in the advanced CAD group (0.4 (0.3-0.6) ng/ml *vs*. 0.6 (0.4-0.9) ng/ml respectively, $p<0.001$). The relationship between the Gensini score and lumican level of all patients was evaluated by Spearman correlation analysis. As the Gensini score increased, a statistically significant increase was also observed in lumican levels, with a good correlation (r=0.556 and $p<0.001$) (Figure1).

Parameters that significantly differed between the groups in the logistic regression analysis were further evaluated with univariate and multivariate analyses. Initially, age, gender, BMI, HT, DM, smoking, GFR, CRP, HbA1C, LVEF, and lumican levels were assessed by univariate analysis, and the parameters that were found to be statistically significant were subsequently evaluated by multivariate analysis. In the multivariate analysis, DM, EF and lumican level were found to be statistically significant for prediction of advanced CAD (AA, OR 4.649, $p = 0.010$; AS, OR 1.749, $p < 0.001$; AWT, OR 0.729, $p = 0.042$; Table II).

We finally evaluated the specificity and sensitivity of lumican values with ROC analysis in order to predict CAD severity. The blue line in Figure 2 shows lumican levels; the value for the area under the curve was measured as 0.65 (0.58-0.72). Furthermore, lumican level predicts CAD severity with a sensitivity rate of 64%, specificity rate of 65%, and a cutoff value of 0.52 (Figure 2).

Discussion

The results of this study demonstrate that lumican is associated with CAD severity in patients who underwent coronary angiography for stable angina pectoris. Serum lumican levels were found to be higher in the advanced CAD group. As lumican level increased, the Gensini score also increased with a good correlation between variables (r= 0.556, $p<0.001$). In the multivariate analysis, DM, EF, and lumican were found to be statistically significant for predicting advanced

Table I. Clinical demographic characteristics of patients according to Gensini score.

Patient (n)	Score≤40 (n: 167)	Score>40 (n: 88)	p
Age, years	60.4 ± 9.4	62.9 ± 9.5	0.047
Gender, (male%)	113 (67%)	64 (72%)	0.404
BMI, kg/m^2	30.3 ± 5.3	29.4± 5.1	0.216
HT, n (%)	93 (55%)	54 (61%)	0.549
DM, n (%)	53 (31%)	42 (47%)	0.029
CAD, n (%)	76 (45%)	49 (55%)	0.273
HL n (%)	69 (41%)	44 (50%)	0.201
CVA n (%)	6 (3%)	13 (15%)	0.003
PAH n (%)	12 (7%)	14 (16%)	0.078
COPD n (%)	28 (16%)	9 (10%)	0.273
Family History, n (%)	70 (41%)	45 (51%)	0.207
Smoking Status, n (%)	34 (20%)	11 (12%)	0.281
Smoking Status, years	20 (0-30)	10 (0-30)	0.283
LVEF, %	57.7±4.1	53.2±8.9	<0.001
LA, mm	36.4±3.8	38.0±3.9	0.004
Creatinin, mg/dl	0.7 (0.6-0.8)	0.8 (0.7-0.9)	0.139
Ürea	32 (24-37)	34 (28-43)	0.142
GFR, ml/dk/1.73 m^2	91.4±16.3	89.6±22.8	0.207
Uric asit	5.3±1.3	5.6±1.7	0.191
Glukoz	134.0±63.4	156.7±74.2	0.016
HBA1C	6.4±1.2	7.0±1.5	0.015
CRP, mg/dl	3 (2-7)	4 (2-9)	0.475
Albumine, g/dl	4.0±0.3	4.0±0.4	0.578
TC, mg/dl	186.2±52.9	191.0±52.2	0.491
LDL, mg/dl	120.3±39.4	126.3±38.3	0.248
HDL, mg/dl	42.6±10.8	42.6±10.7	0.993
TG, mg/dl	126 (85-185)	140 (97-196)	0.171
Lumican,	0.4 (0.3-0.6)	0.6 (0.4-0.9)	<0.001
Gensini score,	12.9±11.5	65.9±22.8	<0.001
BB, n (%)	40 (23%)	19 (22%)	0.519
CCB, n (%)	18 (10%)	10 (11%)	0.497
ACEI/ARB, n (%)	38 (22%)	20 (23%)	0.447
Statin, n (%)	36 (21%)	20 (23%)	0.366
ASA n (%)	68 (41%)	33 (37%)	0.457
ASA+P2Y12 n (%)	16 (18%)	13 (33%)	0.071
Insulin, n (%)	4 (4%)	3 (7%)	0.506
OAD, n (%)	24 (27%)	12 (28%)	0.848

BMI: Body Mass Index; HT: Hypertension; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; HL: Hyperlipidemia; CVA: Cerebrovascular Accident; PAH: Pulmonary Arterial Hypertension; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction; LA: Left Atrium; GFR: Glomerular Filtration Rate; CRP: C Reactive Protein; TC: Total Cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglycerides: BB: Beta-Blocker; CCB: Ca Channel Blocker; ACEI/ARB: ACE Inhibitors/Angiotensin II Receptor Blocker; ASA: Acetylsalicylic Acid: OAD; Oral Antidiabetic Drugs.

CAD. Furthermore, lumican level predicts CAD severity with a sensitivity of 64%, specificity of 65%, and a cutoff value of 0.52.

The development and progress of atherosclerosis at arterial walls are mediated by interactions between numerous growth factors, cytokines, and vasoregulatory molecules that regulate cellular function with cells intrinsic to the vascular wall and ECM[16]. ECM is composed of fibrillar collagens, elastic fibers, and proteoglycans[17]. The structure, composition, and turnover of the ECM are crucial in developing atherosclerotic plaque[18]. Vascular smooth muscle cells (VSMCs) play an integral role in atherosclerosis; in this condition, VSMCs transform from a contractile to a synthetic phenotype and migrate into the intima[19]. Subsequently, they proliferate and synthesize ECM, including proteoglycans[18].

Proteoglycans are macromolecules composed of a core protein substituted with covalently linked glycosaminoglycan (GAG) chains and are major constituents of the ECM[19]. Proteoglycans impact disease processes such as inflammation, immune responses, wound healing, and tumor growth[20]. Over the last two decades, proteoglycans have been shown to be involved in ECM remodeling and fibrosis in different diseases[21,22]. Also, recent research[23] has suggested that some SLRPs play a role in various cardiovascular diseases, including the development of atherosclerosis[24-27]. Proteoglycans have been identified in all three layers of the vessel wall[5], with different proteoglycans dominant in different layers. Among proteoglycans, members of the SLRP family seem to play an especially important role in vascular biology. Radhakrishnamurthy et al[28] examined proteoglycan distribution in normal and atherosclerotic coronary arteries and identified low levels of decorin in the intima of normal coronary arteries, consistent with the findings of Merrilees et al[29] decorin has also been shown to result in significant inhibition of neointimal hyperplasia, a precursor of advanced atherosclerosis in an *ex-vivo* human saphenous vein graft model[30]. Kolodgie et al[31] analyzed proteoglycan distribution in coronary atherosclerotic lesions in patients with sudden coronary death and found abundant vesicant expression in lesions with plaque rupture or erosion. However, Nazemi et al[32] reported no correlation between serum decorin levels and coronary artery calcification, based on a small study of 84 coronary artery patients.

Although previous studies[8,13,28-32] have shown that some SLRPs, such as decorin, lumican, and osteoglycin, were associated with atherosclerotic plaque tissue in human or animal models, the relationship between serum lumican levels and the severity of coronary artery disease remains poorly understood. Lumican belongs to the SLRP family and influences cellular migration, proliferation, and apoptosis by interacting with the cell surface[33]. Lumican may also have an important role in the formation of fibrotic lesions[34,35], but little is known about the expression and the role of lumican in atherosclerosis. Lumican gene expression was elevated in arteries from patients with CAD compared to healthy control subjects, as well as in femoral arteries with atherosclerotic plaques from patients with peripheral occlusive arterial disease and in aortic valves from patients with degenerative aortic

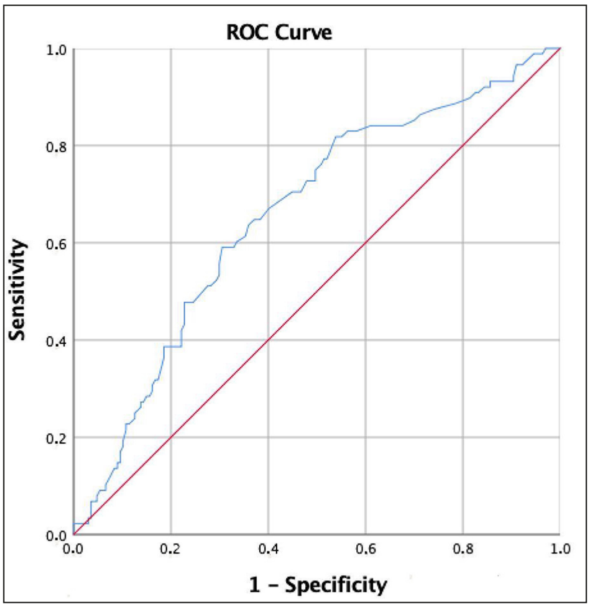

Figure 2. Receiver operating characteristic curve showing the diagnostic value of lumican in predicting CAD severity.

Table II. Univariate and multivariate regression analyzes of predictors of advanced CAD.

Variable	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.02	1.00-1.05	0.04	1.00	0.95-1.04	0.96
Gender	1.27	0.72-2.25	0.40			
BMI	0.96	0.91-1.02	0.21			
HT	1.26	0.74-2.14	0.38			
DM	1.96	1.15-3.33	0.01	2.11	1.06-4.20	0.03
Smoking	1.55	0.74-3.62	0.22			
GFR	0.98	0.97-0.99	0.02	0.99	0.97-1.01	0.64
CRP	1.02	0.99-1.06	0.09			
HBA1C	1.30	1.06-1.59	0.01	1.06	0.79-1.42	0.66
LVEF	0.89	0.85-0.94	<0.001	0.90	0.85-0.96	0.001
Lumican	2.33	1.19-4.54	<0.001	4.27	1.50-10.10	<0.001

BMI: Body Mass Index; HT: Hypertension; DM: Diabetes Mellitus; GFR: Glomerular Filtration Rate; CRP: C Reactive Protein; LVEF: Left Ventricular Ejection Fraction.

stenosis[23]. Yang et al[26] found lumican circulation was independently associated with carotid atherosclerosis plaque in their study of 176 hypertension patients and suggested that SLRPs are a promising potential molecular marker for atherosclerosis. In one study, lumican showed increased mRNA expression level in ischemic and reperfused rat hearts[36]. Likewise, in the study by Engebretsen et al[35], cardiac lumican mRNA and protein levels led to increased experimental and clinical heart failure in a mouse model. In our study, we found a positive correlation between the severity of CAD and serum lumican level. Lumican protein is prominently localized in the fibrous thickened intima and the inner layer of media in coronary atherosclerosis. The lumican protein and its mRNA were expressed in VSMCs that migrated into the intima and localized in the inner layer of the media in atherosclerosis.

In conclusion, severe coronary artery stenosis is associated with poor prognosis, and its association with various biomarkers has been investigated in many studies. The lumican protein and its gene expression were found expressed in human atherosclerotic tissue and ischemia. However, the relationship between proteoglycans CAD severity has not been conclusively determined in previous studies. In this study, we reveal a relationship between serum lumican levels and CAD severity. Further research is warranted to determine the mechanism and prognostic values of lumican in the development of atherosclerosis.

Limitations

There are several limitations regarding our study. Firstly, this study is cross-sectional, based at a single center, and does not comprise a large sample size. Secondly, we evaluated traditional clinical and laboratory parameters, which may only have an impact on the progression of CAD. Finally, we did not calculate the coronary calcium score and did not perform intracoronary imaging techniques, including intravascular ultrasound, to further define the extent of CAD.

Conclusions

In this study, we reveal a relationship between serum lumican levels and CAD severity. More research is warranted to determine the mechanism and prognostic values of lumican in the atherosclerosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

A. Kirankaya, S. Tugrul, S Ozcan, O Ince, E. Donmez, A. Atici, E. Hancioglu, E. Okuyan and I. Sahin designed the study. A. Kirankaya, S. Tugrul, O Ince, E. Donmez, A. Atici, E. Hancioglu, E. Okuyan and I. Sahin collected the data. A. Kirankaya, O Ince, E. Donmez, A. Atici, E. Hancioglu, E. Okuyan and I. Sahin analyzed the data. A. Kirankaya, S. Tugrul, A. Atici, E. Hancioglu, E. Okuyan and I. Sahin and wrote the manuscript. A. Kirankaya, S. Tugrul, S Ozcan, O Ince, E. Donmez, A. Atici, E. Hancioglu, E. Okuyan and I. Sahin contributed to the study design and wrote the manuscript. All authors read and approved the final manuscript.

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Informed Consent

Written consent forms were signed by all the patients who agreed to participate.

Ethics Approval

The Bağcılar Education and Research Clinic Ethics Committee approved this cross-sectional study (2020.05.1.04.036, May 5th, 2020), which was conducted in compliance with the 2013 version of the 1975 Helsinki Declaration.

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