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Lipoprotein (a) Concentration is Inversely Related with Vertebral Arterial Flow

Lipoprotein (a) Konsantrasyonu, Vertebral Arter Akımı ile Ters İlişkilidir

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ABSTRACT

Objectives: Posterior circulation ischemia syndrome is a common feature of the poor blood flow to the posterior cerebral regions which is generally caused by atherosclerotic involvement of vertebral arteries (VA). However, the risk factors for VA atherosclerosis remain largely unknown. Lipoprotein (a) (Lp(a)), a modified low-density lipoprotein, has been implicated as a risk factor for coronary and peripheral artery disease. Our aim was to investigate the possible association of Lp(a) with low vertebral artery flow, a marker representing VA atherosclerosis.

Methods: An institutional registry database was used for the present study. A complete dataset, including Doppler ultrasound imaging of the carotid and VA was available in 135 of 718 cases, and these cases were included in the analysis.

Results: 29 (21.1%) patients had Lp(a)>30 mg/dL, and total VA flow in these patients was significantly less than in patients with Lp(a)<30 mg/dL (243.0 mL/min [212.0–276.0] vs. 256.0 mL/min [230.0–307.0], p=0.03). Lp(a) had a significant correlation with VA flow (r=–0.24, p=0.004), and this association remained significant after adjustment for other lipid parameters (β=–0.244, p=0.004) and demographic variables (β=–0.225, p=0.007). Furthermore, the correlation between Lp(a) and VA flow was stronger in 11 patients with evidence of carotid atherosclerosis on DUS (r=–0.74, p<0.001).

Conclusion: Lp(a) concentration is inversely related with VA flow.

Keywords: Atherosclerosis; duplex ultrasound scanning; lipoprotein (a); vertebral artery.

ÖZET

Amaç: Posterior dolaşım iskemi sendromu, genellikle vertebral arterlerin (VA) aterosklerotik tutulumunun neden olduğu posterior serebral bölgelere zayıf kan akışının ortak bir özelliğidir. Ancak VA aterosklerozu için risk faktörleri büyük ölçüde bilinmemektedir. Modifiye edilmiş düşük yoğunluklu bir lipoprotein olan lipoprotein (a) [Lp(a)], koroner ve periferik arter hastalığı için bir risk faktörü olarak gösterildi. Bu çalışmanın amacı, VA aterosklerozunu temsil eden bir belirteç olan düşük VA akışı ile Lp(a)'nın olası ilişkisini araştırmaktır.

Yöntem: Bu çalışma için kurumsal bir kayıt veri tabanı kullanıldı. Toplam 718 olgudan 135'inde karotid ve vertebral arterlerin Doppler ultrasonografi görüntülemesini içeren eksiksiz bir veri setine ulaşıldı ve bu olgular analize dahil edildi.

Bulgular: Yirmi dokuz (%21,1) hastada Lp(a) seviyesi >30 mg/dL idi ve bu hastalarda total VA akımı, Lp(a) seviyesi <30 mg/dL olan hastalara göre anlamlı olarak düşüktü; 243,0 mL/dakikaya (212,0-276,0) karşı 256,0 mL/dakika (230,0-307,0), (p=0,03). Lp(a), VA akımı ile anlamlı (r=-0,24, p=0,004) bir korelasyona sahipti ve bu ilişki, diğer lipid parametreleri (β=-0,244, p=0,004) ve demografik değişkenler için ayarlandıktan sonra da anlamlı kalmaya devam etti (β=-0,225, p=0,007). Üstelik, Lp(a) ile VA akımı arasındaki korelasyon, DUS'ta karotid ateroskleroz kanıtı olan 11 hastada daha güçlü olarak saptandı (r=-0,74, p<0,001).

Sonuç: Lp(a) konsantrasyonu, VA akımı ile ters ilişkilidir.

Anahtar sözcükler: Ateroskleroz; dupleks ultrason; lipoprotein (a); vertebral arter.

Vertebral arteries (VA) provide circulation to the posterior cerebral regions, and atherosclerotic stenosis of the VA is the most common cause of posterior circulation ischemia syndrome (PCIS). Neither atherosclerotic involvement of the VA nor PCIS is rare, as the former has an incidence between 21% and 56% depending on the population studied, and the latter is responsible for up to a quarter of ischemic strokes.[1-5] Despite these figures, VA has not gained widespread attention (especially when compared to carotid arteries), and only a few studies have investigated risk factors for VA atherosclerosis. Albeit scarce, available evidence indicates that hyperlipidemia might not be a strong risk factor for VA atherosclerosis as it is for other arteries (i.e., coronary or lower extremity arteries), though such analyses were restricted to conventional lipid parameters.[2,6]

Lipoprotein a (Lp(a)) is a modified low-density lipoprotein (LDL) in which apolipoprotein apoB-100 is covalently linked to apolipoprotein (a).[7] Lp(a) is the lipoprotein with the highest capacity to carry oxidized lipoproteins, and it has an affinity to bind connective tissue proteins and interferes with the innate fibrinolytic pathway by competitively binding to plasminogen receptor.[8,9] Lp(a) has been found in atherosclerotic lesions, and several studies have associated high Lp(a) concentration with stroke and intracranial as well as extracranial atherosclerosis.[6,10] Whether Lp(a) has any association with VA atherosclerosis is currently not known.

Direct demonstration of atherosclerotic lesions within the VA is not usually possible with duplex ultrasound (DUS) as the proximal segments of the VA could not be visualized with this method. The real strength of DUS is its ability to measure VA flow, and a low VA flow is consistent with VA stenosis in non-visualized segments.[11,12]

In the present study, we aimed to investigate the hypothesis that Lp(a) is inversely related with VA flow in patients that underwent DUS scan for evaluation of carotid and VA.

Methods

Patient Selection

The present study was done using records from an institutional registry that tracks patients undergoing DUS for assessment of carotid and VA. The present analysis included all patients who were >18 years old and had a workup for lipid parameters at the time of DUS scan. Patients who did not have a complete workup for lipids within 24 h of DUS scan, patients with VA flow reversal and those with diagnosed non-atherosclerotic conditions that could affect VA flow in the absence of atherosclerosis (such as cervical osteophytes or dissection) were excluded. Out of 718 records that were initially screened, 581 patients were excluded (all due to incomplete workup for lipids) and the final analysis was done with 135 patients. Patients' demographic, clinical, laboratory and imaging data were extracted from the institutional electronic medical database.

The study was performed according to the principles of 1975 Declaration of Helsinki and its subsequent revisions, informed consent was obtained from all patients. The study protocol was approved by a local clinical research ethic committee (Date: September 02, 2021, Ethics Committee Decision No; 2/2021.K-62).

DUS Examination

All DUS examinations were performed by a single radiologist expert in DUS procedures. For both VAs, data on blood flows and vessel diameters were recorded. Total blood flow and VA diameter were obtained by summing left and right VA flows and diameters. Carotid artery atherosclerosis was defined as atherosclerotic plaques within at least one carotid artery. Increased intima-media thickness was not considered a marker of carotid atherosclerosis.

Laboratory Analysis

Per institutional protocol, all samples delivered to the laboratory are analyzed within 1 h of collection. A fasting state was not considered as a prerequisite for inclusion to the present analysis. Lp(a) was measured with immunoturbidimetric method using Abbott Architect i1000 autoanalyzer (Abbott Laboratories, Chicago, IL, USA). LDL-C was measured with a direct enzymatic method using the same autoanalyzer. Other biochemical analyses were done using conventional techniques.

Statistical Analysis

Continuous variables were given as mean±SD or median and interquartile range, depending on the pattern of distribution. Categorical variables were given as percentages. For several variables, including VA flow measurements, Lp(a), C-reactive protein, hemoglobin A1c% and glucose, log-transformation was done to reduce skewness. For continuous variables, patterns of distribution were determined using

Table 1. Demographic, clinical and laboratory characteristics of the study groups

Characteristic	Normal Lp(a) (n=106)	High Lp(a) (n=29)	p
Demographic characteristics			
Age (years)	45.8±12.5	45.6±12.8	0.81
Gender (%female)	32 (30.2)	5 (17.2)	0.17
Body mass index (kg/m^2)	28.8±4.1	29.2±4.4	0.70
Clinical characteristics			
Systolic blood pressure (mmHg)	120.0 (110.0–130.0)	125.0 (120.0–130.0)	0.18
Diastolic blood pressure (mmHg)	75.5 (70.0–80.0)	80.0 (78.0–80.0)	0.03
Hypertension (%)	28 (26.4)	11 (37.9)	0.23
Glucose intolerance (%)	27 (25.5)	9 (31.0)	0.55
Diabetes (%)	14 (13.2)	6 (20.7)	0.32
Smoking (%)	45 (42.5)	12 (41.4)	0.91
Regular alcohol consumption (%)	45 (19.8)	12 (17.2)	0.76
Coronary artery disease (%)	4 (3.7)	4 (13.8)	0.07
Cerebrovascular accident (%)	0 (0.0)	1 (3.5)	0.22
Antihyperlipidemic agents (%)	9 (8.4)	4 (13.9)	0.48
Laboratory characteristics			
Glucose (mg/dL)	98.0 (92.3–108.0)	96.0 (92.0–110.0)	0.87
Hemoglobin A1c (%)	5.63 (5.38–6.08)	5.68 (5.43–6.22)	0.51
Creatinine (mg/dL)	0.83±0.12	0.83±0.10	0.73
Aspartate aminotransferase (IU/L)	19.0 (16.0–24.0)	19.0 (17.0–26.0)	0.45
Alanine aminotransferase (IU/L)	21.0 (15.3–31.0)	25.0 (18.0–41.0)	0.12
C-reactive protein (mg/dL)	1.80 (1.10–2.18)	1.90 (1.78–2.10)	0.18
Hemoglobin (g/dL)	14.5±1.53	14.8±1.65	0.35
Total cholesterol (mg/dL)	212.0±60.6	229.0±43.6	0.1
LDL-cholesterol (mg/dL)	136.0±41.1	156.0±35.6	0.02
HDL-cholesterol (mg/dL)	48.0 (41.0–57.8)	46.0 (43.0–57.0)	0.69
Triglycerides (mg/dL)	130.0 (93.3–190.0)	146.0 (100.0–159.0)	0.91
Lipoprotein (a) (mg/dL)	8.25 (4.53–15.3)	59.6 (40.2–74.4)	<0.001

P values that were <0.05 were given in bold. Lp(a): Lipoprotein a; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Q-Q plots and Shapiro–Wilk test. Patients were grouped into those with a low Lp(a) (<30 mg/dL, n=106) and a high Lp(a) (≥30 mg/dL, n=29) for analyses. Either Student's t-test (with or without Welch correction) or Mann–Whitney U test was used for comparisons between groups for continuous variables, and Chi-square test or Fisher's exact test was used for categorical variables. Correlations between continuous variables were analyzed with Pearson test or with Spearman's rho as appropriate. Two linear regression models were used to analyze the relationship between Lp(a) and total VA flow. In the first model, all lipid parameters (including Lp(a)) were included to the model to determine which lipid parameters have an independent association with VA flow. Age, gender, BMI, and Lp(a) were included in the second model to assess whether the association between Lp(a) and VA was independent of demographic confounders. Finally, C-reactive protein was included in this final model to understand the relationship between inflammation, Lp(a) and VA flow. For all analyses, a $p<0.05$ was accepted as statistically significant. All analyses were done using Jamovi 1.6 (the Jamovi project (2021). Jamovi 1.6 for Microsoft Windows) and SPSS 25.0 (IBM Inc, USA).

Results

Demographic, clinical, and laboratory characteristics for patients with low and high Lp(a) were given in Table 1. There were no significant differences between groups in terms of age, gender, BMI, and clinical characteristics except for a higher diastolic blood pressure in the high Lp(a) group. Patients with a high Lp(a) had a higher LDL-cholesterol as compared to those with a low Lp(a) (p=0.02), but otherwise, other laboratory parameters were similar between the two groups.

Table 2. Duplex ultrasound findings for the study groups

Characteristic	Normal Lp(a) (n=106)	High Lp(a) (n=29)	p
Right VA diameter (mm)	36.0 (31.0–39.0)	36.0 (31.0–38.0)	0.88
Left VA diameter (mm)	38.0 (34.0–40.0)	36.0 (31.0–41.0)	0.13
Right VA flow (mL/min)	123.0 (93.3–145.0)	122.0 (98.0–136.0)	0.57
Left VA flow (mL/min)	147.0 (111.0–182.0)	129.0 (98.0–157.0)	0.03
Total VA flow (mL/min)	256.0 (230.0–307.0)	243.0 (212.0–276.0)	0.03
Right CA atherosclerosis (%)	5 (4.7)	3 (10.3)	0.37
Left CA atherosclerosis (%)	7 (6.6)	3 (10.3)	0.45
Atherosclerosis in at least one CA (%)	7 (6.6)	4 (13.8)	0.25

P values were given in bold. For left, right and total vertebral arterial flow, actual values were given but p values were calculated after log-transformation. Lp(a): Lipoprotein a; VA: Vertebral artery; CA: Carotid artery.

Patients with a high Lp(a) had a lower total VA flow as compared to those with a low Lp(a), and this difference was primarily driven by a lower flow in the left VA (Table 2 and Fig. 1). There were no differences between groups in terms of VA diameters, right VA flow, or the frequency of atherosclerotic lesions in the carotid arteries.

Correlations between Total Vertebral Artery Flow and other Parameters

Total VA flow had a significant linear correlation with age, systolic blood pressure, glucose, hemoglobin A1c%, C-reactive protein, and Lp(a) (Table 3). None of the lipid parameters except Lp(a) had a statistically significant correlation with the total VA flow.

When all lipid parameters were included in a linear regression model, only Lp(a) had a statistically significant association with the total VA flow (β=−0.244, p=0.004) (Fig. 2). In the second model in which demographic parameters were included in the model along with Lp(a), both age (β=−0.270, p=0.001) and Lp(a) (β=−0.225, p=0.007) were independent predictors of total VA flow. When C-reactive protein was included in this latter model, the association between Lp(a) and total VA flow was lost (p=0.137). In this latter model, only CRP remained as the predictor of VA flow (β=−0.523, p<0.001) (Fig. 2).

Association of Lp(a) with VA Flow in Specific Subgroups

The correlation coefficients were higher for subgroups of patients that were older, obese, smoking, diagnosed with hypertension, having abnormal fasting glucose, and those with carotid atherosclerosis (Table 3). The strengths of correlation were rather similar in males and females. The strongest association between Lp(a) and VA flow was found in 11 patients with evidence of carotid atherosclerosis on DUS (Table 4).

Discussion

The present study has analyzed the association between Lp(a) and VA flow in a random sample of individuals without symptoms of PCIS. Our findings indicate that Lp(a) is the only lipid parameter that was associated with the total VA flow, and the association between Lp(a) and VA flow is independent of demographic factors. However, this association was not independent from CRP concentration, suggesting an interaction between inflammation, Lp(a), and VA atherosclerosis.

While atherosclerosis is a disease of cholesterol accumulation, arterial vasculature in different locations tends to have a non-uniform susceptibility toward individual risk factors. Dyslipidemia is an established risk factor for coronary artery disease and ischaemic stroke, and LDL-C lowering reduces

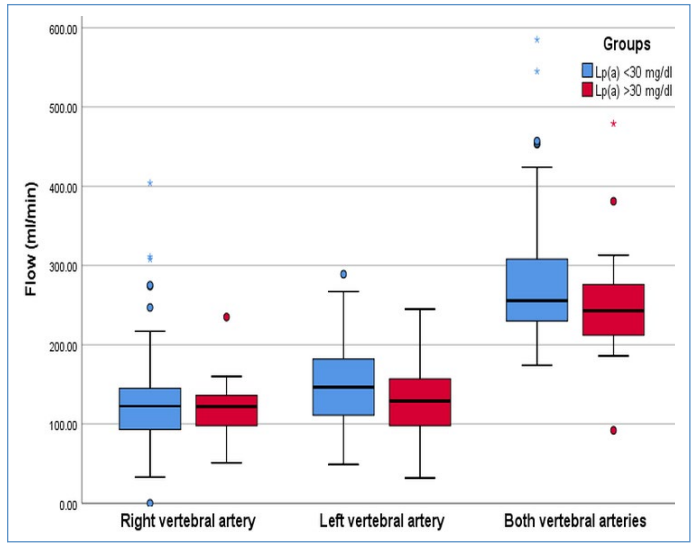

Figure 1. Box plots showing vertebral arterial flow in left, right, and both vertebral arteries in patients with normal and high blood lipoprotein (a) concentrations. Circles and asterisks' show outliers and extreme outliers, respectively.

Table 3. Correlations between total vertebral arterial flow and various demographic, clinical and laboratory parameters

Variables	Correlation coefficient	p
Age	−0.30	<0.001
Body mass index	−0.12	0.15
Systolic blood pressure	−0.18	0.04
Diastolic blood pressure	−0.13	0.13
Glucose	−0.32	<0.001
Hemoglobin A1c%	−0.48	<0.001
Total cholesterol	−0.02	0.85
LDL-cholesterol	−0.02	0.81
HDL-cholesterol	0.06	0.49
Triglycerides	−0.08	0.24
Creatinine	−0.10	0.24
C-reactive protein	−0.53	<0.001
Lipoprotein (a)	−0.24	0.004

LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

the risk for myocardial infarction, stroke, and cardiovascular mortality, albeit the reduction in stroke was somewhat smaller than the reductions in myocardial infarction or cardiovascular mortality.[13-15] The importance of dyslipidemia in the pathogenesis of vertebrobasilar atherosclerosis is uncertain and an observational study did not find dyslipidemia as a risk factor for VA calcification.[4] To note, Lp(a) was not included in the latter analysis. Lp(a) has been shown as a strong predictor of intracranial and extracranial artery stenosis in patients with a history of stroke.[6] Moreover, Lp(a) was found to be a risk factor for stroke in several studies that included patients with PCIS.[16] The present study furthers available evidence and suggests that the only lipid parameter that had an association with VA flow was Lp(a), thus supporting an association between Lp(a) and atherosclerotic VA obstruction. This association seems particularly strong in patients with evidence of carotid atherosclerosis, as well as in those with risk factors for atherosclerosis. Flow limitation is probably of atherosclerotic origin in these latter subgroups, hence explaining a stronger negative association between Lp(a) and VA flow. In younger patients without risk factors, there was either no flow limitation of flow limitation was a result of nonatherosclerotic causes, so a lack of association between Lp(a) and VA flow was not surprising.

In the present study, patients with high Lp(a) also had evidence of inflammatory activation, and the significance of the association between Lp(a) and VA flow was lost after adjusting for CRP concentration. This is not unexpected given that Lp(a) is a strong proinflammatory molecule, and some of its proatherogenic properties are thought to originate from its ability to activate inflammatory cascades. In turn, inflammation promotes Lp(a) oxidization, thus facilitating its proinflammatory and proatherogenic properties.[17] It remains unclear whether Lp(a) only acts as an intermediary or whether it accumulates within the VA, as there is insufficient evidence to suggest either, but it would be plausible to consider that both mechanisms probably contribute to the proatherogenic effects of Lp(a). Regardless of the mechanisms involved, Lp(a) lowering could be a novel strategy for the treatment of PCIS if a causal relationship could be confirmed since a novel agent that can effectively lower Lp(a) is now available.[18]

Lp(a) has been shown as a significant predictor of atherosclerosis and major atherosclerotic events, and the evidence is strongest for coronary artery disease, myocardial infarction, and stroke.[19-21] The association between Lp(a) and atherosclerosis in other arteries, such as lower extremity disease, is somewhat weaker, and not all studies were able to demonstrate such an association.[22] Similarly, while present findings indicate an association between Lp(a) and

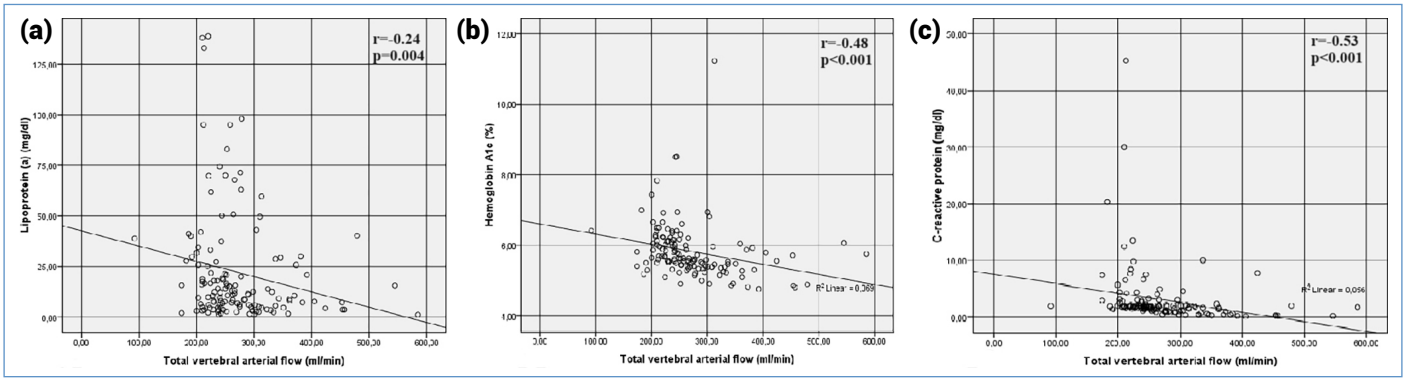

Figure 2. Scatter plots showing linear correlations between total vertebral arterial flow with lipoprotein (a) **(a)**, hemoglobin A1c% **(b)**, and C-reactive protein **(c)**. Correlation coefficients and p values shown here were obtained after log transformation.

Table 4. Correlations between lipoprotein (a) and vertebral artery flow for various demographic and clinical subgroups

Strata	Correlation coefficient	p
Age		
Age <40 years (n=49)	−0.28	0.054
Age 40-65 years (n=71)	−0.19	0.11
Age >65 years (n=15)	−0.39	0.15
Gender		
Male (n=98)	−0.24	0.02
Female (n=37)	−0.25	0.14
Body mass index		
BMI <30 kg/m^2 (n=91)	−0.17	0.11
BMI >30 kg/m2 (n=44)	−0.37	0.01
Hypertension		
Absent (n=96)	−0.20	0.047
Present (n=39)	−0.32	0.047
Smoking		
Absent (n=78)	−0.10	0.41
Present (n=78)	−0.41	0.002
Abnormal glucose metabolism		
Absent (n=79)	−0.17	0.13
Abnormal fasting glucose (n=36)	−0.36	0.03
Diabetes (n=20)	−0.05	0.82
Carotid atherosclerosis		
Absent (n=124)	−0.18	0.04
Present (n=11)	−0.74	0.008

BMI: Body mass index.

VA flow, the strength of this association was rather modest, and the relative importance of Lp(a) as a risk factor for VA atherosclerosis remains somewhat ambiguous, especially when compared to other risk factors such as inflammation or abnormal glucose metabolism. That said, VA flow is only a surrogate marker of VA atherosclerosis, and further work is needed to ascertain whether Lp(a) is associated with outcomes related to the posterior cerebral circulation.

To the best of our knowledge, the present analysis is the first one studying the association between Lp(a) and low VA flow, and these findings indicate that Lp(a) may play a role in VA atherosclerosis. However, this study had several limitations. The design of the study was cross-sectional, which does not allow the determination of any cause-effect relationship. The sample size of the study was small (135 subjects), and a large fraction (81.2%, n=583) of the initial cohort was excluded due to the unavailability of an Lp (a) concentration at baseline. Since the requisitions were done per the discretion of an attending cardiologist, such requisitions might indicate that the physician believed the subject was at a higher risk for atherosclerosis, thus creating a possible source of bias. Furthermore, the subjects were enrolled from outpatient cardiology clinics rather than from the general population, which limits the generalizability of these findings. Finally, while the patients with known skeletal deformities or exophytes were excluded from the study, those without a diagnosis could have been possibly included to the study, thus creating a possible source of bias. That said, these subjects (if there is any) should be distributed to the groups in a random fashion and, thus limiting the possible bias caused by inadvertent inclusion of such subjects. Prospective observational studies that enroll subjects from general population and include both flow measurements and anatomic data are needed to better characterize the VA stenosis risk attributable to Lp(a), as well as to understand the mechanisms leading to the reduction of VA flow in subjects with high Lp(a).

Conclusion

Vertebrobasilar atherosclerosis is a rather frequent condition, but data on the risk factors for VA atherosclerosis remains largely unknown. The present study found an association between Lp(a) and VA flow, which is a surrogate marker of VA atherosclerosis, and therefore, these findings were suggestive of a pathophysiologic role for Lp(a) for the development and progression of VA atherosclerosis. Given that Lp(a) lowering agents are now available, this could bring up Lp(a) lowering as an option for preventing or treating PCIS.

Disclosures

Ethics Committee Approval: The study was approved by İstinye University Clinical Research Ethics Committee, Date: 02.09.2021, decision number: 2/2021.K-62.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.N., T.S.G.; Design – A.N., T.S.G., A.B.; Supervision – A.B., K.I., R.Ç.G.; Materials – A.N.; Data collection &/or processing – A.N., K.I.; Analysis and/or interpretation – A.N., T.S.G., A.B.; Literature search – K.I., R.Ç.G., A.B.; Writing – A.N., T.S.G.; Critical review – K.I., R.Ç.G., A.B.

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