The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 555-561. http://doi.org/10.5551/jat.56457

Relationship Between Lipoprotein(a) and Angiographic Severity of Femoropopliteal Lesions

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Aim: High levels of lipoprotein(a) [Lp(a)] are a risk factor for peripheral artery disease (PAD). However, the relationship between Lp(a) levels and the severity of femoropopliteal lesions in patients with PAD has not been systematically studied. This study aimed to assess the impact of Lp(a) levels on angiographic severity of femoropopliteal lesions in patients with PAD.

Methods: We retrospectively analyzed a single-center database including 108 patients who underwent endovascular therapy for *de novo* femoropopliteal lesions and measured the Lp(a) levels before therapy between June 2016 and September 2019. Patients were divided into low Lp(a) [Lp(a) <30 mg/dL; 77 patients] and high Lp(a) [Lp(a) ≥ 30 mg/dL; 31 patients] groups. Trans-Atlantic Inter-Society Consensus (TASC) II classification, calcification [referring to the peripheral arterial calcium scoring system (PACSS) classification], and lesion length were compared between the groups.

Results: The prevalence of TASC II class D (13% vs 38%, $P<0.01$) and severe calcification (PACSS 4) (6% vs 23%, $P=0.02$) was significantly higher and the lesion length longer (123±88 mm vs 175±102 mm, $P<0.01$) in the high Lp(a) group than in the low Lp(a) group. In multivariate analysis, Lp(a) ≥ 30 was an independent predictor for the prevalence of TASC II class D (HR=3.67, 95% CI 1.27–10.6, $P=0.02$) and PACSS 4 (HR=4.97, 95% CI 1.27–19.4, $P=0.02$).

Conclusion: The prevalence of TASC II class D and severe calcification of femoropopliteal lesions was higher in patients with high Lp(a) than those with low Lp(a).

Key words: Lipoprotein(a), Femoropopliteal lesion, Endovascular therapy

Introduction

Lipoprotein(a) [Lp(a)] is formed by apoprotein(a), which has a similar structure to plasminogen, and apolipoprotein B of low-density lipoprotein-like particles. Lp(a) promotes arteriosclerosis and blood coagulation[1-4]. In clinical practice, several studies have reported that elevated Lp(a) levels are associated with atherosclerotic cardiovascular disease[5-6], including peripheral artery disease (PAD)[7-8]. Previous studies have revealed that high Lp(a) levels are associated with not only angiographic severity but also the prevalence of CAD[9]. In the field of PAD, another study investigated the relationship between Lp(a) and clinical severity[10]. However, the association between Lp(a) levels and angiographic severity of lesions in patients with PAD has not been systematically studied.

Aim

This study aimed to assess the impact of Lp(a) levels on angiographic severity of femoropopliteal (FP) lesions in patients with PAD.

Methods

Study Design and Participants

We conducted a retrospective analysis using a

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Received: March 13, 2020 Accepted for publication: June 29, 2020

single-center database. In total, 156 patients underwent EVT for FP lesions between June 2016 and September 2019. Patients with restenosis lesions and lack of a data for Lp(a) levels were excluded. Finally, 108 patients who underwent EVT for *de novo* femoropopliteal lesions and whose Lp(a) levels were measured before EVT were enrolled. Patients were divided into two groups: low Lp(a) [LP(a) <30 mg/dL; 77 patients] and high Lp(a) [LP(a) ≥ 30 mg/dL; 31 patients] groups. Angiographic severity of FP lesions was compared between the two groups. The study protocol conformed to the Declaration of Helsinki and was approved by our institutional ethics committee. Informed consent was directly obtained from all the patients.

Angiographic Analysis and Definition

Angiographic data were analyzed by two independent observers in a blinded fashion. Angiographic severity of FP lesions was evaluated by Trans-Atlantic Inter-Society Consensus (TASC) II classification[11], peripheral arterial calcium scoring system (PACSS) classification, and lesion length. PACSS classified the severity of vessel calcification into five grades *via* fluoroscopy and digital subtraction angiography (grade 0, no visible calcification at the target lesions; grade 1, unilateral calcification <5 cm; grade 2, unilateral calcification ≥ 5 cm; grade 3, bilateral calcification <5 cm; and grade 4, bilateral calcification ≥ 5 cm)[12]. Severe calcification was defined as PACSS 4. Hypertension was diagnosed as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or receiving antihypertensive medication. Dyslipidemia was defined as serum low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥ 150 mg/dL, or treatment with medication for dyslipidemia. Diabetes was diagnosed as HbA1c ≥ 6.5% or patients having been treated with insulin and/or an oral hypoglycemic agent. Critical limb ischemia was defined according to the TASC II guideline[9].

Intravascular Ultrasound

Intravascular ultrasound (IVUS) analysis was conducted using echoPlaque (Indec Systems, Santa Clara, CA, USA) by an independent experienced observer. The proximal and distal reference segments were selected as the site without atherosclerotic lesions on IVUS. The minimum lumen area (MLA) was selected from all image slice in IVUS results after EVT. About 71 patients in the low Lp(a) group and 28 patients in the high LP(a) group underwent IVUS. Among that, the MLA of 70 patients in the low Lp(a) group and 25 patients in the high Lp(a) group could be analyzed.

Blood Sampling

Plasma Lp(a) levels were measured *via* latex agglutination immunoassays (Special Reference Laboratories, Hachioji, Tokyo, Japan) the day before EVT.

Statistical Analysis

Data were expressed as the mean and standard deviation or median (interquartile range) for continuous variables or as percentages for dichotomous variables, unless otherwise stated. The differences in the continuous variables of the two groups were compared using the unpaired Student's *t*-test for normal distributions and signed-rank tests for non-normal distributions. In addition, categorical variables were compared using the chi-squared test. The odds ratios and 95% confidence intervals were calculated *via* logistic regression analysis. Variables with $P<0.10$ by univariate analysis were inserted into the multivariate model in order to evaluate the predictors for the prevalence of TASC II class D and severe calcification. Variables with a significant influence on the multivariate model were defined as independent risk factors of angiographic severity of FP lesions. Statistical significance was set at $P<0.05$. The JMP software (v. 13.1; SAS Institute, Cary, NC, USA) was used to conduct the analyses.

Results

Baseline Characteristics

The baseline characteristics, medications, and laboratory parameters are presented in **Table 1**. The mean age of the patients was 74±8 years, and 69% were male. The prevalence of critical limb ischemia was 31%. The median Lp(a) was 16 (7–31) mg/dL. Differences in baseline characteristics between the high Lp(a) and low Lp(a) groups were observed. The prevalence of critical limb ischemia was not different between the two groups.

Angiographic and IVUS Analysis

Angiographic analysis is presented in **Table 2 and Fig. 1**. The high Lp(a) group had more advanced TASC II classification ($P=0.01$). TASC II class D was more frequent in the high Lp(a) group than in the low Lp(a) group (38% vs 13%, $P<0.01$). PACSS classification was also more advanced in the high Lp(a) group, although the difference did not reach statistical significance. If focused on severe calcification (PACSS 4), it was significantly more frequent in the high Lp(a) group (23% vs 6%, $P=0.02$). The length of the lesion was significantly longer in the high Lp(a) group (175

Table 1. Patient baseline characteristics

	Overall (n = 108)	Lp(a) < 30 mg/dL (n = 77)	Lp(a) ≥ 30 mg/dL (n = 31)	P value
Age (yrs)	74 ± 8	72 ± 7	79 ± 8	< 0.01
Male	75 (69)	53 (69)	22 (71)	0.82
BMI	22.6 ± 3.6	23.0 ± 3.7	21.4 ± 3.0	0.04
Hypertension	93 (86)	64 (83)	29 (94)	0.15
Dyslipidemia	81 (75)	62 (81)	19 (61)	0.04
Diabetes Mellitus	58 (54)	47 (61)	11 (36)	0.02
CKD	49 (45)	34 (44)	15 (48)	0.69
Hemodialysis	25 (22)	18 (23)	7 (23)	0.92
CVD	18 (17)	10 (13)	8 (26)	0.11
CAD	50 (46)	39 (51)	11 (35)	0.15
Smoking	46 (43)	35 (45)	11 (35)	0.34
Atrial fibrillation	9 (8)	6 (8)	3 (10)	0.75
CLI	34 (31)	24 (31)	10 (32)	0.91
Medication				
Aspirin	89 (82)	64 (83)	25 (81)	0.76
Clopidogrel	76 (70)	51 (66)	25 (81)	0.14
Cilostazol	29 (27)	21 (27)	8 (26)	0.88
Statin	61 (56)	48 (62)	13 (42)	0.06
Oral hypoglycemic agent	42 (39)	35 (45)	7 (23)	0.03
Insulin	15 (14)	11 (14)	4 (13)	0.85
Laboratory data				
Hb, g/dL	12.1 ± 4.4	12.2 ± 2.2	11.7 ± 1.7	0.20
Total-cholesterol, mg/dL	171 ± 41	167 ± 45	179 ± 31	0.16
LDL-cholesterol, mg/dL	95 ± 30	91 ± 31	104 ± 25	0.04
HDL-cholesterol, mg/dL	50 ± 15	50 ± 16	49 ± 11	0.66
Triglycerides, mg/dL	113 (78–157)	115 (77–164)	108 (87–137)	0.83
HbA1c, %	6.3 (5.8–7.4)	6.5 (6–7.6)	6.0 (5.7–7.1)	0.08
Lp(a), mg/dl	16 (7–31)	11 (5–19)	43 (36–65)	< 0.01

Date given as mean ± SD, median (25th–75th) or number (percentage)
Lp(a): Lipoprotein(a), BMI: Body Mass Index, CKD: Chronic Kidney disease, CVD: Cerebrovascular Disease, CAD: Coronary Artery Disease, CLI: Critical Limb Ischemia, Hb: Hemoglobin, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

Table 2. Angiographic severity of femoropopliteal lesion

	Overall (n = 108)	Lp(a) < 30 mg/dL (n = 77)	Lp(a) ≥ 30 mg/dL (n = 31)	P value
TASC II classification				0.01
TASC II class A	32 (30)	27 (35)	5 (16)	
TASC II class B	33 (31)	26 (34)	7 (23)	
TASC II class C	21 (19)	14 (18)	7 (23)	
TASC II class D	22 (20)	10 (13)	12 (38)	
PACSS Grade				0.09
PACSS 0	23 (21)	17 (22)	6 (19)	
PACSS 1	34 (31)	26 (34)	8 (26)	
PACSS 2	9 (9)	5 (6)	4 (13)	
PACSS 3	30 (28)	24 (31)	6 (19)	
PACSS 4	12 (11)	5 (6)	7 (23)	
Severe Calcification (PACSS4)	12 (11)	5 (6)	7 (23)	0.02
Lesion length, mm	138 ± 95	123 ± 88	175 ± 102	< 0.01
CTO	40 (37)	26 (34)	14 (45)	0.20

Date given as mean ± SD or number (percentage)
Lp(a): Lipoprotein(a), TASC: Trans-Atlantic Intersociety Consensus, PACSS: Peripheral arterial calcium scoring system, CTO: Chronic Total Occlusion

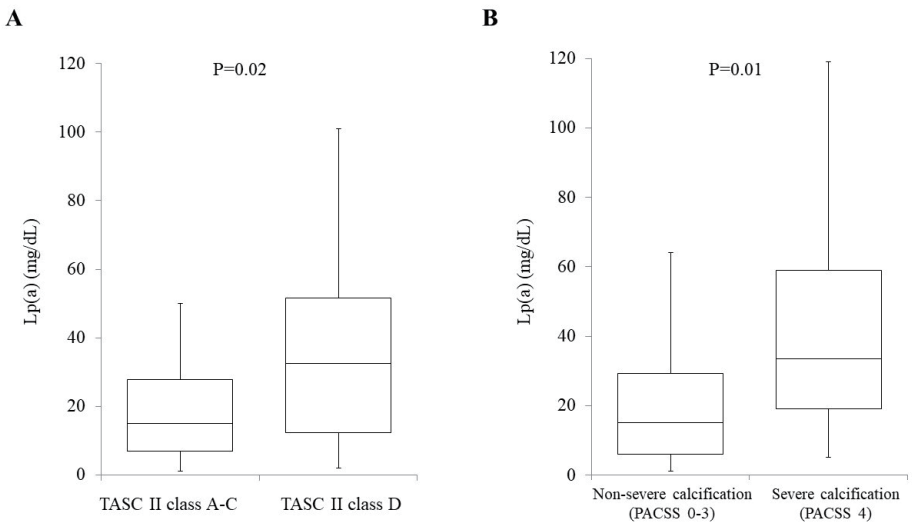

Fig. 1.

A, Comparison of Lp(a) levels in patients with Trans-Atlantic Inter-Society Consensus (TASC) II class A–C and D. B, Comparison of Lp(a) levels in patients with non-severe calcification [peripheral arterial calcium scoring system (PACSS) 0-3] and severe calcification (PACSS4).

Table 3. IVUS findins

	Lp(a) < 30 mg/dL	Lp(a) ≥ 30 mg/dL	*P* value
Proximal healthy site			
Vessel diameter, mm	7.1 ± 1.3 (*n* = 71)	7.3 ± 1.4 (*n* = 28)	0.73
Vessel area, mm^2	41.7 ± 16.1 (*n* = 71)	43.1 ± 16.8 (*n* = 28)	0.74
Lumen diameter, mm	5.6 ± 1.2 (*n* = 71)	5.7 ± 1.2 (*n* = 28)	0.61
Lumen area, mm^2	25.6 ± 11.8 (*n* = 71)	26.9 ± 12.2 (*n* = 28)	0.54
Minimum lumen area, mm^2	15.9 ± 5.8 (*n* = 70)	15.6 ± 4.8 (*n* = 25)	0.84

Date given as mean ± SD.
IVUS: intravenous ultrasound, Lp(a): Lipoprotein(a)

± 102 mm vs 123 ± 88 mm, $P < 0.01$). In addition, Lp(a) was higher in patients with TASC II class than those with TASC II classes A–C [32 (12–51) vs 15(7–27), $P = 0.02$] and in patients with severe calcification than those without [33 (19–59) vs15(6–29), $P = 0.01$]. However, the IVUS findings were not different between the two groups **(Table3)**.

Tables 4 and 5 present the univariate and multivariate analyses for the predictors of TASC II class D and PACSS 4. The multivariate analysis revealed that Lp(a) ≥ 30 was independently associated with the prevalence of TASC II class D (HR = 3.67, 95% CI 1.27–10.6, $P = 0.02$) and PACSS 4 (HR = 4.97, 95% CI 1.27–19.4, $P = 0.02$).

Discussion

We compared the severity of the FP lesions between the patients in the low Lp(a) [LP(a) < 30 mg/dL] and high Lp(a) [LP(a) ≥ 30 mg/dL] groups who underwent EVT for FP lesions. The prevalence of TASC II D lesions and severe calcification (PACSS 4) was significantly higher, and the length of the lesion was longer in the high Lp(a) than in the low Lp(a) groups. In multivariate analysis, Lp(a) ≥ 30 was independently associated with the prevalence of TASC II class D and PACSS 4.

Previous studies revealed that the Lp(a) levels were higher in patients with critical limb ischemia than those with intermittent claudication[10]. However, in FP disease, little is known about the angiographic severity of the lesions. Our study suggests that high Lp(a) levels are associated with angiographic severity, such as TASC II class D, and severe calcification of FP lesions in patients with PAD. In our study, the prevalence of critical limb ischemia was not significantly

Table 4. Univariate and multivariate analysis for predictors of TASC II class D

Predictors	Univariate model		Multivariate model	
	Odds ratio [95% CI]	*P* value	Odds ratio [95% CI]	*P* value
Age (yrs)	1.05 [0.99–1.11]	0.09	1.02 [0.96–1.09]	0.50
Male	2.29 [0.71–7.39]	0.17		
BMI	0.91 [0.80–1.05]	0.21		
Hypertension	1.03 [0.26–4.01]	0.97		
Dyslipidemia	0.65 [0.23–1.81]	0.41		
Diabetes Mellitus	1.04 [0.40–2.67]	0.93		
CKD	0.62 [0.24–1.65]	0.34		
Hemodialysis	0.51 [0.11–2.45]	0.40		
CVD	1.65 [0.52–5.26]	0.40		
CAD	0.60 [0.23–1.58]	0.29		
Smoking	1.84 [0.71–4.71]	0.20		
Atrial fibrillation	1.35 [0.33–5.48]	0.67		
CLI	1.11 [0.38–3.25]	0.84		
Hb	0.98 [0.79–1.23]	0.88		
Total-cholesterol	0.99 [0.98–1.01]	0.44		
LDL-cholesterol	0.99 [0.98–1.01]	0.85		
HDL-cholesterol	0.97 [0.94–1.01]	0.25		
Triglycerides	0.99 [0.99–1.01]	0.35		
HbA1c	1.31 [0.95–1.83]	0.11		
LP(a) ≥ 30 mg/dL	4.23 [1.59–11.3]	<0.01	3.67 [1.27–10.6]	0.02

TASC: Trans-Atlantic Intersociety Consensus, Lp(a): Lipoprotein(a), BMI: Body Mass Index, CKD: Chronic Kidney disease, CVD: Cerebrovascular Disease, CAD: Coronary Artery Disease, CLI: Critical Limb Ischemia, Hb: Hemoglobin, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

Table 5. Univariate and multivariate analysis for predictors of heavy calcification (PACSS 4)

Predictors	Univariate model		Multivariate model	
	Odds ratio [95% CI]	*P* value	Odds ratio [95% CI]	*P* value
Age (yrs)	1.05 [0.98–1.13]	0.18		
Male	0.87 [0.24–3.10]	0.82		
BMI	1.02 [0.87–1.02]	0.77		
Hypertension	0.78 [0.15–3.98]	0.77		
Dyslipidemia	1.00 [0.25–4.00]	0.99		
Diabetes Mellitus	0.85 [0.25–2.81]	0.79		
CKD	7.31 [1.52–6.16]	0.01	4.29 [0.75–24.6]	0.10
Hemodialysis	1.79 [0.49–6.52]	0.38		
CVD	1.00 [0.20–5.00]	0.98		
CAD	0.81 [0.24–2.73]	0.73		
Smoking	0.96 [0.28–3.24]	0.95		
Atrial fibrillation	1.72 [0.33–8.99]	0.52		
CLI	1.10 [0.30–3.94]	0.88		
Hb	0.63 [0.44–0.90]	<0.01	0.69 [0.45–1.09]	0.11
Total-cholesterol	0.99 [0.98–1.01]	0.27		
LDL-cholesterol	0.99 [0.97–1.01]	0.33		
HDL-cholesterol	1.00 [0.96–1.04]	0.92		
Triglycerides	0.98 [0.96–1.00]	0.06		
HbA1c	0.98 [0.62–1.54]	0.93		
LP(a) ≥ 30	4.20 [1.21–14.5]	0.02	4.97 [1.27–19.4]	0.02

TASC: Trans-Atlantic Intersociety Consensus, Lp(a): Lipoprotein(a), BMI: Body Mass Index, CKD: Chronic Kidney disease, CVD: Cerebrovascular Disease, CAD: Coronary Artery Disease, CLI: Critical Limb Ischemia, Hb: Hemoglobin, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein

different between the high Lp(a) and low Lp(a) groups. One possible reason for the difference in the results of our study and those of previous ones is that our study included only patients who underwent EVT for FP lesions. Future research is needed to study the relationship between Lp(a) and the severity of PAD.

TASC II class D in FP lesions was associated with the loss of primary patency following EVT[13-14]. Iida O *et al.* reported that the primary patency after FP stenting was 80% versus 69% at 1 year and 62% versus 48% at 3 years in their TASC II A–C group versus their TASC II D group[14]. Severe calcification in FP lesions was also associated with restenosis and major adverse limb events following EVT[15-17]. Especially, a recent study has demonstrated that PACSS grade 4 was significantly associated with major adverse limb events and mortality[16]. Additionally, the length of FP lesion is a risk factor of restenosis after stenting[18-19]. Soga *et al.* reported that primary patency of FP lesions treated with bare nitinol stents decreased linearly with longer lesion length[19]. Angiographic severity of FP lesions, such as TASC II class D, PACSS 4, and long lesion, was associated with clinical outcomes following EVT. Our study revealed that the prevalence of TASC II class D, severely calcified femoropopliteal lesion, and long diseased lesion was higher in patients with high Lp(a) than those with low Lp(a). Thus, high Lp(a) levels might be a risk factor of adverse events in patients with FP disease. Actually, a previous study revealed the relationship between Lp(a) levels and clinical outcomes in patients with symptomatic PAD. Patients with PAD who had Lp(a) levels >30 mg/dL were at a higher risk for myocardial infarction, ischemic stroke, or limb amputation than those with normal levels[20].

Clinical studies reported that statin therapy has no effect on the lowering of Lp(a) levels[21]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduced Lp(a) levels by approximately 20%[22, 23]. A sub-study of ODYSSEY trial demonstrated that lowering of Lp(a) by PCSK9 inhibitors is an independent contributor to the reduction of major adverse cardiovascular events (MACE) after acute coronary syndrome. Moreover, a sub-study of FOURIER trial reported that the PCSK9 inhibitors significantly reduced the risk for MACE and major adverse limb events in patients with PAD[24]. Thus, strengthening of lipid-lowering therapy, such as PCSK9 inhibitors, is needed in patients with PAD, especially those with high Lp(a) level.

This study has several limitations. First, the study was a single-center retrospective investigation and included only Japanese patients. Second, the angiographic assessment for TASC II classification and PACSS grade was not verified by a core laboratory review. Third, the number of PAD patients in this study was small. Fourth, the cut-off levels of Lp(a) in patients with PAD were determined to be 30 mg/dL. While previous studies reported that Lp(a) levels >30 mg/dL were a risk factor for adverse events in patients with symptomatic artery disease[20] and myocardial infarction in the general population[25], the European Society of Cardiology and European Atherosclerosis Society guideline state that the risk of cardiovascular disease is regarded as significant when Lp(a) is above 50 mg/dL[26]. Thus, the optimum cut-off levels of Lp(a) in patients with PAD are unclear. Finally, it is certain that basic experiments using endothelial cell are needed to demonstrate the direct relationship between serum protein and clinical phenomenon. We would like to treat this task as the subject of our future study, since the current study is a clinical research.

Conclusion

The prevalence of TASC II class D, severely calcified femoropopliteal lesion, and long diseased lesion was higher in patients with high Lp(a) than those with low Lp(a). High Lp(a) level might be associated with angiographic severity of femoropopliteal lesions in patients with PAD.

Conflict of Interest

None declared.

Acknowledgements

The authors would like to thank the medical staff who offered continuing support.

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