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Lupus Anticoagulant and Anticardiolipin Antibody IgG are Associated with Increased Atherosclerosis at the Suprainguinal Elastic and Infrainguinal Muscular Arteries in the Abdomen and Lower Extremities

Jong Kwon Park^{1*}  and Jisook Yi²

Abstract

Purpose: Whether antiphospholipid antibodies (aPLs) cause atherosclerosis in certain arteries with specific compositions and locations remains unknown. We investigated the relationship between aPLs and their association with locations of atherosclerosis in the arteries of the abdomen and lower extremities.

Methods: Of 2273 patients, 697 who underwent computed tomography angiography of the abdomen and lower extremities and aPL evaluation were included. Atherosclerosis distribution score (ADS) was employed to quantify atherosclerosis severity. Multiple linear regression analysis was performed using the ADS of the suprainguinal elastic and infrainguinal muscular arteries as dependent variables and all aPLs, conventional risk factors of atherosclerosis, and coagulation-related factors as independent variables.

Results: In the suprainguinal elastic and infrainguinal muscular arteries, common risk factors for higher ADS were age, smoking, hypertension, higher glycated hemoglobin, male sex, decreased protein S, and increased homocysteine. Lupus anticoagulant (LA) and increased triglyceride level in the suprainguinal elastic arteries and anticardiolipin antibody (aCL) immunoglobulin (Ig)G, longer alcohol consumption duration, and increased fibrinogen level in the infrainguinal muscular arteries were also risk factors for higher ADS.

Conclusion: LA and aCL IgG were associated with atherosclerosis in the suprainguinal elastic and infrainguinal muscular arteries, respectively. aPLs could predict the location of atherosclerosis.

Keywords: Lupus anticoagulant, Anticardiolipin IgG antibody, Suprainguinal elastic arteries, Infrainguinal muscular arteries, Atherosclerosis

1 Introduction

Antiphospholipid antibodies (aPLs), which are substances that cause antiphospholipid syndrome (APS), have been reported to be closely related to the development of atherosclerosis [1, 2]. However, it remains unknown whether each aPL causes atherosclerosis in certain arteries with specific compositions and locations. In this study, we investigated the association between aPLs

*Correspondence: jparkvk@gmail.com

¹ Department of Surgery, Haeundae Paik Hospital, College of Medicine, Inje University, 875, Haeundae-ro, Haeundae-gu, Busan 48108, Republic of Korea
Full list of author information is available at the end of the article



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and specific locations of atherosclerosis in the arteries of the abdomen and lower extremities.

To avoid confounding factors for aPLs, a multivariate study, including all aPLs, conventional atherosclerosis risk factors, and coagulation-related factors, was performed. Additionally, to directly evaluate atherosclerosis severity, images of whole arteries, except for the splanchnic arteries, taken by computed tomography (CT) angiography of the abdomen and lower extremities were analyzed. The arteries of the abdomen and lower extremities were divided into the suprainguinal elastic and infrainguinal muscular arteries according to their compositions and locations [3]. The atherosclerosis distribution score (ADS) was defined as an objective numerical value to quantify atherosclerosis severity and to study the relationship between the location of atherosclerosis and aPLs.

2 Materials and Methods

2.1 Participants

From March 2010 to February 2021, 2273 patients were treated at the Division of Vascular Surgery in our hospital. For the 2273 patients, we retrospectively analyzed the imaging study, blood tests, and medical history taking.

2.2 Clinical and Hematologic Factors

The imaging study consisted of CT angiography of the abdomen and lower extremities or ultrasonography (US) of the lower extremity veins. This study was performed using the results of the first blood test at the Division of Vascular Surgery in our hospital, and the blood tests consisted of conventional atherosclerosis risk factors, coagulation-related factors, and aPLs. The conventional atherosclerosis risk factors were age, body mass index [BMI; body weight (kg)/height² (m²)], smoking.pack.year (cigarette packs smoked per day × years as a smoker), hypertension, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and homocysteine.

Coagulation-related factors were protein C/S, antithrombin III, fibrinogen, and factor VIII. The aPLs included lupus anticoagulant (LA), anticardiolipin antibody (aCL) immunoglobulin (Ig)G/IgM, and anti-β₂glycoprotein (GP)1 IgG/IgM. The laboratory criteria for determining positive aPLs were as follows [1, 4–6]: (1) LA present in plasma was detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies); (2) the aCL IgG/IgM isotype was present in serum or plasma with medium or high titer [>40 IgG phospholipid units (GPL) or IgM phospholipid units (MPL); or $>$ the 99th-percentile level],

quantified by a standardized enzyme-linked immunosorbent assay (ELISA); and (3) the anti-β₂GP1 IgG/IgM isotype was present in serum or plasma with a titer $>$ the 99th-percentile level, quantified by a standardized ELISA according to recommended procedures. Hypertension was defined as being on antihypertensive medication or having a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg. Medical history taking was performed for the days of alcohol consumption and pregnancy-related morbidities. Days of alcohol consumption were calculated using the following equation: average number of days of alcohol consumption per month \times 12 months \times number of years of alcohol consumption. In women, pregnancy-related morbidity for premature fetal death at or beyond the 10th week, premature birth of neonates before the 34th week, and unexplained consecutive spontaneous abortions before the 10th week of gestation were investigated for obstetric APS diagnosis [1]. As previously reported, indications for aPL testing could be classified as justified, potentially justified, and not adequately justified [7]. However, there is no current consensus on the indication for aPL testing. In this study, the aPL test was performed for patients with coagulation abnormalities, vascular thrombosis, symptoms and signs of autoimmune diseases, pregnancy-related morbidity, and those who chose to be tested.

2.3 Elastic and Muscular Arteries of the Abdomen and Lower Extremities

Elastic arteries are located near the heart and composed of more elastic tissue in the tunica media than muscular arteries, while muscular arteries are located peripherally and made up of more smooth muscle cells in the tunica media than the elastic arteries [3]. We classified the abdominal and lower extremity arteries, excluding the splanchnic arteries, into the suprainguinal elastic and infrainguinal muscular arteries bordered by the inguinal ligament.

2.4 Inclusion Criteria and Characteristics of Participants

Individuals who underwent both CT angiography of the abdomen and lower extremities and aPL testing were included in the study. Those without any of these measurements were excluded. Of the 2273 patients, 697 (303 men, 394 women) were enrolled in this study. Of these 697 participants, 617 (262 men, 355 women) also underwent US of the lower extremity veins to diagnose venous thrombus or reflux, 82 had arterial diseases requiring surgical treatment or endovascular intervention, 204 had venous diseases, and 411 had vascular diseases that did not require surgery or endovascular intervention. Of the 82 patients with arterial diseases, 13 underwent open vascular surgery, 64 underwent endovascular intervention,

and 5 underwent hybrid surgery consisting of open surgery and endovascular intervention. Of the 204 patients with venous diseases, 196 underwent varicose vein surgery, 6 underwent excision for venous malformation, and 2 underwent sclerotherapy. Of the 411 participants with vascular diseases that did not require surgery or endovascular intervention, 362 had atherosclerotic arterial diseases and were treated pharmacologically, 37 had thrombotic diseases and received anticoagulation therapy, and 12 were only followed up.

2.5 Blood Tests

Blood tests were carried out as previously described [8]. Blood sampling was performed in the morning after overnight fasting. All measurements were performed according to the manufacturer's instructions. Serum levels of total, HDL and LDL cholesterol, and homocysteine were measured using enzyme kits (Cholesterol Gen.2, HDL-Cholesterol Gen.4, LDL-Cholesterol Gen.3, and Homocysteine Enzymatic Assay, respectively; Roche Diagnostics, Mannheim, Germany). Measurements of protein C, protein S, antithrombin III, factor VIII, and fibrinogen levels were performed using an analyzer (CA-7000; Sysmex, Kobe, Japan). All reagents were purchased from Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany). LA was measured using LA 1 screening reagent/LA 2 confirmation reagent (Dade Behring Inc. Newark, NJ, USA). Levels of aCL IgG/IgM were measured using ELISA with the autoimmune aCL IgG/IgM test kits (Bio-Rad Laboratories, Hercules, CA, USA). Serum concentrations of anti- β_2 GP1 IgG/IgM were evaluated using Triturus (Grifols, Barcelona, Spain) with the REAADS anti- β_2 GP1 IgG/IgM test kits (Corgenix Inc., Denver, CO, USA).

2.6 Imaging Studies

2.6.1 CT Angiography and ADS

All examinations were performed at a single center with two multidetector row CT systems on the axial plane covering from the diaphragm to the foot in the supine position using a 128-slice system (Definition AS+, Siemens Healthineers, Forchheim, Germany) and a 64-slice system (Discovery CT 750 HD, GE Healthcare, Waukesha, WI, USA). From the popliteal area to the foot, a delayed image was acquired 10 s after post-contrast imaging to minimize the possibility of delayed enhancement of the peripheral arteries due to the variability of the hemodynamic status of each participant. Axial images were automatically reconstructed with a 5-mm thickness and no gaps. On CT angiography, all the 23 target arteries were scored as 0 (absence of atherosclerosis) or 1 (presence of atherosclerosis). The sum of the scores is the ADS of a particular participant, which ranged from 0 to 7 in the

suprainguinal elastic arteries, 0 to 16 in the infrainguinal muscular arteries, and 0 to 23 in the total arteries of the abdomen and lower extremities. A higher ADS indicated higher atherosclerosis severity (Fig. 1; Table 1).

2.6.2 US Acquisition

Two US scanners were used (IU22, Philips, Bothell, WA, USA; LOGIQ E9, GE Healthcare, Wauwatosa, WI, USA) with linear transducers (L9-3 MHz linear array and L9-5 MHz linear array, respectively). During the examination, two image sets (without compression and with compression of the vessels) were acquired at the same level to evaluate the presence or absence of venous thrombosis (Fig. 2).

2.7 Image Analysis

Both CT angiography and US data were retrospectively reviewed by a radiologist who was blinded to the clinical data. For controversial cases of lower-leg CT angiography, both the radiologist and vascular surgeon reached a consensus. The presence of any degree of calcified, mixed, and non-calcified plaques (soft plaque) in the arteries was reported as atherosclerosis [9]. Anatomic variations of below-knee arteries, including hypoplasia or aplasia, were not assigned as atherosclerosis [10]. Both pre- and post-contrast source images were compared, and reconstructed images were assessed to evaluate the presence or absence of atherosclerotic plaque. Arterial thrombosis was also diagnosed in 23 arterial segments. Venous thrombosis was evaluated for the inferior vena cava, right and left common iliac, external iliac, internal iliac, common femoral, femoral, deep femoral, popliteal, posterior tibial, peroneal, and anterior tibial veins, intramuscular vein of the calf, and great and small saphenous veins. Arterial or venous thrombosis was defined as follows: (1) low-attenuated complete or partial filling defect of the vessel lumen in at least two consecutive images with or without distension of the vessel; (2) centered or eccentric round filling defects (on axial images) and the "railway track" sign on sagittal images with or without collateral flows; and (3) intramural thrombosis of aneurysm [11, 12]. For US, venous thrombosis was evaluated in the deep and superficial venous systems of the bilateral lower extremities from the inguinal to the ankle levels. Venous thrombosis was defined as either a complete or partial intra-luminal filling defect, lack of vessel compression, and complete or partial absence of the Doppler signal regardless of the chronicity of the lesion [13].

2.8 Statistical Analysis

Because not all the continuous variables in this study showed normal distribution by the Shapiro–Wilk test, non-parametric tests were used in comparative studies.

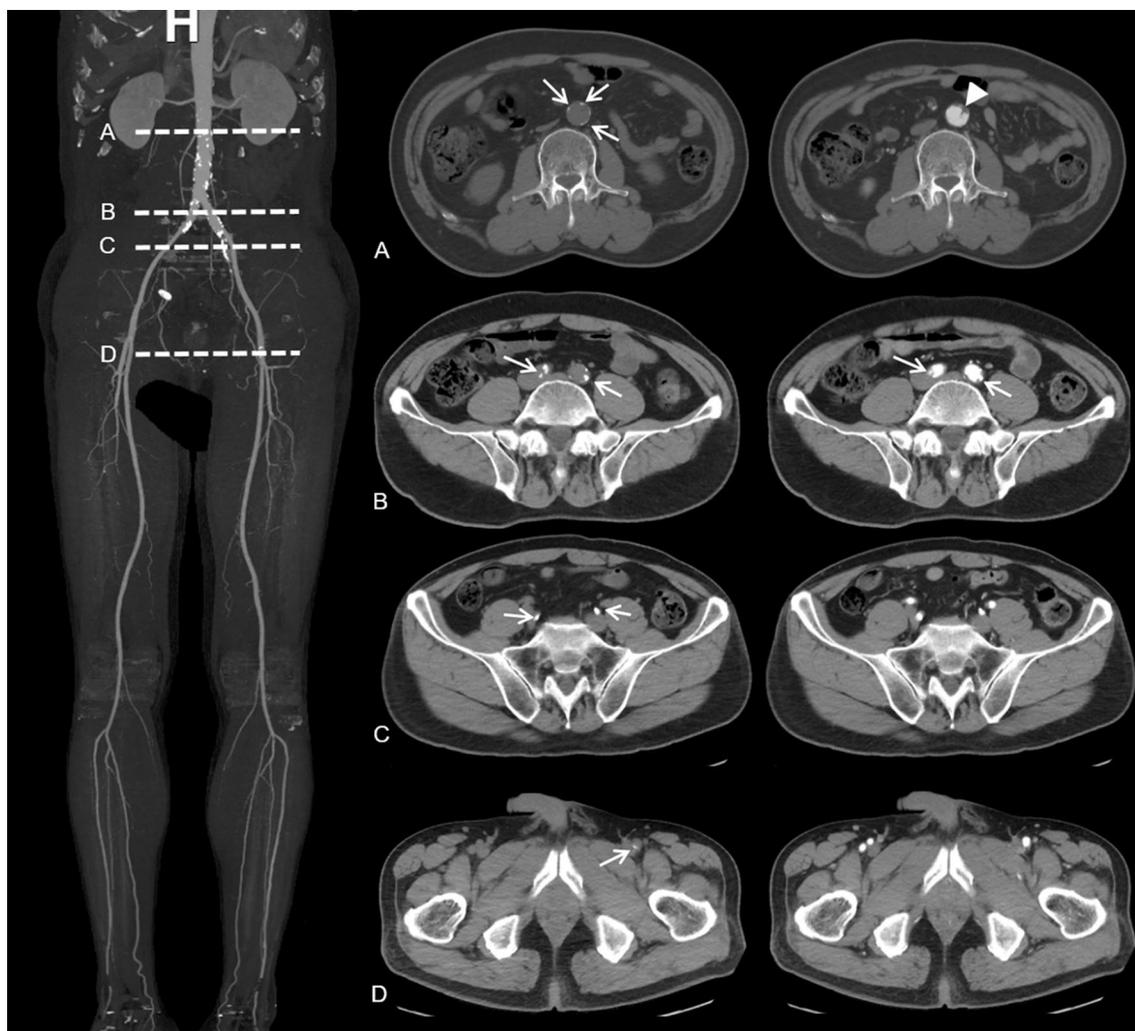


Fig. 1 CT angiography for lower extremity atherosclerosis and thrombosis. A 62-year-old man with aPLs showed an ADS of 6 points in the total arteries of the abdomen and lower extremities. **A** Calcified atherosclerotic plaques were observed in the infrarenal abdominal aorta (arrows, point = 1) on the pre-contrast CT image. A partial thrombus was observed in the infrarenal abdominal aorta on the post-contrast CT image (arrowhead). **B, C** Mixed atherosclerotic plaques were observed in the bilateral common iliac arteries (arrows in **B**, point = 2) and bilateral internal iliac arteries (arrows in **C**, point = 2). **D** A calcified atherosclerotic plaque was observed in the left proximal femoral artery (arrow, point = 1). Abbreviations: ADS atherosclerosis distribution score, aPLs antiphospholipid antibodies, CT computed tomography

The numbers of the atherosclerotic arteries between the suprainguinal elastic and infrainguinal muscular arteries were compared using the Mann–Whitney *U* test. Nominal variables could be used in a multiple linear regression analysis by converting them into dummy variables [14]. Therefore, sex (man = 0, woman = 1), hypertension (normal = 0, hypertension = 1), and five aPLs (negative = 0, positive = 1) were converted into dummy variables using the statistical program of this study. The ADS of the APS and non-APS participants was compared using the Mann–Whitney *U* test. A

comparison of the ADS among the participants with different numbers of positive aPLs was performed by the Kruskal–Wallis test. Finally, a multiple linear regression analysis was performed, with the ADS of the suprainguinal elastic and infrainguinal muscular arteries as dependent variables and all continuous and nominal dummy variables as independent variables. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using PASW Statistics 18 release 18.0.0 (WinWrap Basic, Polar Engineering and Consulting, Nikiski, AK, USA).

Table 1 The 23 arterial segments, ADS, and comparison of the number of atherosclerotic arteries

23 Arteries	Laterality	ADS absence/presence of atherosclerosis	Number of atherosclerotic arteries out of 697 participants	Mean \pm SD	<i>p</i> *
<i>Suprainguinal elastic arteries</i>					
Abdominal aorta		0/1	499	335.57 \pm 152.81	0.001
Common iliac artery	Right	0/1	444		
	Left	0/1	411		
External iliac artery	Right	0/1	119		
	Left	0/1	122		
Internal iliac artery	Right	0/1	379		
	Left	0/1	375		
Sum		0/7			
<i>Infrainguinal muscular arteries</i>					
Common femoral artery	Right	0/1	216	109.44 \pm 50.93	
	Left	0/1	229		
Femoral artery	Right	0/1	144		
	Left	0/1	137		
Deep femoral artery	Right	0/1	67		
	Left	0/1	68		
Popliteal artery	Right	0/1	120		
	Left	0/1	119		
Anterior tibial artery	Right	0/1	98		
	Left	0/1	92		
Tibio-peroneal trunk	Right	0/1	85		
	Left	0/1	80		
Peroneal artery	Right	0/1	66		
	Left	0/1	57		
Posterior tibial artery	Right	0/1	87		
	Left	0/1	86		
Sum		0/16			
Total		0/23			

ADS atherosclerosis distribution score (atherosclerosis: absence = 0, presence = 1), mean mean of the number of atherosclerotic arteries, SD standard deviation

**p*, Mann–Whitney *U* test

3 Results

3.1 Frequency of Atherosclerosis in the Suprainguinal and Infrainguinal Arteries

The most frequent location of atherosclerosis was the abdominal aorta (499/697, 71.6%), followed by the right common iliac (444/697, 63.7%) and left common iliac (411/697, 59%) arteries. The number of atherosclerotic arteries in the suprainguinal elastic arteries was significantly higher than that in the infrainguinal muscular arteries ($p = 0.001$, Table 1).

3.2 Vascular Thrombosis

A total of 252 vascular thrombotic lesions, consisting of 188 arterial (188/252, 74.6%) and 64 venous (64/252, 25.4%) thrombotic lesions, were observed in 136 patients (136/697, 19.5%). In the arteries, thrombotic lesions were most frequently observed in the aorta (69/188, 36.7%), followed by the left common

iliac (23/188, 12.2%), left femoral (20/188, 10.6%), left external iliac (17/188, 9%), right femoral (14/188, 7.4%), right common iliac (14/188, 7.4%), right external iliac (6/188, 3.2%), right internal iliac (6/188, 3.2%), left popliteal (6/188, 3.2%), left internal iliac (4/188, 2.1%), right popliteal (4/188, 2.1%), right common femoral (2/188, 1%), left common femoral (2/188, 1%) arteries, and the right tibioperoneal trunk (1/188, 0.5%). In the veins, thrombotic lesions were most frequently observed in the right popliteal vein (11/64, 17.2%), followed by the left femoral (10/64, 15.6%), right femoral (7/64, 10.9%), left popliteal (7/64, 10.9%), left common femoral (4/64, 6.3%), right external iliac (3/64, 4.7%), left external iliac (3/64, 4.7%), left soleus (3/64, 4.7%), right peroneal (3/64, 4.7%), left peroneal (3/64, 4.7%), left posterior tibial (3/64, 4.7%), right common iliac (2/64, 3.1%), right common femoral (2/64, 3.1%), right internal iliac (1/64, 1.6%), and left great saphenous vein (1/64, 1.6%).

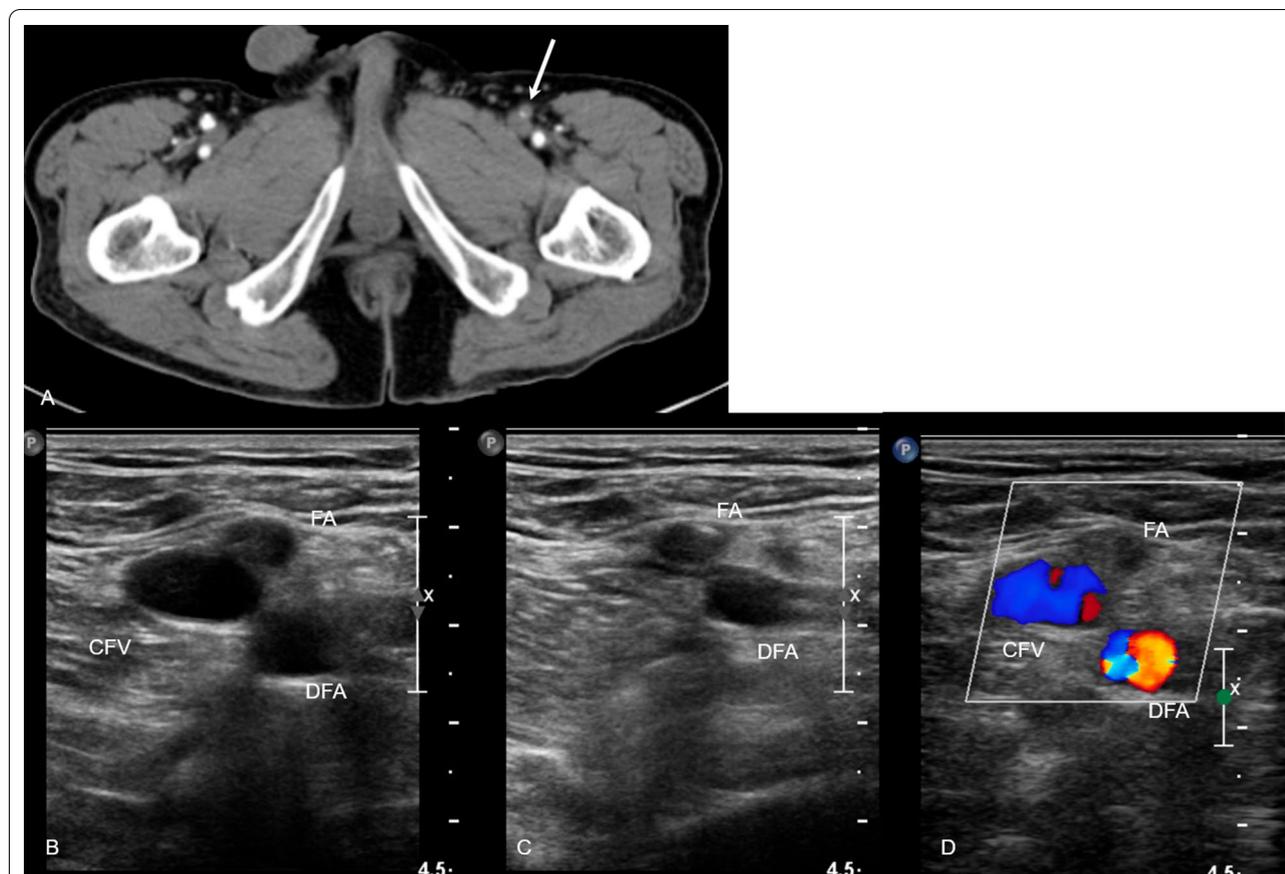


Fig. 2 CT angiography and US findings of arterial thrombosis in a 65-year-old man with aPLs. **A** A near-complete intra-luminal filling defect was observed in the left proximal FA on CT angiography. On US, **B** an echogenic filling defect was observed in the left proximal FA on gray-scale image without compression and **C** with compression by probe. **D** No color signal was observed in the left proximal FA on color Doppler image. Abbreviations: aPLs antiphospholipid antibodies, CFV common femoral vein, CT computed tomography, DFA deep femoral artery, FA femoral artery, US ultrasonography

3.3 Pregnancy-Related Morbidity

Of the 697 participants, 142 (142/697, 20.4%) showed positive aPLs in the initial tests. Of these 142 participants, 79 (40 men and 39 women) underwent the required diagnostic studies for APS, including reexaminations of aPLs at least 12 weeks apart, radiologic studies, and clinical history taking [1]. Of the 39 women, 20 showed pregnancy-related morbidity. Specifically, one woman experienced unexplained fetal death after the 10th week of gestation twice. Six women experienced premature births of morphologically normal neonates before the 34th week of gestation. Thirteen women experienced three or more unexplained consecutive spontaneous abortions before the 10th week of gestation. However, none of the 20 women showed repeated positivity for aPLs, tested at least 12 weeks apart. Thus, there was no female patient with obstetric APS.

3.4 Comparison of ADS Between APS and Non-APS Participants

Of the 79 participants (40 men, 39 women) who fulfilled the required diagnostic tests for APS, 13 patients (16.5%, 13/79) were diagnosed with APS. All of them were men. APS patients had significantly higher ADS than the non-APS participants in both the suprainguinal elastic and infrainguinal muscular arteries ($p=0.012$ and 0.005 , respectively; Table 2).

3.5 Comparison of ADS Among the Participants with Different Numbers of Positive aPLs

Of the five aPLs, the maximal number of positivity was three. ADS showed a tendency to increase as the number of positive aPLs increased in the suprainguinal elastic and infrainguinal muscular arteries. However, there was no significant difference in ADS among the participants

Table 2 Comparison of the ADS between 13 APS patients and 66 non-APS participants

Arteries	APS (number)	Mean \pm SD of ADS	<i>p</i> *
Suprainguinal elastic arteries	Presence (13)	5.31 \pm 1.93	0.012
	Absence (66)	3.58 \pm 2.47	
Infrainguinal muscular arteries	Presence (13)	6.23 \pm 4.85	0.005
	Absence (66)	3.27 \pm 4.92	

ADS atherosclerosis distribution score, APS antiphospholipid syndrome, SD standard deviation

**p*, Mann–Whitney *U* test

with 0, 1, 2, and 3 positive aPLs in the suprainguinal elastic and infrainguinal muscular arteries ($p=0.193$ and 0.211 , respectively; Table 3).

3.6 Risk Factors for Higher ADS in the Suprainguinal Elastic and Infrainguinal Muscular Arteries

Tables 4 and 5 show the continuous and nominal variables used as independent variables in the multiple linear regression analysis. In the suprainguinal elastic and infrainguinal muscular arteries of the abdomen and lower extremities, the common significant risk factors for higher ADS were increased age, higher tobacco consumption, hypertension, higher HbA1c level, male sex, decreased protein S level, and increased level of homocysteine. Meanwhile, LA and increased level of triglycerides in the suprainguinal elastic arteries and aCL IgG, longer duration of alcohol consumption, and increased fibrinogen level in the infrainguinal muscle arteries were other significant risk factors for higher ADS (Table 6).

4 Discussion

In this study, the number of atherosclerotic arteries of the suprainguinal elastic arteries was significantly higher than that of the infrainguinal muscular arteries. This finding is consistent with the finding in our recent study,

Table 4 List of continuous variables, including conventional risk factors of atherosclerosis and coagulation-related factors

Variables	Number of participants	Mean \pm SD
Age (years)	697	65.25 \pm 12.61
BMI	697	24.95 \pm 3.90
Smoking.pack.year	697	14.85 \pm 26.08
Days of alcohol consumption	697	3013.94 \pm 5222.92
HbA1c (%)	694	5.91 \pm 1.02
Total cholesterol (mg/dL)	697	183.51 \pm 40.74
HDL cholesterol (mg/dL)	696	49.47 \pm 14.00
LDL cholesterol (mg/dL)	696	107.25 \pm 33.23
Triglyceride (mg/dL)	696	151.71 \pm 108.50
Homocysteine (μ mol/L)	695	10.32 \pm 5.61
Protein C (%)	690	104.82 \pm 25.10
Protein S (%)	689	80.55 \pm 21.93
Antithrombin III (%)	691	95.15 \pm 15.01
Fibrinogen (mg/dL)	688	288.69 \pm 90.76
Factor VIII (%)	691	121.26 \pm 27.82

BMI body mass index body (weight [kg]/height² [m²]); days of alcohol consumption, average number of days of alcohol consumption per 1 month \times 12 months \times number of years of alcohol consumption, HbA1c glycated hemoglobin, HDL high-density lipoprotein, LDL low-density lipoprotein, smoking.pack.year cigarette packs smoked per day \times years as a smoker; SD standard deviation

in which atherosclerosis occurred more frequently in the elastic arteries of the abdomen than in the muscular arteries of the lower extremities [8].

In this study, 19.5% (136/697) of the participants had vascular thrombotic lesions. While the precise mechanism of thrombosis by aPLs remains unknown, the complex of plasma protein β_2 GP1 and platelet factor 4 reportedly could activate platelets in the presence of anti- β_2 GP1 antibodies, leading to thrombosis [15]. A previous study reported that a higher number of aPLs was associated with a higher risk of developing atherosclerosis [16]. In this study, 13 APS patients had a significantly higher

Table 3 Comparison of the ADS among the participants with different numbers of positive aPLs

Arteries	Number of positive aPLs	Number of participants	Mean \pm SD of ADS	<i>p</i> *
Suprainguinal elastic arteries	0	555	3.31 \pm 2.37	0.193
	1	100	3.47 \pm 2.52	
	2	39	3.79 \pm 2.22	
	3	3	5.67 \pm 1.16	
Infrainguinal muscular arteries	0	555	2.40 \pm 4.12	0.211
	1	100	3.00 \pm 4.70	
	2	39	2.62 \pm 3.92	
	3	3	6.33 \pm 6.03	

ADS atherosclerosis distribution score, aPLs antiphospholipid antibodies, SD standard deviation

**p*, Kruskal–Wallis test

Table 5 List of nominal variables, including conventional risk factors of atherosclerosis and aPLs

Variables	Category (dummy variable number)	Number of participants (%)
Sex	Men (0)	303 (43.5)
	Women (1)	394 (56.5)
Hypertension	No (0)	400 (57.4)
	Yes (1)	297 (42.6)
LA	Negative (0)	678 (97.3)
	Positive (1)	19 (2.7)
aCL IgG	Negative (0)	664 (95.3)
	Positive (1)	33 (4.7)
aCL IgM	Negative (0)	628 (90.1)
	Positive (1)	69 (9.9)
Anti- β_2 GP1 IgG	Negative (0)	693 (99.4)
	Positive (1)	4 (0.6)
Anti- β_2 GP1 IgM	Negative (0)	635 (91.1)
	Positive (1)	62 (8.9)

aCL, anticardiolipin antibody; anti- β_2 GP1, anti- β_2 glycoprotein 1; aPLs, antiphospholipid antibodies; IG, immunoglobulin; LA, lupus anticoagulant

ADS than the remaining 66 non-APS participants. However, there were no significant differences in the ADS among the participants with 0, 1, 2, or 3 aPLs. From these results, we hypothesized that specific aPLs might be involved in the pathogenesis of atherosclerosis.

In our multivariate analysis, LA of the suprainguinal elastic arteries and aCL IgG of the infrainguinal muscular arteries were significant risk factors for higher ADS, along with the conventional risk factors of atherosclerosis, alcohol consumption, and hypercoagulable state. Aging, smoking, hypertension, high HbA1c level, increased homocysteine and triglyceride levels, hypercoagulable state, and male sex are well-known conventional risk factors of atherosclerosis [17, 18]. In this study, the decreased protein S and increased fibrinogen levels might act as significant risk factors for higher ADS in the hypercoagulable state.

Although the relationship between alcohol consumption and atherosclerosis has not been well established, moderate alcohol consumption reduced the severity of atherosclerosis and the risk of heart failure [19, 20]. However, our findings showed that prolonged alcohol consumption increased the risk of atherosclerosis in the infrainguinal muscular arteries. Thus, we speculated that long-term continuous, but not moderate, alcohol consumption might enhance the development of atherosclerosis in the infrainguinal muscular arteries.

Regarding the relationship between aPLs and atherosclerosis, the currently proposed mechanism is that the plasma protein β_2 GP1 binds to oxidized low-density lipoprotein (oxLDL) to form oxLDL/ β_2 GP1 complexes, which enhance the development of atherosclerosis by promoting monocyte and T cell activation and accelerating their influx into macrophages via anti- β_2 GP1-mediated phagocytosis [21–25]. In this study, aCL IgG was a significant risk factor for higher ADS in the infrainguinal muscular arteries. The mechanism by which aCL IgG induces atherosclerosis is not well understood. In one report, 46% of systemic lupus erythematosus patients had increased concentrations of aCL IgG, and there was a cross reaction between aCL IgG and oxLDL [26]. This finding suggested that aCL IgG might participate in the development of atherosclerosis. Contrary to its name, LA causes vascular thrombosis [27–29]. In this study, LA was a significant risk factor for higher ADS in the suprainguinal elastic arteries. A meta-analysis of 21 studies comprising 6,057 aPL-positive patients revealed that all aPLs were related to peripheral arterial disease, and LA was related to critical limb ischemia and failed revascularization [30]. In this study, we found that LA and aCL IgG were likely to induce atherosclerosis in the suprainguinal elastic and infrainguinal muscular arteries, respectively, suggesting that aPL could be used as a tool to predict the location of atherosclerosis.

While aPLs have been linked to the pathogenesis of atherosclerosis, the precise underlying mechanism of this association is not completely understood. Furthermore, whether each aPL causes atherosclerosis in a specific area of the arteries remains unknown. Thus, we believe that our study may be novel because it revealed a relationship between certain aPLs and the specific locations of atherosclerosis.

This study had some limitations. This clinical study was retrospective by nature and a single center study. However, our study was conducted with participants over a period of 11 years under the same diagnostic principles. Therefore, we believe that our data were homogeneous and reliable.

5 Conclusion

The severity of atherosclerosis in APS patients was significantly higher than that in non-APS individuals. In addition to the conventional risk factors for atherosclerosis, hypercoagulable state, and prolonged consumption of alcohol, LA of the suprainguinal elastic arteries and aCL IgG of the infrainguinal muscular arteries were significant risk factors for atherosclerosis. These findings suggest that aPLs could be utilized to predict the location of atherosclerosis.

Table 6 Risk factors for higher ADS identified in a multiple linear regression analysis

Model	Unstandardized coefficients	Standardized coefficients	<i>p</i> *	95.0% Confidence interval for B	
	<i>B</i>	Beta		Lower bound	Upper bound
<i>Suprainguinal elastic arteries</i>					
Constant	−5.205		<0.001	−6.208	−4.202
Age	0.105	0.553	<0.001	0.095	0.115
Smoking	0.015	0.167	<0.001	0.010	0.021
Hypertension	0.718	0.149	<0.001	0.470	0.967
HbA1c	0.275	0.119	<0.001	0.162	0.389
Sex	−0.472	−0.098	0.001	−0.759	−0.184
Protein S	−0.009	−0.081	0.001	−0.014	−0.003
Homocysteine	0.031	0.074	0.005	0.009	0.053
LA	0.975	0.067	0.005	0.294	1.657
Triglyceride	0.001	0.055	0.028	0.000	0.002
<i>Infrainguinal muscular arteries</i>					
Constant	−9.273		<0.001	−11.460	−7.087
Age	0.078	0.231	<0.001	0.056	0.100
Smoking	0.024	0.146	<0.001	0.011	0.036
HbA1c	0.849	0.206	<0.001	0.599	1.099
Hypertension	1.153	0.134	<0.001	0.613	1.692
Days of alcohol consumption	0.000	0.136	<0.001	0.000	0.000
Fibrinogen	0.005	0.116	<0.001	0.003	0.008
Homocysteine	0.070	0.093	0.004	0.022	0.117
Protein S	−0.017	−0.090	0.003	−0.029	−0.006
aCL IgG	1.449	0.072	0.014	0.295	2.603
Sex	−0.800	−0.094	0.017	−1.456	−0.144

The ADSs of the suprainguinal elastic and infrainguinal muscular arteries were the dependent variables. The independent variables were all the continuous and nominal variables (dummy variables)

aCL anticardiolipin antibody, ADS atherosclerosis distribution score, HbA1c glycated hemoglobin, Ig immunoglobulin, LA lupus anticoagulant

**p*, multiple linear regression analysis

Abbreviations

aCL: Anticardiolipin antibody; ADS: Atherosclerosis distribution score; aPLs: Antiphospholipid antibodies; CT: Computed tomography; ELISA: Enzyme-linked immunosorbent assay; GP: Glycoprotein; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; Ig: Immunoglobulin; LA: Lupus anticoagulant; LDL: Low-density lipoprotein; oxLDL: Oxidized low-density lipoprotein; US: Ultrasonography.

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Authors' contribution

J.Y. is co-first author with J.P. J.P.: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, guarantor of integrity of the entire study. J.Y.: conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, guarantor of integrity of the entire study. Both authors read and approved the final manuscript.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval and Consent to Participate

This study was conducted according to the Declaration of Helsinki, and the study protocol was reviewed and approved by Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital, Busan, Republic of Korea, approval number HPIRB 2021–12-017. The need for consent was waived by the IRB because of the minimal risk to participants.

Consent for Publication

Not applicable.

Author details

¹Department of Surgery, Haeundae Paik Hospital, College of Medicine, Inje University, 875, Haeundae-ro, Haeundae-gu, Busan 48108, Republic of Korea.

²Department of Radiology, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, Republic of Korea.

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