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Coronary calcification is associated with elevated serum lipoprotein (a) levels in asymptomatic men over the age of 45 years

A cross-sectional study of the Korean national health checkup data

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Abstract

Lipoprotein a (Lp (a)) and coronary artery calcification (CAC) are markers of coronary artery and cardiovascular diseases. However, the association between Lp (a) and CAC in asymptomatic individuals remains unclear. In this study, we aimed to determine the influence of Lp (a) on CAC in asymptomatic individuals.

We included 2019 asymptomatic Korean adults who underwent testing for a coronary artery calcium score (CACS) and Lp (a) at the Gangnam Severance Hospital Health Checkup Center in Korea from January 2017 to August 2019. Participants were divided into 2 groups: CACS = 0 and CACS > 0. Factors affecting the CACS were analyzed by sex. Because age is a major risk factor for atherosclerosis, ≥45 years in men and ≥55 years in women, we further divided participants into 4 subgroups (≥45 and <45 in men, ≥55 and <55 in women). Factors affecting the CACS in the 4 groups were analyzed.

There was a positive correlation between the CACS and traditional cardiovascular risk factors. Lp (a) positively correlated with the CACS in men ($P < .01$) and remained significant after multivariable logistic regression ($P < .01$). The same result was observed in men aged ≥45 years ($P < .01$).

Lp (a) is an independently associated factor of CAC and a marker of coronary atherosclerosis in asymptomatic men aged ≥45 years. In asymptomatic men aged ≥45 years, Lp (a) should be measured, and intensive Lp (a)-lowering treatment should be considered.

Abbreviations: apo(a) = apolipoprotein (a), apoB-100 = apolipoprotein B-100, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CAC = coronary artery calcification, CACS = coronary artery calcium score, CAD = coronary artery disease, CHD = coronary heart disease, CRP = C-reactive protein, CT = computed tomography, CVD = cardiovascular disease, EBCT = electron-beam computed tomography, HDL-cholesterol = high-density lipoprotein cholesterol, LDL-cholesterol = low-density lipoprotein cholesterol, Lp (a) = lipoprotein (a), MDCT = multi-detector computed tomography.

Keywords: atherosclerosis, cardiovascular risk factor, coronary artery calcium score, lipoprotein (a), multi-detector computed tomography

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This study was approved by the Institutional Review Board, Yonsei University Gangnam Severance Hospital (approval no. 3-2020-0017) and performed in accordance with the declaration of Helsinki. The participants provided informed consent for participation in the study.

The authors have no conflicts of interest to disclose.

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

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1. Introduction

Cardiovascular disease (CVD) is the leading global cause of death and is expected to account for >23.6 million deaths by 2030. In addition, CVD and coronary heart disease (CHD) caused by atherosclerosis were the leading causes of death in the United States in 2015.[1] Although the development of new technologies for the diagnosis and treatment of CVD and CHD has considerably improved the clinical outcomes of patients, the incidence of fatal cardiovascular events such as myocardial infarction has still not decreased. Many studies have reported that eliminating the risk factors associated with the occurrence of CVD reduces the incidence of cardiovascular events caused by atherosclerosis.[2] Approximately 50% of coronary deaths occur in previously asymptomatic patients. For these reasons, it is essential to identify the risk factors for CHD and CVD early and to further assess the relationship between these risk factors with the aim of reducing the incidence of fatal cardiovascular events. Age, sex, smoking history, body mass index (BMI), hypertension, diabetes mellitus, total cholesterol, low-density lipoprotein cholesterol (LDL-cholesterol), and high-density lipoprotein cholesterol (HDL-cholesterol) are conventional risk factors; however, triglycerides, homocysteine, lipoprotein (a) (Lp (a)), fibrinogen, and indices of inflammatory responses, such as C-reactive protein (CRP), are also risk factors for CHD that may provide additional information in the diagnosis of CVD.

Lp (a) is a lipoprotein that was discovered by Berg et al in 1963.[3] It consists of a lipid core composed of cholesteryl ester and triglycerides, where apolipoprotein B-100 (apoB-100) is bound to apolipoprotein (a) (apo(a)) with a characteristic disulfide bond.[4] The apo(a) in Lp (a) is structurally similar to plasminogen and is known to interfere with plasminogen's antithrombotic functions by competitively inhibiting the binding of plasminogen to fibrin.[5] Lp (a) is composed of a moiety that is essentially indistinguishable from LDL in both lipid composition and the presence of apoB-100.[4] These characteristics suggest that Lp (a) is involved in the process of atherosclerosis and thrombogenesis. Many studies have reported the association between Lp (a) and CHD[6–9]; therefore, Lp (a) has been recognized as a cardiovascular risk factor by the European Society of Cardiology and the European Atherosclerosis Society guidelines.[10] However, unlike LDL-cholesterol, Lp (a) is still not a primary target for therapeutic intervention.

With the development of computed tomography (CT) technology, multi-detector CT (MDCT) was introduced in the late 1990s. As a result of this technological advancement, cardiac CT has become the main test for non-invasive assessment of coronary atherosclerosis. It can provide comprehensive information about the site of stenosis, the presence of non-stenotic coronary artery stiffness, atherosclerotic plaque characteristics, and coronary artery stenosis severity. The assessment of coronary artery stenosis using cardiac CT has very high sensitivity and specificity – with a 95% to 99% negative predictive value – when compared to invasive coronary angiography.[11] Because of the high accuracy and non-invasive nature of this test, MDCT is included as part of the health screening program in major Korean hospitals.[12] Several studies have reported that the coronary artery calcium score (CACS) measured using electron-beam computed tomography (EBCT) is a specific marker of CHD and directly related to the atherosclerotic plaque burden.[13] In addition, the CACS has also shown to be valuable risk predictors of cardiovascular events in patients with a high cardiovascular risk.[14] Nevertheless, studies that investigated the relationship between Lp (a) as a cardiovascular risk factor and the CACS as a specific marker of CHD have reported contradictory results.[15,16]

If Lp (a) can predict coronary artery calcification (CAC) in asymptomatic adults, a simple blood test can be used to evaluate the CAC without a CT scan. In addition, intensive Lp (a)-lowering therapy could prevent cardiovascular events in people with a high Lp (a). For these reasons, we aimed to determine the association between Lp (a) and the CACS in asymptomatic adults using the large volume of data from the health screening program in Korea.

2. Methods

2.1. Study design and patient selection

Among 2858 patients with no cardiac symptoms who had undergone a routine health examination at the Gangnam Severance Hospital Health Checkup Center in Korea from January 2017 to August 2019, a total of 2019 patients who had both the CACS and serum Lp (a) measurements were selected for this study. The participants were divided into those with CACS = 0 and CACS > 0. First, factors affecting the CACS by sex were analyzed. Because the risk of developing coronary artery disease (CAD) increases with age, ≥45 years in men and ≥55 years in women,[17] we divided the participants into 4 subgroups (≥45 and <45 in men, ≥55 and <55 in women). Second, the factors affecting the CACS in the 4 subgroups were analyzed.

2.2. Definition of variables

The following variables were investigated in all participants: Hypertension was defined as antihypertensive drug use or having a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg. Diabetes mellitus was defined as the use of hypoglycemic agents or insulin, a fasting plasma glucose level of ≥126 mg/dL, glycosylated hemoglobin (HbA1c) level of ≥6.5%, or known but untreated hyperglycemia. Hypercholesterolemia was defined as a total cholesterol level of >200 mg/dL or cases where the patient was treated with lipid-lowering drugs. Smoking was defined as cases in which the subject was either currently smoking or had a history of smoking in the past. Each participant's height and weight were measured, and BMI was calculated as weight/height^2 (kg/m^2).

2.3. Measurement of Lp (a)

After blood collection, plasma samples were immediately sent to our laboratory and analyzed.

Lp (a) measurement was performed according to the latex agglutination method with an anti-human Lp (a) monoclonal antibody using a commercial kit [Lp (a) Daiichi Pure Chemicals Co., Ltd] with an auto-analyzer (Hitachi 7600-110) that is not affected by the different apo(a) isoforms.

2.4. Coronary artery calcium scanning

CT scans were performed with a 64-MDCT scanner (Revolution CT; GE Healthcare, Milwaukee, WI). All patients with an initial heart rate ≥60 beats/min were given an oral beta-blocker (metoprolol, 40 mg) to achieve a target heart rate of 50 to 60 beats/min. Sublingual nitroglycerin was administered immedi-

ately before scanning was performed. A body weight-adjusted volume (0.6–0.7 mL/kg) of iodine contrast agent (iopamidol 370 mg iodine per milliliter, Iopamiro; Bracco, Milan, Italy) was administered into the antecubital vein in 10 seconds followed by 25 mL of saline solution injected at 5.0 mL/second. The CT-reconstructed imaging data were transferred to a GE Centricity system (GE Healthcare Bio-Sciences Corp., Piscataway, NJ) for postprocessing and subsequent image analysis. The coronary arteries were assessed with a rapid acquisition (100 millisecond) of 30 to 40 contiguous slices (each 3 mm in thickness) during end-diastole using an ECG-triggering method in a single 30 to 35 seconds breath-hold. A radiologist read each scan independently at a centralized reading center. The quantitative CACS was calculated according to the method described by Agatston et al.[18] CACS > 0 was defined as having a detectable CAC.

2.5. Statistical analysis

Statistical analyses were performed using the Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC). Continuous data were presented as mean ± standard deviation, and categorical data were presented as percentages or the absolute number. In cases of continuous variables, an independent *t* test was used for comparison; for categorical variables, a chi-square test (Fisher's exact test) was used. We used logistic regression in the univariable and multivariable models to determine the 95% confidence intervals (CI) and odds ratios (OR) for the presence of CAC and Lp (a) that adjusted for CAD risk factors including hypertension, diabetes mellitus, smoking, BMI, and LDL-cholesterol. The Turkey–Kramer post hoc test after Kruskal–Wallis test was used to analyze the difference in the CACS according to serum Lp (a) level. We also used the Wilcoxon rank-sum test to analyze the effects of menopause on Lp (a) and CACS. A *P* value of <.05 was considered statistically significant.

3. Results

A total of 2019 asymptomatic Korean adults who underwent health checkups were enrolled in this study, including 1518 males (75.2%). Differences in baseline characteristics between the 2 groups divided by sex are shown in Table 1. In males, the group with CACS > 0 (n = 763) showed statistically significant differences ($P < .05$) in Lp (a), age, smoking, hypertension, diabetes mellitus, hypercholesterolemia, total cholesterol, LDL-cholesterol, and waist circumference when compared to the CACS = 0 group (n = 755). Notably, Lp (a) levels were significantly higher in the CACS > 0 group (16.63 ± 20.44 vs 13.82 ± 16.06, $P = .003$).

In females (CACS > 0, n = 125; CACS = 0, n = 376), the 2 groups also showed statistically significant differences in age, hypertension, diabetes mellitus, triglycerides, HDL-cholesterol, BMI, waist circumference, and menopause ($P < .05$). However, there was no significant difference in the Lp (a) level between the CACS > 0 and CACS = 0 groups (18.97 ± 21.92 vs 16.53 ± 17.43, $P = .26$).

Subsequently, we carried out a univariable logistic regression for the 2 groups (Table 2) and multivariable logistic regression after adjusting for Lp (a), smoking, hypertension, diabetes mellitus, LDL-cholesterol, and BMI (Table 3). We found that Lp (a) was significantly associated with the presence of CAC in males (95% CI OR 1.004–1.016, $P = .001$). However, in females, Lp (a) did not show a significant correlation with the CACS (95% CI OR 0.996–1.018, $P = .23$).

We divided our study cohort into 4 subgroups (≥45 or <45 years in men, and ≥55 or <55 years in women) (Table 4).

Table 1

Baseline characteristics of the groups divided by sex.

	Men (n = 1518)			Women (n = 501)		
Variables	**CACS > 0 (n = 763)**	**CACS = 0 (n = 755)**	***P***	**CACS > 0 (n = 125)**	**CACS = 0 (n = 376)**	***P***
Lp (a) (mg/dL)	16.63 ± 20.44	13.82 ± 16.06	.003	18.97 ± 21.92	16.53 ± 17.43	.26
Age (yr)	59.06 ± 8.66	51.56 ± 9.92	<.001	63.39 ± 8.05	54.20 ± 9.33	<.001
Smoking status			.04			.60
Non-smoker, n (%)	202 (26.47)	235 (31.13)		110 (88.00)	324 (86.17)	
Smoker, n (%)	561 (73.53)	520 (68.87)		15 (12.00)	52 (13.83)	
HTN			<.001			<.001
No, n (%)	387 (50.72)	552 (73.11)		52 (41.60)	294 (78.19)	
Yes, n (%)	376 (49.28)	203 (26.89)		73 (58.40)	82 (21.81)	
DM			<.001			<.001
No, n (%)	574 (75.23)	681 (90.20)		95 (76.00)	352 (93.62)	
Yes, n (%)	189 (24.77)	74 (9.80)		30 (24.00)	24 (6.38)	
Hypercholesterolemia			<.001			.07
No, n (%)	200 (26.21)	261 (34.57)		22 (17.60)	96 (25.53)	
Yes, n (%)	563 (73.79)	494 (65.43)		103 (82.40)	280 (74.47)	
BMI (kg/m^2)	26.12 ± 3.39	25.95 ± 3.51	.32	25.44 ± 3.63	24.07 ± 4.04	<.001
Waist circumference (cm)	91.52 ± 8.86	90.47 ± 9.35	.03	83.79 ± 8.89	78.93 ± 9.96	<.001
Total cholesterol (mg/dL)	197.55 ± 46.59	206.13 ± 38.44	<.001	215.97 ± 48.36	215.45 ± 41.24	.91
Triglycerides (mg/dL)	160.30 ± 107.47	152.34 ± 89.27	.12	136.12 ± 64.46	111.13 ± 59.19	<.001
HDL-cholesterol (mg/dL)	50.87 ± 10.87	51.88 ± 11.12	.08	56.94 ± 12.41	61.38 ± 13.73	.001
LDL-cholesterol (mg/dL)	127.48 ± 37.63	134.67 ± 31.77	<.001	140.06 ± 41.03	135.81 ± 33.41	.30
Menopause						<.001
No, n (%)				25 (20.00)	180 (47.87)	
Yes, n (%)				100 (80.00)	196 (52.13)	

Continuous data are shown as mean ± 1SD. Dichotomous data are shown as n (%). BMI = body mass index, CACS = coronary artery calcium score, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), SD = standard deviation.

Table 2

Predictors of coronary artery calcium score by univariable logistic regression in the 2 groups.

	Men (n = 1518)		Women (n = 501)	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Lp (a)	1.008 (1.003–1.014)	.003	1.007 (0.996–1.017)	.21
Age	1.091 (1.078–1.105)	<.001	1.133 (1.100–1.168)	<.001
Smoking	1.255 (1.004–1.568)	.04	0.850 (0.460–1.570)	.60
HTN	2.642 (2.132–3.274)	<.001	5.033 (3.268–7.751)	<.001
DM	3.030 (2.266–4.053)	<.001	4.632 (2.586–8.294)	<.001
Hypercholesterolemia	1.487 (1.193–1.854)	<.001	1.605 (0.958–2.686)	.07
BMI	1.015 (0.986–1.045)	.32	1.087 (1.034–1.143)	.001
Waist circumference	1.013 (1.001–1.024)	.03	1.050 (1.029–1.072)	<.001
Total cholesterol	0.995 (0.993–0.998)	<.001	1.000 (0.996–1.005)	.91
Triglycerides	1.001 (1.000–1.002)	.12	1.006 (1.003–1.009)	<.001
HDL-cholesterol	0.992 (0.983–1.001)	.08	0.974 (0.958–0.990)	.002
LDL-cholesterol	0.994 (0.991–0.997)	<.001	1.003 (0.998–1.009)	.25
Menopause			0.980 (0.938–1.025)	.38

BMI = body mass index, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), OR = odds ratio.

In males aged ≥45 (n = 1313), the group with CACS > 0 showed a significantly higher Lp (a) level than the group with CACS = 0 (16.74 ± 20.53 vs 13.97 ± 16.10, $P = .006$). In contrast, a significant difference in Lp (a) levels between the 2 groups was not found in males aged <45 years (n = 205), or either subgroups of females (<55 years (n = 192) and ≥55 years (n = 309)) (14.03 ± 18.15 vs 13.31 ± 15.97, $P = .82$, 16.48 ± 22.59 vs 14.68 ± 16.55, $P = .70$, 19.31 ± 21.91 vs 18.16 ± 18.06, $P = .64$, respectively).

Subsequently, a univariable logistic regression (Table 5) and multivariable logistic regression (Table 6) after adjusting for Lp (a), smoking, hypertension, diabetes mellitus, LDL-cholesterol, and BMI were carried out on the 4 subgroups. In males aged ≥45 years, Lp (a) was significantly associated with the presence of CAC in both univariable and multivariable regression analyses (95% CI OR 1.002–1.014, $P = .008$, 95% CI OR 1.003–1.016, $P = .003$, respectively).

In contrast, Lp (a) did not show a significant correlation with the CACS in univariable and multivariable regression analyses in males aged <45 years (95% CI OR 0.980–1.026, $P = .82$, 95% CI OR 0.973–1.023, $P = .85$, respectively), females aged <55 years (95% CI OR 0.978–1.034, $P = .70$, 95% CI OR 0.988–1.052, $P = .23$, respectively), and females aged ≥55 years (95% CI OR 0.991–1.015, $P = .62$, 95% CI OR 0.992–1.017, $P = .53$, respectively).

In the analysis of the difference in the CACS according to serum Lp (a) level (Fig. 1), the CACS was significantly higher in the Lp (a) >50 mg/dL group than in the 15 to 30 mg/dL group ($P < .05$).

We also analyzed the effects of menopause, one of the risk factors for atherosclerosis, on Lp (a) and CACS (Fig. 2). We found that the CACS and Lp (a) significantly differed among the menopause groups (Yes or No) ($P < .05$).

4. Discussion

In the present study, we found that Lp (a) significantly correlated with CAC in asymptomatic adult males, particularly in those aged ≥45 years, independent of traditional cardiovascular risk factors, including hypertension, diabetes mellitus, smoking, LDL-cholesterol, and BMI. These data imply that Lp (a) could potentially play an important role as an independent risk factor for CHD in asymptomatic adult males aged ≥45 years. A previous study of 861 asymptomatic relatives of patients with premature atherosclerotic cardiovascular disease (ASCVD) reported a clear relation between Lp (a) elevation and atherosclerotic burden assessed by CACS.[19] Another study involving a similar cohort to our study's population found that Lp (a) level was positively associated with a CACS > 0 in the highest quartile of Lp (a), suggesting a possible correlation between Lp (a) level and CACS.[20] Our results are consistent with these findings. However, we showed that Lp (a) is independently associated with CAC in men, especially those ≥45 years, who are a population at major risk of atherosclerosis.

In several studies, the CACS measured by MDCT predicted future cardiovascular events in multiple populations. Furthermore, the CACS was able to detect coronary atherosclerosis and improve the risk stratification of individuals beyond traditional

Table 3

Predictors of coronary artery calcium score by multivariable logistic regression in the 2 groups.

	Men (n = 1518)		Women (n = 501)	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Lp (a)	1.010 (1.004–1.016)	.001	1.007 (0.996–1.018)	.23
Smoking	1.181 (0.934–1.494)	.16	1.032 (0.531–2.005)	.93
HTN	2.334 (1.858–2.932)	<.001	4.374 (2.774–6.897)	<.001
DM	2.588 (1.910–3.506)	<.001	3.536 (1.869–6.688)	<.001
BMI	0.995 (0.964–1.027)	.76	1.048 (0.990–1.109)	.11
LDL-cholesterol	0.998 (0.995–1.001)	.28	1.006 (0.999–1.012)	.08

BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), OR = odds ratio.

Table 4

Baseline characteristics of 4 subgroups divided by sex and age.

	Men (n = 1518)						Women (n = 501)					
	Age < 45 (n = 205)			Age ≥ 45 (n = 1313)			Age < 55 (n = 192)			Age ≥ 55 (n = 309)		
Variables	CACS > 0 (n = 31)	CACS = 0 (n = 174)	P	CACS > 0 (n = 732)	CACS = 0 (n = 581)	P	CACS > 0 (n = 15)	CACS = 0 (n = 177)	P	CACS > 0 (n = 110)	CACS = 0 (n = 199)	P
Lp (a) (mg/dL)	14.03 ± 18.15	13.31 ± 15.97	.82	16.74 ± 20.53	13.97 ± 16.10	.006	16.48 ± 22.59	14.68 ± 16.55	.70	19.31 ± 21.91	18.16 ± 18.06	.64
Smoking status			.75			.25			.53			.07
Non-smoker, n (%)	11 (35.48)	67 (38.51)		191 (26.09)	168 (28.92)		13 (86.67)	137 (77.40)		97 (88.18)	187 (93.97)	
Smoker, n (%)	20 (64.52)	107 (61.49)		541 (73.91)	413 (71.08)		2 (13.33)	40 (22.60)		13 (11.82)	12 (6.03)	
HTN			.03			<.001			<.001			<.001
No, n (%)	20 (64.52)	143 (82.18)		367 (50.14)	409 (70.40)		7 (46.67)	154 (87.01)		45 (40.91)	140 (70.35)	
Yes, n (%)	11 (35.48)	31 (17.82)		365 (49.86)	172 (29.60)		8 (53.33)	23 (12.99)		65 (59.09)	59 (29.65)	
DM			.07			<.001			.03			<.001
No, n (%)	27 (87.10)	167 (95.98)		547 (74.73)	514 (88.47)		12 (80.00)	171 (96.61)		83 (75.45)	181 (90.95)	
Yes, n (%)	4 (12.90)	7 (4.02)		185 (25.27)	67 (11.53)		3 (20.00)	6 (3.39)		27 (24.55)	18 (9.05)	
Hypercholesterolemia			.01			.01			.51			.87
No, n (%)	5 (16.13)	69 (39.66)		195 (26.64)	192 (33.05)		4 (26.67)	62 (35.03)		18 (16.36)	34 (17.09)	
Yes, n (%)	26 (83.87)	105 (60.34)		537 (73.36)	389 (66.95)		11 (73.33)	115 (64.97)		92 (83.64)	165 (82.91)	
BMI (kg/m^2)	28.34 ± 7.33	26.82 ± 4.09	.27	26.03 ± 3.09	25.68 ± 3.27	.05	26.06 ± 2.91	23.53 ± 4.39	.03	25.36 ± 3.72	24.56 ± 3.64	.07
Waist circumference (cm)	93.90 ± 14.99	91.39 ± 10.96	.38	91.42 ± 8.51	90.20 ± 8.80	.01	83.90 ± 7.82	76.55 ± 9.84	.005	83.77 ± 9.06	81.04 ± 9.60	.02
Total cholesterol (mg/dL)	218.94 ± 42.10	213.37 ± 42.66	.50	196.65 ± 46.58	203.96 ± 36.84	.002	220.60 ± 40.27	213.98 ± 42.11	.56	215.34 ± 49.48	216.75 ± 40.52	.80
Triglycerides (mg/dL)	213.36 ± 146.50	148.45 ± 87.28	.02	158.05 ± 105.05	153.50 ± 89.90	.40	148.87 ± 72.47	106.38 ± 51.29	.04	134.38 ± 63.46	115.35 ± 65.26	.01
HDL-cholesterol (mg/dL)	48.39 ± 10.27	51.86 ± 11.38	.11	50.98 ± 10.89	51.89 ± 11.05	.14	53.60 ± 13.31	61.36 ± 13.70	.04	57.39 ± 12.27	61.40 ± 13.78	.01
LDL-cholesterol (mg/dL)	146.68 ± 35.52	141.05 ± 35.85	.42	126.66 ± 37.53	132.76 ± 30.21	.001	147.33 ± 33.99	135.02 ± 34.95	.19	139.06 ± 41.94	136.51 ± 32.05	.58
Menopause									<.001			.83
No, n (%)							4 (26.67)	140 (79.10)		21 (19.09)	40 (20.10)	
Yes, n (%)							11 (73.33)	37 (20.90)		89 (80.91)	159 (79.90)	

Continuous data are shown as mean ± 1SD. Dichotomous data are shown as n (%). BMI = body mass index, CACS = coronary artery calcium score, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), SD = standard deviation.

cardiovascular risk factors.[21,22] The current guidelines also suggest that CACS assessment with CT may be considered a risk modifier in the cardiovascular risk assessment of asymptomatic individuals at low or moderate risk.[10] However, because of the high costs and unavoidable radiation exposure involved in determining the CACS, CT only has limited clinical value in the screening of CAC in unselected individuals. Therefore, researchers now aim to identify a biomarker that can be easily measured and become a suitable alternative to screening for CAC.[23,24] Finding a biomarker that is associated with cardiovascular risk and can predict CAC, particularly in asymptomatic individuals, is a priority in cardiovascular disease prevention. The results of the present study suggest that Lp (a) can be used as a biomarker to predict CAC and screen men aged ≥45 years who are asymptomatic but expected to have a high CACS.

Lp (a) can be freely fluxed across the endothelial barrier because of its small diameter, <70 nm in length. It can be retained similar to LDL-cholesterol within the arterial wall, which may increase the risk of ASCVD. Lp (a) may also promote atherosclerosis as it is a prominent carrier of proinflammatory oxidized phospholipids.[25] Furthermore, it is suspected to be prothrombotic based on the similarity of apo(a) to plasminogen and may, therefore, interfere with plasminogen's antithrombotic functions.[26]

Lp (a) has already been identified as a predictor of cardiovascular events in the 2002 PRIME Study.[6] In addition, Lp (a) has been recognized as a cardiovascular risk factor by the European Society of Cardiology and the European Atherosclerosis Society guidelines.[10] In addition, several studies have suggested that elevated serum Lp (a) levels are strongly and

Table 5

Predictors of coronary artery calcium score by univariable logistic regression in the 4 subgroups.

	Men (n = 1518)				Women (n = 501)			
	Age < 45 (n = 205)		Age ≥ 45 (n = 1313)		Age < 55 (n = 192)		Age ≥ 55 (n = 309)	
Variables	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Lp (a)	1.003 (0.980–1.026)	.82	1.008 (1.002–1.014)	.008	1.006 (0.978–1.034)	.70	1.003 (0.991–1.015)	.62
Smoking	1.138 (0.513–2.525)	.75	1.152 (0.903–1.470)	.26	0.527 (0.114–2.433)	.41	2.088 (0.918–4.751)	.08
HTN	2.537 (1.104–5.830)	.03	2.365 (1.880–2.975)	<.001	7.652 (2.535–23.103)	<.001	3.427 (2.106–5.577)	<.001
DM	3.534 (0.969–12.891)	.06	2.595 (1.914–3.517)	<.001	7.125 (1.583–32.074)	.01	3.271 (1.707–6.269)	<.001
Hypercholesterolemia	3.416 (1.252–9.324)	.02	1.359 (1.071–1.725)	.01	1.483 (0.453–4.851)	.52	1.053 (0.563–1.968)	.87
BMI	1.060 (0.987–1.139)	.11	1.035 (1.000–1.072)	.05	1.114 (1.006–1.233)	.04	1.061 (0.996–1.130)	.07
Waist circumference	1.018 (0.986–1.050)	.27	1.017 (1.004–1.030)	.01	1.066 (1.016–1.118)	.008	1.031 (1.006–1.057)	.02
Total cholesterol	1.003 (0.994–1.012)	.50	0.996 (0.993–0.999)	.002	1.004 (0.992–1.016)	.56	0.999 (0.994–1.005)	.79
Triglycerides	1.005 (1.002–1.008)	.003	1.000 (0.999–1.002)	.41	1.011 (1.003–1.019)	.006	1.004 (1.001–1.008)	.02
HDL-cholesterol	0.971 (0.935–1.007)	.12	0.992 (0.983–1.002)	.14	0.955 (0.914–0.997)	.04	0.977 (0.959–0.995)	.01
LDL-cholesterol	1.004 (0.994–1.015)	.42	0.995 (0.992–0.998)	.002	1.009 (0.995–1.023)	.19	1.002 (0.996–1.009)	.55
Menopause					0.926 (0.840–1.021)	.12	0.981 (0.929–1.037)	.50

BMI = body mass index, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), OR = odds ratio.

Table 6

Predictors of coronary artery calcium score by multivariable logistic regression in the 4 subgroups.

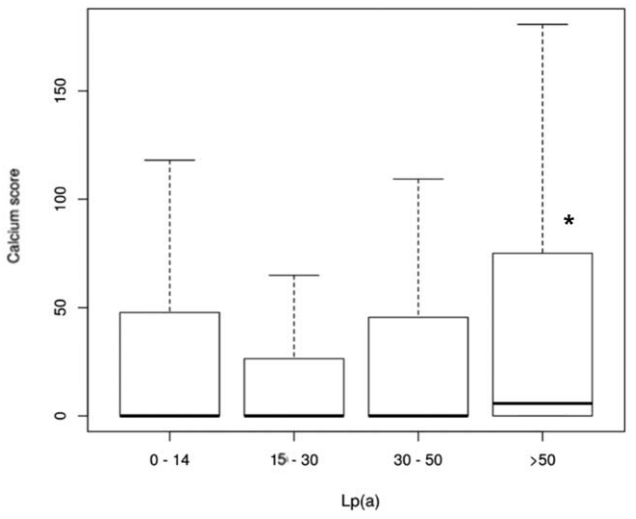
	Men (n = 1518)				Women (n = 501)			
	Age < 45 (n = 205)		Age ≥ 45 (n = 1313)		Age < 55 (n = 192)		Age ≥ 55 (n = 309)	
Variables	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Lp (a)	0.998 (0.973–1.023)	.85	1.010 (1.003–1.016)	.003	1.019 (0.988–1.052)	.23	1.004 (0.992–1.017)	.53
Smoking	0.924 (0.399–2.140)	.85	1.143 (0.886–1.475)	.30	0.380 (0.068–2.112)	.27	2.381 (0.998–5.679)	.05
HTN	2.252 (0.911–5.564)	.08	2.116 (1.659–2.700)	<.001	7.397 (2.250–24.318)	.001	3.301 (1.962–5.555)	<.001
DM	2.323 (0.501–10.771)	.28	2.287 (1.668–3.136)	<.001	8.073 (1.360–47.931)	.02	2.701 (1.352–5.395)	.005
BMI	1.023 (0.941–1.111)	.60	1.017 (0.980–1.055)	.38	1.131 (0.994–1.287)	.06	1.017 (0.947–1.091)	.65
LDL-cholesterol	1.006 (0.995–1.017)	.31	0.999 (0.995–1.002)	.41	1.010 (0.994–1.026)	.22	1.005 (0.998–1.012)	.18

BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, LDL = low-density lipoprotein, Lp (a) = lipoprotein (a), OR = odds ratio.

specifically associated with an increased risk of CHD. Kwon et al found that elevated Lp (a) levels have an incremental prognostic value in type 2 diabetic patients with symptomatic CAD.[27] Furthermore, in a large-scale cohort study conducted on 1560 European patients with suspected CHD (1123 men, age 59.3 ± 20.8 years), the multivariable analysis revealed a strong independent association between serum Lp (a) levels and the CACS.[15] Qasim et al enrolled 1299 patients with type 2 diabetes mellitus (480 women) and 860 patients without diabetes mellitus (403 women) and found that Lp (a) was associated with CAC in diabetic women.[5]

Despite abundant evidence of causality, and the fact that one-fifth of the general community has elevated Lp (a) levels >50 mg/dL,[28] Lp (a) has been considered a "conditional risk factor" that is dependent on coexisting conditions and the individual's background such as age, ethnicity, sex, and diabetes, and thus, not an "independent risk factor."[5]

However, our findings suggest that Lp (a) should be considered as an "independent risk factor" rather than a "conditional risk factor," and should be routinely measured for cardiovascular assessment of asymptomatic men over the age of 45 years.



*$P < .05$ vs. 15-30 mg/dL serum Lp (a) level group.

Figure 1. Difference in the coronary artery calcium score according to serum Lp (a) level.

Conversely, other studies have reported conflicting data on the relationship between Lp (a) and the CACS. The GENOA study conducted on 756 Caucasians found no association between Lp (a) and the CACS.[29] Similarly, the multi-ethnic Dallas Heart Study that studied 761 African Americans and 527 Caucasians also found no clear association.[16]

In our study, we did not find an association between Lp (a) and the CACS in males aged <45 years or females of all age groups; the exact reason for this is unclear; however, there may be several reasons. The number of women (n = 501) was one-third that of men (n = 1518), and additionally, there was a small number of participants enrolled in 3 of the 4 age subgroups. The males ≥45 years subgroup (n = 1313) accounted for over 60% of our sample population. In the group of males aged <45 years, the low prevalence of CAC may have prevented the detection of association. Cassidy et al found no association between the presence of CAC and Lp (a) in females aged <55 years,[30] which was consistent with our findings. Importantly, this is consistent with the fact that the risk for atherosclerosis is higher in men, not women, especially men over the age of 45 years.

Although no significant results were found between Lp (a) and the CACS in the female group, both Lp (a) and the CACS were significantly increased in the postmenopausal group. This is consistent with the well-known fact that serum Lp (a) levels increase after menopause. Although it is expected that elevated serum Lp (a) levels may be correlated with a higher incidence of atherosclerosis in postmenopausal women, few studies have analyzed the correlation between Lp (a) and the CACS in asymptomatic postmenopausal women. In addition, a previous study[31] did not show a significant correlation between Lp (a) and the CACS. However, our findings show that Lp (a) may be correlated with the CACS in asymptomatic postmenopausal women. Further studies are needed to determine whether these results are related to sex hormones.

In the case of LDL-cholesterol, which is a well-known cardiovascular risk factor, our study showed that the group with CACS > 0 had a lower serum level of LDL-cholesterol than the group with CACS = 0. This is believed to be because more subjects in the group with CACS > 0 were receiving lipid-lowering medication (15.1% vs 32.9%, data not shown).

5. Limitations

There are several limitations to this study. First, this was retrospective, single center, cross-sectional study. Therefore, we could not show a causal relationship between Lp (a) and CACS. Second, because of further categorizing participants into 4

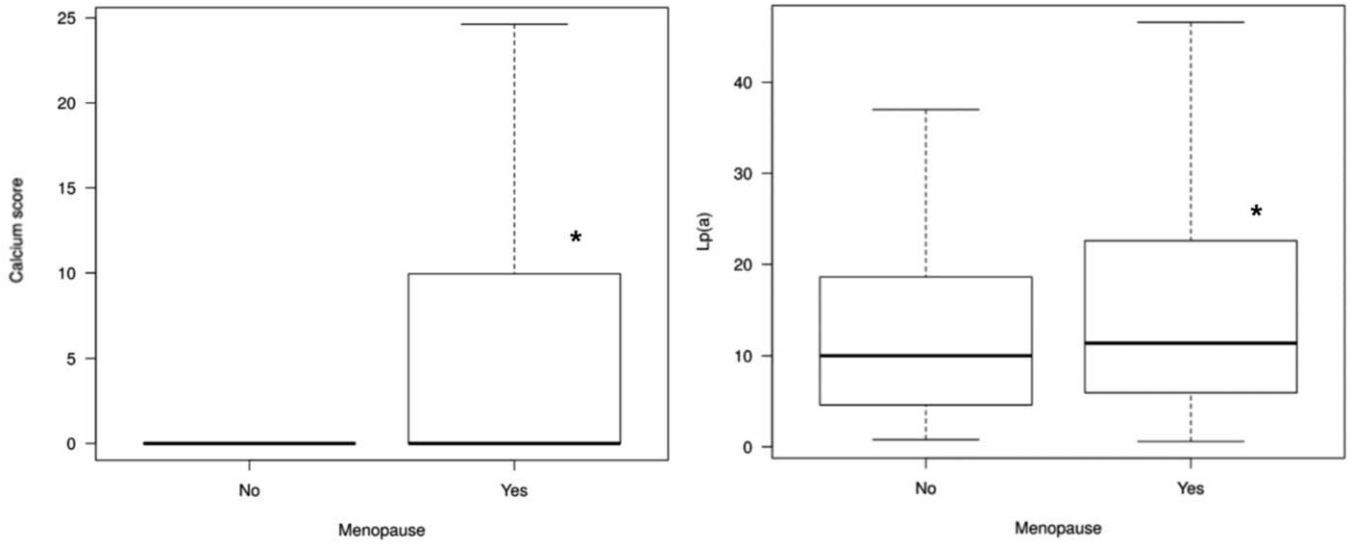


Figure 2. Difference in the coronary artery calcium score and serum Lp (a) level according to the menopause groups.

subgroups, 3 groups, excluding the subgroup of males aged ≥45 years, included a very limited number of patients. Thus, our findings cannot be applied to either the general population or women. Third, as this study was conducted only on asymptomatic adults, there is a possibility that our analysis of the association between serum Lp (a) level and CACS had less power compared to that found in other studies.

6. Further directions

To overcome these limitations, further studies involving a large number of participants at multiple centers is required. In addition, while CACS is a good marker for predicting CVD, future studies should analyze CVD events together to confirm the association between Lp (a), CACS, and CVD events.

7. Conclusion

Lp (a) is an independently associated factor of CAC and a marker of coronary atherosclerosis in asymptomatic men aged ≥45 years. Therefore, Lp (a) should be measured, and intensive Lp (a)-lowering treatment should be considered in this population.

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