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The Association Of Lipoprotein (A) With Coronary Artery Calcification Patterns Detected By Intravascular Ultrasound (IVUS) In Ischemic Patients Presented For PCI

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ABSTRACT

Background: Coronary artery disease (CAD), driven by atherosclerosis and risk factors like hypertension, diabetes, and hyperlipidemia, is a major global health burden, particularly in low- and middle-income countries. Coronary artery calcification (CAC), a regulated process linked to atherosclerosis, is prevalent in CAD patients, complicating percutaneous coronary intervention (PCI). Techniques such as balloon angioplasty, rotational atherectomy, and stenting are tailored to plaque calcification. Intravascular ultrasound (IVUS) is highly accurate in detecting CAC. Elevated lipoprotein (a) (Lp(a)), associated with residual risk of cardiovascular disease, has an unclear role in CAC and its impact on PCI.[1-3]

Objective: To determine the relation between serum lipoprotein (a) levels and coronary plaque calcification burden detected by intravascular ultrasound (IVUS) in ischemic patients undergoing PCI procedures.

Patients and Methods: 90 patients with ischemic heart disease presented for percutaneous coronary interventions. IVUS was used for assessment of plaque morphology and calcifications. Serum LP(a) was measured to all eligible patients.

Results: The study demonstrated a positive correlation between LP(a) level and measures of calcium assessment including angiographic calcium and IVUS detected calcium. LP(a) level was higher in patient with higher calcium arc and calcium length by IVUS. Higher LP(a) was associated with more mixed calcium sites (superficial and deep). After diving the study population into 2 groups depending on the LP(a) level (below or above 50 mg/dl), patient with higher LP(a) > 50 mg have higher calcification burden by IVUS (calcium length, calcium arc, mixed calcium sites). LP(a) was associated with lower minimal luminal area (MLA) and higher plaque burden.

Conclusion: high LP(a) levels is associated with more coronary plaque calcification burden by IVUS with possible need for calcium modification strategies during PCI.

Keywords: coronary calcification, LP(a), coronary angiography, minimal luminal area (MLA)

INTRODUCTION

Coronary artery disease (CAD) is a leading global health burden caused by atherosclerosis, where plaque buildup narrows coronary arteries. It presents as angina, myocardial infarction, or heart failure. Advances in diagnosis and treatments have improved outcome , but CAD continues to demand robust prevention and research efforts.[4]

Coronary artery calcification (CAC) is a hallmark of coronary artery disease (CAD), resulting from the calcification of atherosclerotic plaques. CAC is closely linked to risk factors like hypertension, diabetes, and hyperlipidemia, and it predicts adverse cardiovascular outcomes. While advances in diagnostics, such as intravascular ultrasound, and treatments like PCI have improved management, CAC complicates interventions and remains a significant challenge in CAD care, highlighting the need for further research and prevention strategies.[5, 6]

Lipoprotein (a) is an independent cardiovascular risk factor linked to atherosclerosis and vascular calcification. Elevated Lp(a) levels contribute to calcified valvular diseases and may play a role in coronary calcification, although this relationship is not fully understood. Studies suggest that Lp(a) promotes inflammation, oxidative stress, and pro-calcific processes, potentially accelerating CAC progression. However, its impact on procedural outcomes, such as percutaneous coronary intervention (PCI), remains underexplored, necessitating further research to clarify its role in CAC and coronary artery disease management.[7]

So, we assessed association of LP(a) with calcification burden detected by IVUS

PATIENTS AND METHODS

Single center cross-sectional study which was conducted in National heart institute. The study is approved by the ethics committee of Menoufia faculty of medicine and National heart institute ethical committee. The study performed between November 2022 to June 2024., on 90 ischemic patients presented for percutaneous coronary intervention including IVUS assessment of the coronaries .Serum LP(a) was measured to all eligible patients, We excluded any patient with previous stent in the same vessel, chronic kidney disease ,hyperparathyroism, hypercalcemia ,hyperphosphatemia, known patients with malignancies ,patients with chronic inflammatory or autoimmune diseases, patient with familial hypercholesterolemia and advanced stages of liver cell failure.

Each individual in the study population underwent a detailed clinical examination and thorough history taking, Electrocardiogram (ECG), complete transthoracic echo cardiography ,laboratory investigations including complete blood picture , serum creatinine and urea , random blood glucose , HbA1c , serum AST , ALT, serum calcium , phosphate , complete lipid profile including total cholesterol, HDL, LDL and triglycerides , CRP (c reactive protein) and Serum lipoprotein (a) which was measured during admission using an automated enzyme-linked immunosorbent assay (ELISA).Coronary angiography with IVUS assessment was done to all patients to assess the calcification burden including calcium arc , length , and site . MLA and plaque burden were also assessed using IVUS.

Statistical analysis

The statistical analysis and data management were performed using SPSS version 28 software, which was developed by IBM in Armonk, New York, United States. In order to assess the normality of the quantitative data, the Shapiro-Wilk test and direct data visualization techniques were implemented. In accordance with the principle of normality, means and standard deviations, medians and ranges were employed to summarize the quantitative data.

RESULTS

The majority of patients were male (71.1%), with mean age of 58.48 years. The mean BMI was 27.27 kg/m² with a range of 21.0 to 40.0 kg/m². Among the patients, 51.1% were smokers. 62.2% were hypertensive and 61.1% were diabetic. Among the patients, 24.4% had a positive family history of CAD. mean serum creatinine level was 0.94 mg/dL with range of 0.50 to 1.50 mg/dL. The ALT and serum calcium levels results were within the normal range for all patients. The estimated glomerular filtration rate (eGFR) had a mean of 87.43 ml/min/1.73m². The mean ejection fraction (EF) was 57.17% (SD = 8.0), with a range of 35.0% to 70.0%. **(Table 1)**

Table 1 general characteristics of the study population

	Ischemic patients (n = 90)	
	No.	**%**
Sex		
Male	64	71.1 %
Female	26	28.9 %
Smoking	46	51.1 %
HTN	56	62.2 %
DM	55	61.1 %
Dyslipidemia	65	72.2 %
Family history	22	24.4 %
Age (years) Mean ± SD.	58.48 ± 9.47	
BMI (kg/m^2) Mean ± SD.	27.27 ± 3.18	
Serum creatinine (mg/dL) Mean ± SD.	0.94 ± 0.24	
ALT (U/L) Mean ± SD.	29.26 ± 2.30	
Serum calcium (mg/dL) Mean ± SD.	8.89 ± 1.03	
eGFR (ml/min/1.73m^2) Mean ± SD.	87.43 ± 17.88	
EF (%) Mean ± SD.	57.17 ± 8.0	

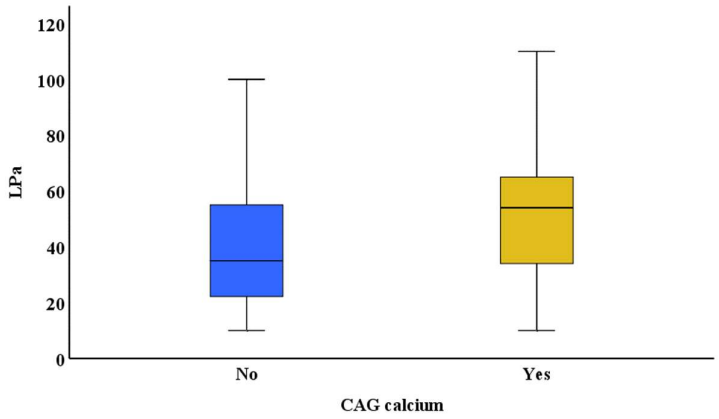

Figure 1: Boxplot chart for association between LP(a) and angiographic calcium.

Among the 90 patients, 90.0% had at least one vessel affected with obstructive stenosis, while 10.0% did not have any affected vessels with obstructive stenosis. The LAD was the most commonly affected vessel, observed in 77.8% of patients. The LCX and RCA were affected in 15.6% and 10.0% of patients, respectively. The LM artery was affected in 40.0% of patients .47.8% of the patients had coronary angiographic detected calcium, IVUS detected calcium was observed in 81.1% of patients. The location of calcium was predominantly mixed (57.5%), followed by superficial (35.6%) and deep (6.8%). The arch of calcium was most commonly found in the 1–90-degree range (50.7%). The mean calcium length was 7.58 mm, with a standard deviation of 3.95 mm. (Table 2)

Table 2 CA and IVUS findings in the study population

	Ischemic patients (n = 90)	
	No.	%
Patients with obstructive stenosis		
No	9	10.0
Yes	81	90.0
Vessels with obstructive stenosis		
LAD	70	77.8
LCX	14	15.6
RCA	9	10.0
LM	36	40.0
Calcium measurements		
Angiographic calcium	43	47.8
IVUS calcium	73	81.1
Location of calcium		
Superficial	26	35.6
Deep	5	6.8
Mixed	42	57.5
Arch of calcium		
1-90	37	50.7
91-180	19	26.0
181-270	6	8.2
271-360	11	15.1
Calcium length (mm)		
(Mean ± SD.) 7.58 ± 3.95		

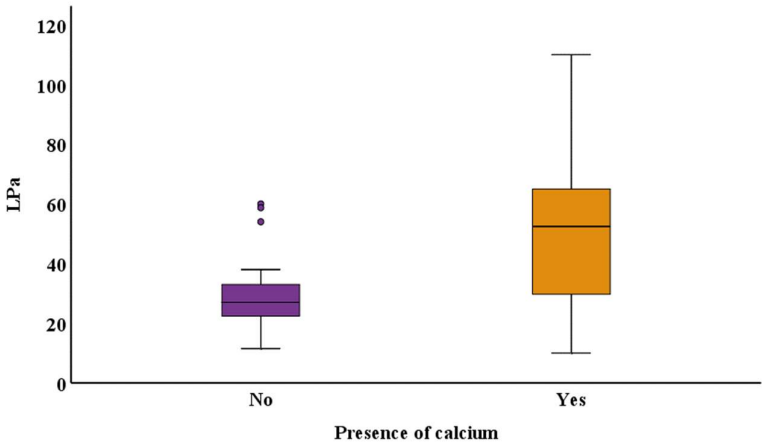

Figure 2: Boxplot chart for association between LP(a) and IVUS detected calcium.

No statistically significant association was found between serum LP(a) levels and sex, smoking, hypertension, diabetes mellitus, age or BMI. the LP(a) level was higher in individuals with a family history of CAD compared to those without, showing a significant difference with a p-value of 0.049. (Table 3)

Table 3 Correlation between LP a level and CVD risk factors

	LP(a) Mean ± SD.	Test	P
Sex			
Male, n=64	47.16 ± 22.24	U=717.0	0.306
Female, n=26	42.0 ± 25.04		
Smoking (n=46)	48.56 ± 23.12	U=1182.5	0.169
HTN (n=56)	46.90 ± 23.19	U=1039.0	0.469
DM (n=55)	48.39 ± 25.18	U=1114.5	0.208
Dyslipidemia (n=65)	46.22 ± 23.10	U=847.5	0.753
Family history of CAD (n=22)	55.0 ± 25.21	U=958.0*	0.049*

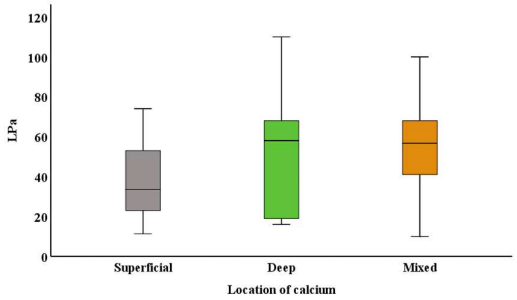

Figure 3: Boxplot chart for association between LP(a) and location of calcium.

The study reveals significant association between high LP(a) level with presence of obstructive stenosis mainly in LAD. However, there were no significant differences in mean LP(a) levels based on individual vessel types (LCX, RCA, LM) as all p-values were above 0.05. The study shows that patients with angiographically or IVUS detected calcium have higher LP(a) levels with more calcifications in deep or mixed locations. Also, patients with higher LP(a) levels have higher arch of calcification degrees. (Table 4)

Table 4 Correlation between LPa levels and CA and IVUS findings

	LP(a) Mean ± SD.	Test	P
Patients with obstructive stenosis			
(n=81)	47.44 ± 23.40	U=525.5*	0.030*
Vessels with obstructive stenosis			
LAD (n=70)	47.92 ± 22.74	U=895.5	0.048*
LCX (n=14)	43.94 ± 28.29	U=489.5	0.636
RCA (n=9)	42.88 ± 19.44	U=340.5	0.747
LM (n=36)	43.79 ± 22.88	U=896.5	0.534
Angiographic calcium			
(n=43)	51.42 ± 21.36	U=1324.5*	0.011*
IVUS detected calcium			
(n=73)	49.18 ± 23.34	U=908.0*	0.003*
Calcium Location			
Superficial, n=26	38.04 ± 18.88	H= 9.202*	0.010*
Deep, n=5	54.20 ± 38.78		
Mixed, n=42	55.47 ± 21.68		
Arch of calcification			
1-90, n=37	40.59 ± 20.42	H= 9.777*	0.021*
91-180, n=19	55.32 ± 23.67		

181-270, n=6	65.40 ± 27.61		
271-360, n=11	58.60 ± 20.78		

between LP(a) and location of calcium.

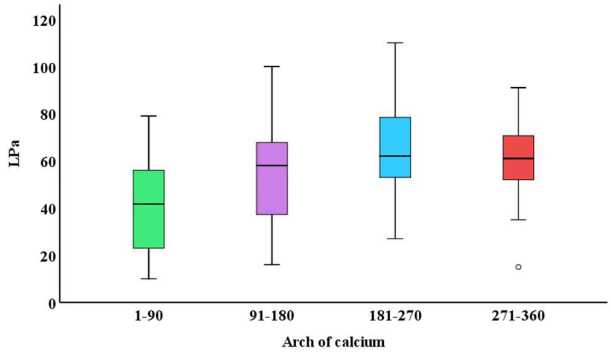

Figure 4: Boxplot chart for association between LP(a) and arch of calcium.

Patients with LP(a) ≥50 were more likely to have angiographic calcium (p = 0.012) as well as IVUS detected calcium. On the other hand, the location of calcium deposits differed significantly between the two groups (p = 0.012), with a higher proportion of patients in the LP(a) ≥50 group having deep or mixed calcium deposits. Moreover, higher proportion of patients in the LP(a) ≥50 group had higher arch (p=0.009). Additionally, the mean calcium length was significantly higher in the LP(a) ≥50 mg group compared to the LP(a) <50 group (p = 0.006). These findings suggest a strong association between elevated serum LP(a) levels and the presence and extent of coronary artery calcification. (Table 5)

Table 5 Correlation between LPa level (< or > 50 mg) and calcification indices

	LP(a) <50 n = 48 No.(%)		**LP(a) ≥50 n = 42 No.(%)**		**Test**	**p**
Angiographic calcium						
	17 (35.4)		26 (61.9)		χ^2=6.299*	0.012*
IVUS detected calcium						
	34 (70.8)		39 (92.9)		χ^2=7.092*	0.008*
Calcium Location						
Superficial	18	52.9	8	20.5	χ^2= 8.394*	MC 0.012*
Deep	2	5.9	3	7.7		
Mixed	14	41.2	28	71.8		
Calcification Arch						
1-90	24	70.6	13	33.3	χ^2= 11.077*	MC 0.009*
91-180	7	20.6	12	30.8		
181-270	1	2.9	5	12.8		
271-360	2	5.9	9	23.1		
Calcium length (mm)						
Mean ± SD.	6.44 ± 3.85		8.56 ± 3.82		U= 909.0*	0.006*

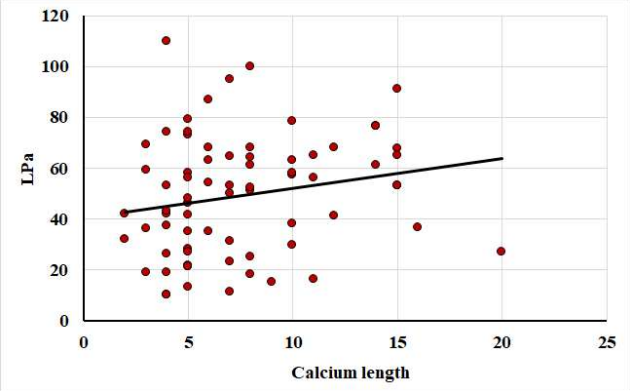

Figure 5: Correlation between LP(a) and calcium length.

The correlation analysis reveals significant negative correlation between LP(a) levels and MLA (correlation coefficient = -0.351, p = 0.001) and significant positive correlation between LP(a) levels and calcium length. (Table 6)

Table 6 Correlation between LPa level and calcium length and MLA detected by IVUS.

	LP(a)	
	rs	p
Calcium length	0.241*	0.040*
MLA	-0.351*	0.001*

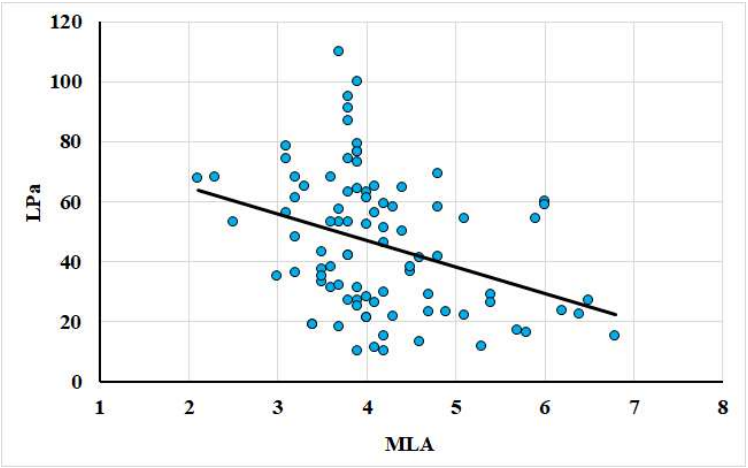

Figure 6: Correlation between LP(a) and MLA.

DISCUSSION

Cardiovascular disease (CVD) is still a leading cause of morbidity and mortality, despite all the progress achieved as regards to both prevention and treatment. [8]Having high levels of Lp(a) is a risk factor for cardiovascular disease that operates independently. [9]

Coronary artery calcification (CAC) is a risk factor for adverse outcomes in the general population and in patients with coronary artery disease.. Efforts to control CAC with medical therapy have not been successful. Although using intracoronary imaging like IVUS and devices for plaque modification have modestly improved outcomes in calcified vessels, adverse event rates are still high. [10, 11]

The aim of the study is to determine the relation between LP(a) and coronary plaque calcification burden detected by intravascular ultrasound (IVUS) in ischemic patients presented for PCI.

The study was conducted on 90 ischemic patients presented for PCI including IVUS assessment of intracoronary calcifications. Serum LP(a) was measured to all patient. IVUS was used to evaluate degree of calcification in the coronaries regarding the calcification presence, site either superficial, deep or mixed, calcification length and arc. Patients with possible causes of increased vascular calcifications are excluded from the study (malignancy, chronic renal failure, chronic inflammatory conditions).

The result of our study pointed that LP(a) has positive correlation with the calcification burden detected by either angiography alone, or by using IVUS. The length of calcification as well as arc of calcification are higher in patients with higher LP(a) levels, the site of calcification showed variations in the LP(a) levels, with significant differences between superficial and deep locations, Patients with higher LP(a) levels have more deep and mixed calcifications than those with lower LP(a) levels. We also noticed also a positive correlation between LP(a) level and plaque burden and negative correlation with MLA, high serum levels of LP(a) are associated with higher plaque burden and lower MLA.

In accordance with our study, the meta-analysis published by Martignoni FV, et al. in which he evaluated the association between Lp(a) and CAC in asymptomatic patients. The findings of this meta-analysis suggest that Lp(a) is positively associated with a higher likelihood of CAC. [12]

Another study by Ong KL, et al. showed that higher Lp(a) was associated with larger absolute increase in coronary artery calcium (CAC) volume. The association was more evident in patients with Lp(a) (≥30 mg/dL) and high serum levels of IL-2 soluble receptor α, soluble tumor necrosis factor alpha receptor 1 and fibrinogen. [13]

In a study based on the population of MESA study (The Multi-Ethnic Study of Atherosclerosis) by Garg PK, et al. showed that high Lp(a) serum levels were associated with more calcification progression during follow up imaging. The adjusted prospective analyses, revealed that participants with Lp(a) ≥50 mg/dL have higher risk for rapid coronary calcification progression .[14]

Another study by Jia Peng et al. which investigated the relationship between Lp(a) serum levels and the presence of vascular calcification . Higher Lp(a) levels were independently associated with coronary calcifications severity. Lp(a) is suggested to be involved in coronary calcifications by activation of Notch1-NF-κB and Notch1-BMP2-Smad1/5/9 pathways. [15]

In the study of Pechlivanis S et al. , The study revealed significant association between log-transformed Lp(a) levels and CAC. Furthermore, the LP(a) SNP rs10455872 showed a statistically significant association with CAC. The study provides evidence that LP(a) SNP rs10455872 was associated with high Lp(a) levels and more coronary calcifications.[16]

Another study by Nurmohamed NS et al. have shown that higher Lp(a) levels were associated with increased progression of coronary plaque burden and increased presence of low-density noncalcified plaque and pericoronary adipose tissue inflammation. [17]

Vazirian F et al, `s systematic review and meta-analysis in asymptomatic patients with evident of CAD by imaging (MSCT coronary) found that elevated blood level of Lp(a) in asymptomatic CVD individuals are associated with a 58% increased risk of high CAC score The study found a significant association between Lp(a) and CAC.[18]

In another study by Verweij SJ et al, to evaluate the association between Lp(a) levels and atherosclerotic coronary plaque burden, assessed by coronary calcium score by Multisclice CT scan of the coronary arteries. The study imply that Lp(a) accelerates progression of atherosclerosis and contribute to increased cardiovascular risk.[19]

On the other hand, other clinical studies have shown lack of association between Lp(a) and calcification burden. Those studies have assigned higher threshold values for Lp(a), mostly higher than 50mg/dl.

In the study by Sheng Z. et al on 123 patients to evaluate the relationship between serum Lp(a) levels and coronary calcification by IVUS in patient with stable CAD. The LP(a) threshold was 150 mg/dl and the participants were divided into 2 groups: LP(a) < 150mg/L and ≥ 150mg/L. The low Lp(a) group had significantly higher calcification arch with increased thickness. Multivariate logistic regression analysis confirmed that low serum Lp(a) levels was an independent factor predicting increased calcification burden. The possible explanation of the difference in outcome could be due to the very high cutoff value of LP(a) level (150 mg /dl) and the type of patients selected in the study (Asian ethnicity) [20]

Another study by Mehta A, et al and colleagues studied patients with advanced stable coronary artery disease using a threshold of ≥ 50 mg/dl for high Lp(a). This study evaluated the separate and joint associations of Lp(a) and coronary artery calcification (CAC) with the risk of atherosclerotic cardiovascular disease (ASCVD). It found that both Lp(a) and CAC are independently associated with ASCVD risk, including death, myocardial infarction (MI), and stroke, but that they did so “independently” of one another. But distant relation is noticed, in patients without evidence of coronary calcifications, there was no association between level Lp(a) and ASCVD risk. And, in the highest Quintile (Q5) of Lp(a), the risk was highly dependent on CAC.[21]

In discordance with our results, the Dallas Heart Study which investigated the relationship between Lp(a) level, apolipoprotein(a) isoform sizes, and coronary calcification presence. No association was found between coronary artery calcium (CAC) and Lp(a) level, apolipoprotein(a) isoform size, or a combination of these 2 variables and in both whites or blacks. No correlation was observed between plasma levels of Lp(a) and coronary calcium scores in any group. [22]

As regarding presence of plaque burden > 70 % and MLA less than 4 $cm^{2.}$ There was a study by Hartmann M et al. in which retrospective analysis of serial intravascular ultrasound (IVUS) studies of 60 left main stems to evaluate plaque progression in relation to Lp(a) and fibrinogen levels. Serial IVUS showed a positive correlation between Lp(a) and fibrinogen levels and plaque progression. Lp(a), but not fibrinogen, remains independently associated with plaque progression.[23]

Another study that showed association of serum lipoprotein (a) levels and coronary atheroma volume by intravascular ultrasound by Huded CP et al. which is based on post hoc analysis of multiple previous trials. The patients were classified into 2 groups with high (≥60 mg/dL) and low (<60 mg/dL) Lp(a) level. The primary outcome was baseline coronary percent atheroma volume. Percent atheroma volume was significantly higher in patients with high Lp(a) levels in both unadjusted (P=0.01) and risk-adjusted analyses (P<0.001).[24]

In agreement of our results, the Miami Heart Study—a community-based, prospective cohort study—which included 1795 asymptomatic adults aged 40 to 65 years evaluated using coronary computed tomography angiography, Elevated Lp(a) was defined as ≥125 nmol/L (59 mg/dl). The study concluded that elevated Lp(a) was independently associated with the presence of coronary plaque. [25]

On the contrary, Kaiser et al. study on 191 patients with stable CAD undergoing MSCT coronary and coronary calcium score at baseline and after 1 year to evaluate the progression of total, calcific, noncalcific, and low-attenuation plaque (necrotic core). Lp(a) ≥ 70 mg/dL was used as threshold for high LP(a)levels. Although, at baseline, there was no difference in coronary artery disease severity or plaque burden. Patients with Higher levels of Lp(a) was associated with rapid progression of low-attenuation plaque compared with low Lp(a) group. The relation was confirmed between the level of Lp(a) and low-attenuation plaque volume progression by multivariable regression analysis.

The study by Kaiser et al have used high threshold for Lp(a) (> 70 mg/dl), and examined the progression of CAC volume. The study revealed a 20-fold greater progression of calcific volume in patients with high Lp(a) >70 mg/dl over a 12-month period without reaching statistical significance (p = 0.2). Since these threshold values are within the highest quintiles, a significant correlation could be present. Also no significant difference was found in plaque type or plaque volume progression.[26]

CONCLUSION

The study suggested that higher levels of LP(a) are associated with higher calcification burden in the coronaries detected by IVUS.

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