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The diagnostic value of lipoprotein-related phospholipase A2 and matrix metalloproteinase-9 in identifying patients with coronary plaque or stenosis

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ABSTRACT

Background: Coronary computed tomography angiography (CCTA) is the gold standard method for detecting the presence of coronary plaque and stenosis in atherosclerosis. However, the nephrotoxic effects of contrast agents applied during angiography and the adverse effects of radiation are known. Alternative diagnostic tools are always needed to evaluate coronary arteries. Therefore, combining the results of CCTA with Lipoprotein-associated phospholipase A2 (Lp-PLA2) and Matrix metalloproteinase (MMP)-9, which are thought to be associated with atherosclerotic plaque, may reduce cardiovascular events in patients with suspected atherosclerosis.

Methods: In the serum samples collected from the control group and patients, CRP, triglyceride, total cholesterol, LDL-C, HDL-C, Lp-PLA2, and MMP-9 levels were analyzed. Receiver Operating Characteristic (ROC) analysis was applied to determine optimal cut-off values in identifying patients with coronary plaque or stenosis. The significance level was accepted as $p<0.05$.

Results: Fifty-four patients with suspected CAD who underwent both CCTA and serum Lp-PLA2 and MMP9 measurements were evaluated. Patients in the stenosis/plaque group had a significantly higher LpPLA2 and MMP-9 than the control group. Lp-PLA2 is positively associated with MMP-9 and MMP-9 with non-HDL. Except for Lp-PLA2 and CRP, sdLDL is associated with all assayed parameters. Lp-PLA2 and MMP-9 had 91.7% and 100% sensitivity in identifying patients with coronary plaque or stenosis at cut-off values of 183.34 and 24, respectively. MMP-9 and sdLDL-C had 100% and 92.9% specificity at cut-off values of 24 and 48.1.

Conclusions: By evaluating Lp-PLA2, MMP-9, sdLDL-C levels together with CT angiography findings, it is thought that these parameters can be used as an alternative to CT in controlling patients at risk and patients who have undergone cardiological intervention before.

Keywords: coronary CT angiography, coronary plaque, Lp-PLA2, MMP-9, sdLDL

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INTRODUCTION

Coronary artery diseases (CAD) are among the leading causes of death in developed societies [1]. The condition that occurs due to narrowing of the coronary artery lumen by atheromatous plaque or obstruction is generally called CAD [2].

Atherosclerotic vascular disease is a common inflammation and lipid accumulation that develops due to risk factors such as age, gender, genetic factors, dyslipidemia, smoking, hypertension, diabetes mellitus, physical inactivity, and obesity on the vascular structure. Plaques or lesions formed by lipid accumulation reveal the disease process, atherosclerosis, which causes deterioration of blood flow in the arteries [3].

If the risk factors persist, inflammation in the plaque continues, and subendothelial accumulation gradually increases. LDL cholesterol accumulating in the intima increases the inflammatory response [4]. T lymphocytes begin to accumulate in the intima and release pro-inflammatory cytokines. Another task of T cells is to activate macrophages and promote the release of collagen, MMP, and cytokines [5,6]. The smooth muscle cells that come to the area both enlarge and strengthen the plaque by contributing to collagen production. In the atheroma plaque, growth is first outward and then inward, and the plaque gradually begins to narrow the lumen.

Most myocardial infarctions are caused by rupture of delicate plaques that create less than 50% stenosis rather than occlusion of the critically narrowed vessel [7].

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When the continuity of the endothelium is disrupted in the ruptured plaque, it comes into contact with blood. Thrombogenic core, a thrombus forms, and the vessel is occluded. It determines plaque sensitivity, lipid content, degree of inflammation, fibrous framework, necrotic and apoptotic cell content, and neovascularization [8].

The rupture of atherosclerotic plaques in the development of acute coronary syndromes is also caused by the instability of the fibrous capsule in the atheroma plaque. Many factors affect the stability of the fibrous capsule, and one of them is the Matrix metalloproteinase (MMP) enzyme. This is the main enzyme that breaks down the proteins in the fibrous capsule and stands out among MMP, MMP-9, atherosclerosis, and CAD [9].

Lowering serum total cholesterol (TC) and low-density cholesterol (LDL-C) levels indicates a reduced risk of CAD. In contrast, LDL-C levels are not always high in patients with CAD [10,11]. C-reactive protein (CRP) triggers the transition of monocytes to the intima by interacting with its receptors. Therefore, CRP simultaneously initiates endothelial dysfunction, inflammation, plaque instability, and thrombosis in many ways, especially in ACS or those at risk[12].

LP-LPA2 is a calcium-dependent lipase and pro-inflammatory enzyme associated with major cardiovascular events, independent of traditional risk factors and other markers of inflammation [13]. In plasma, LP-LPA2 binds to LDL-C and is also associated with HDL-C [14-16].

Conventional coronary angiography is currently accepted as the gold standard in evaluating coronary artery disease and has significant advantages. However, the method is invasive and can cause severe and even fatal complications, although rarely. This situation reveals the necessity of a non-invasive, effective, and reliable alternative diagnostic method [17].

With the development of multislice computed tomography (MDCT) systems, cardiac examinations have become one of the most common application areas of CT. Unlike catheter angiography, coronary CT angiography can detect early atherosclerotic changes in the wall (calcific or soft plaque) that do not cause significant stenosis in the lumen, as it can show the vessel wall and vessel lumen [18].

However, the nephrotoxic effect of contrast agents applied in both methods and the negative effects of radiation to which patients are exposed for a brief time is also known. Alternative diagnostic tools are always needed to evaluate coronary arteries in people with kidney failure and other chronic diseases [19]. For this reason, it is necessary to investigate whether these biomarkers can be used in the follow-up of CAD patients from the data obtained by measuring Lp-PLA2 and MMP-9 levels, which define the character of atherosclerotic plaque structure and comparing them with CT angiographic findings [20].

METHODS

Participants

This study is a human case-control study. The study was approved by the Erciyes University Clinical Research Ethics Committee on 01.01.2016 with Decision No:2016/240. Informed consent was obtained from all human participants included in the study.

Between May and December 2017, 54 patients who underwent angiography in Erciyes University Medical Faculty Radiology Clinic CT Angiography Unit were included in the study.

The control group of 30 people suspected of coronary artery disease underwent CT angiography in the radiology clinic. No problem was detected in their coronary arteries. Twenty-four people with a plaque and/ or stenosis were divided into two as the patient group.

The inclusion criteria were determined as a) patients aged between 18 and 65; b) patients who were suspected of having coronary artery disease; c) patients were not on lipid lowering therapies (e.g. statins).

The exclusion criteria were a) women who were pregnant; b) patients with a history of myocardial infraction; c) those who had previously undergone coronary artery bypass surgery or stenting; d) patients with a history of allergies to contrast media; e) those who had renal failure or estimated glomerular filtration rate <30 mL/min.

Samples

Following CT angiography, venous blood samples were drawn from the patients into tubes without additives. Tubes were centrifuged for 10 minutes at 2000 g after 30 minutes. The separated serum samples were aliquoted into Eppendorf tubes and stored at -80°C until the day they were analyzed.

Multislice CT coronary angiographic evaluation

After CT angiography, expert radiologists examined the images of the patients. In coronary arteries, plaque, the plaque structure, stenosis, and its degree were reported.

Laboratory measurements

From the serum samples, CRP was determined using the immuno-turbidimetric method. Triglyceride, total cholesterol, and HDL-C levels were determined by the spectrophotometric method in a Roche brand Cobas c- 702 autoanalyzer using appropriate commercial kits. Lp-PLA2, MMP-9, and sdLDL-C were analyzed using commercial kits: ELISA, Cusabio, catalogue number: CSB-E08319h; (ELISA, Invitrogen, catalogue number: BMS-2016/2); and Randox brand kits on Cobas c-501 (Roche), respectively.

Statistical assessment

IBM SPSS Statistics 20 was used for analysis. Statistical distribution of data was evaluated with the Shapiro-Wilk test. Variables were stated as means with standard deviation, or median with the 25th and 75th percentile. The difference between the two groups with and without normal distribution was compared with the independent samples t-test and the Mann-Whitney test, respectively. The Pearson and Spearman's tests were used for correlation analysis. The chi-squared test was used to check if there is a significant difference in categorical variables between the two groups. Receiver Operating Characteristic (ROC) analysis was applied to determine optimal cut-off values in identifying patients with coronary plaque or stenosis. The significance level was accepted as $p<0.05$.

RESULTS

The mean age of 30 volunteers with normal CT angiography and the mean age of 24 patients with pathology in CT angiography were shown in Table 1. There was no statistical difference between the groups ($p>0.05$). Coronary artery stenosis was detected in 45.8% and coronary plaque in 54.2% of the patient group (Table 1).

The routine and biochemical study findings obtained from the patient and control groups are shown in Table 2. It was determined that there was no statistical difference between the study groups in terms of C-Reactive protein and HDL-C levels ($p>0.05$) (Table 2). Compared with the control group, triglyceride, total cholesterol, LDL-C, non-HDL-C, sdLDL-C levels, and LDL-C/HDL-C ratio were found to be higher in the patient group ($p<0.05$) (Table 2).

MMP-9 levels in control and patient groups were 20.4 ng/mL (17.4-22.4) and 197.5 ng/mL (172.2-231.7), respectively. LpPLA2 levels were 198±59 ng/mL and 261±63 ng/mL, respectively. As seen in Figure 1, MMP-9 and Lp-PLA2 levels were found to be higher in the group with stenosis/ plaque compared to the control group ($p<0.05$).

As a result of the correlation analysis between the variables, a positive correlation was found between triglyceride and non-HDL-C and between sdLDL-C and non-HDL-C ($p<0.05$). Correlations between variables are shown in Table 3. Lp-PLA2 with MMP-9; non-HDL-C with MMP-9; a positive correlation between sdLDL-C and MMP-9. It was determined that there was a negative correlation between sdLDL-C and HDL-C ($p<0.05$).

Lp-PLA2 and MMP-9 had 91.7% and 100% sensitivity in identifying patients with coronary plaque or stenosis at cut-off values of 183.34 ng/mL and 24 ng/mL, respectively (Figure 1 and Figure 2). MMP-9 and sdLDL-C had 100% and 92.9% specificity at cut-off values of 24 ng/mL and 48.1 mg/dL, respectively (Figure 2 and Figure 3).

DISCUSSION

Despite advances in treating cardiovascular diseases, Coronary Artery Disease (CAD) continues to be the leading cause of death in many countries today (21). Today, atherosclerosis is accepted as a chronic inflammatory disease. It has been suggested that the severity of inflammation is more important than the degree of lumen narrowing in terms of the clinical consequences of oxidized LDL, genetic, metabolic, and environmental damage, and coronary atherosclerosis [22,23].

Table 1. Demographic and CT angiography findings of the study groups variables

	Negative CT angiography (n=30)	Positive CT angiography (n=24)	*p* value
Age (years)	47 ± 9	52 ± 10	0.056
Sex	15 Male (50%) 15 Female (50%)	15 Male (62.5%) 9 Female (37.5%)	0.358
Undergoing CT scan	30 (100%)	11 (45.8%)	
≤50% stenosis	0 (0.0%)	9 (37.5%)	
>50% stenosis	0 (0.0%)	2 (8.3%)	
Non-stenosing plaque	0 (0.0%)	13 (54.2%)	

Table 2. Comparation of lipid profile, CRP, MMP-9 and Lp-PLA2

	Negative CT angiography (n=30)	Positive CT angiography (n=24)	*p* value
Triglyceride (mg/dL)	109.0 (79.5-222.2)	161 (116.5-220.2)	0.034
Total cholesterol (mg/dL)	190.9±43.3	218.4±39.5	0.018
LDL-C (mg/dL)	114.6±29.2	134.0±31.7	0.025
HDL-C (mg/dL)	47.5 (42.0-62.0)	48.5 (40.7-57.7)	0.595
Non-HDL-C (mg/dL)	138±45.9	170±37.3	0.001
sdLDL-C (mg/dL)	35.1 (29.8-41.6)	47.0 (33.7-57.0)	0.009
LDL-C/HDL-C	2.2±0.89	2.9±0.91	0.007
CRP (mg/L)	1.3 (0.7-2.9)	1.2 (0.7-2.9)	0.855
MMP-9 (ng/mL)	20.4 (17.4-22.4)	197.5 (172.2- 231.7)	<0.001
Lp-PLA2 (ng/mL)	198±59	261±63	<0.001

Data were presented as mean± standard deviation or median (25%-75% percentile)

When the literature on this subject is reviewed, many studies show that myocardial infarction results from rupture of fragile plaques that produce stenosis rather than from occlusion of a critically narrowed vessel [24].

It has been reported that clinical atherosclerotic events are uncommon in individuals with deficient cholesterol levels throughout their lifetime. In support of these studies, when the study groups were compared in our study TC and LDL-C levels were found to be higher in the patient group than in the control group. On the other hand, LDL-C levels are not always high in CAD patients [25,26].

The occurrence and progression of coronary atherosclerosis have recently been highlighted by evidence that the specific nature and levels of lipoproteins are related [27]. Indeed, clinical studies have shown that the risk of CAD is associated with sdLDL-C dominance. sdLDL particles are more atherogenic than large-sized LDLs due to several characteristics: rapid penetration into the arterial wall, low-affinity binding to the LDL-receptor, long plasma half-life, and low resistance to oxidative stress [28].

The presence of high sdLDL-C levels in plasma causes deposition of LDL particles in the arterial wall, oxidation, and secretion of various inflammatory mediators. A consequence of these events is disruption of endothe-

Table 3. Cross-correlation table of variables

Variables	**Correlation coefficient (*r*) vs Lp-PLA2**
MMP-9	0.580**
Non-HDL-C	0.242
triglyceride	0.176
HDL-C	0.033
LDL-C	0.294*
LDL-C/HDL-C	0.221
Variables	**Correlation coefficient (*r*) vs MMP-9**
Triglyceride	0.348*
Cholesterol	0.338*
HDL-C	-0.088
LDL-C	0.366
Non-HDL-C	0.407*
LDL-C/HDL-C	0.425*
Variables	**Correlation coefficient (*r*) vs sdLDL-C**
Lp-PLA2	0.098
MMP-9	0.317*
HDL-C	-0.385*
Triglyceride	0.544**
LDL-C/HDL-C	0.638**
LDL-C	0.519**
Variables	**Correlation coefficient (*r*) vs CRP**
MMP-9	0.059
Lp-PLA2	-0.051
HDL-C	0.099
sdLDL-C	0.091
Non-HDL-C	0.080
Triglyceride	0.024

Significance: *p<0.05, **p<0.001.

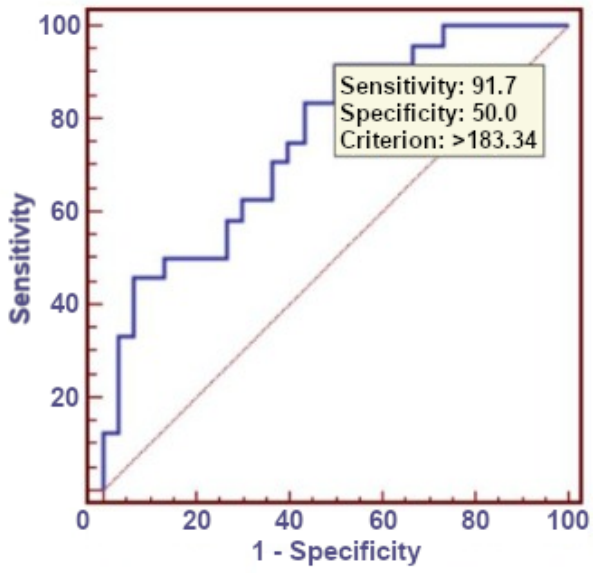

Figure 1. ROC curve of Lp-PLA2

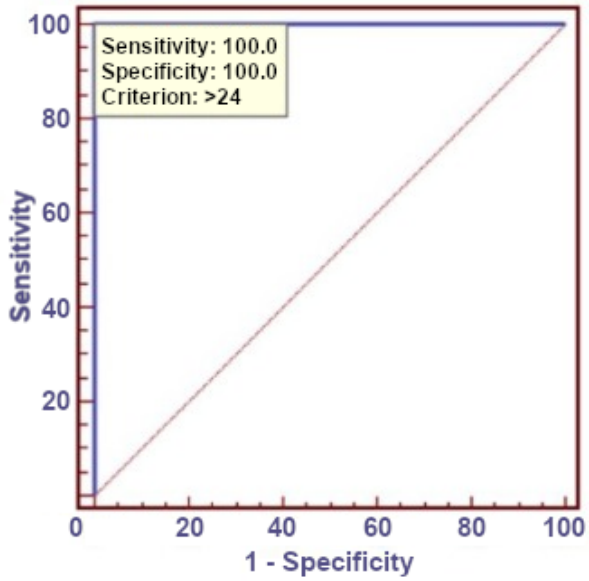

Figure 2. ROC curve of MMP-9

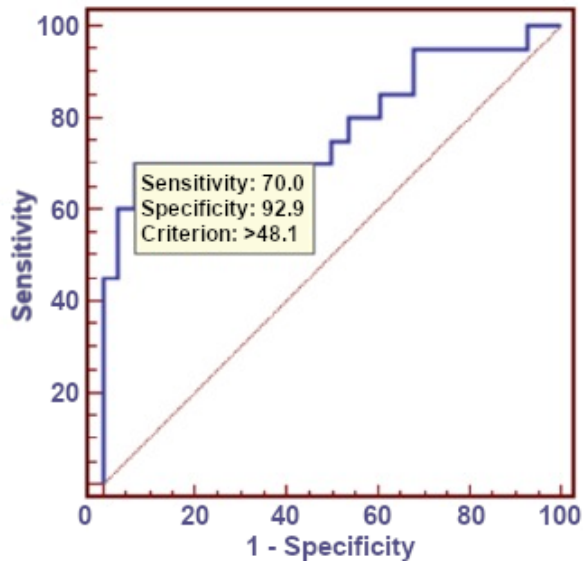

Figure 3. ROC curve of sdLDL-C

lial cell functions by oxidized LDL and a consequent reduction in nitric oxide production. Treating high sdLDL levels restores the normal vasodilator response to acetylcholine [29-31].

Nishikura et al. [25] found that sdLDL-C levels and sdLDL-C/LDL-C and LDL-C/HDL-C ratios were significantly higher, with a high Gensini coronary atherosclerotic score in 72 patients with cardiovascular symptoms for the first time.

Similarly to these findings, in our study, the sdLDL-C level was found to be higher in the patient group with plaque and/ or stenosis compared to the control group. Based on these results and studies, we can say that the relationship between serum cholesterol levels and the risk of coronary artery disease is linear. Although other risk factors (smoking, hypertension, diabetes, etc.) are common in societies with low total and sdLDL levels, the risk of coronary heart disease is low [32].

The study conducted by Yanhong Chen et al. investigated the role of sdLDL in the formation and development of coronary artery disease in type 2 diabetic patients over the age of 65. The sensitivity and specificity values were found to be 78.86% and 73.38%, respectively. Higher sdLDL-C was found to be significantly associated with the development of coronary artery disease in T2DM patients over the age of 65 [33].

Another acute phase reactant most studied in the structure of atherosclerotic plaque is CRP levels. It is known that CRP is an important marker for inflammation in coronary artery disease. However, although CRP has been consistently associated with atherosclerotic cardiovascular disease, the cause-effect relationship has yet to be established.

Our study determined no statistical difference between the study groups in terms of CRP level. However, since hs-CRP was not studied in our research, a significant difference may not have been obtained. Looking at the literature review, it is understood that it is possible to reach a meaningful result by looking at the hs-CRP levels with a more considerable number of patients[34].

Huamin Liu et al. investigated the relationship between hs-CRP, Lp-PLA2, and carotid atherosclerosis. In their study, which included 1982 participants, a significant association was found between hs-CRP and Lp-PLA2 levels and carotid stenosis. These two markers are thought to strengthen the prediction of atherosclerosis [35].

Lp-PLA2, a pro-inflammatory enzyme associated with LDL-C, reflects cardiovascular events in the general population, and low Lp-PLA2 and low HDL-C and high LDL-C levels have been observed. Most of the research data suggested that Lp-PLA2 is a specific marker of vascular inflammation. It is important in predicting CAD in epidemiological studies with large numbers of patients, independent of inflammation markers and known cardiovascular risk factors. In particular, the activities of some phospholipases are closely related to atherosclerosis and are the possible mechanisms in atherogenesis [36].

Our findings in this study determined that Lp-PLA2 levels were higher in the group with the plaque and/or stenosis compared to the control group. This is consistent with the view that the presence of plaque rupture or stenosis is associated with Lp-PLA2 levels.

Rancho Bernardo et al. [37] followed 1077 healthy men and women for 16 years after adjusting for risk factors for CAD. It was determined that CAD developed in 228 individuals with a mean age of 72, the LpPLA2 mass level was lower than the ¼ group, and the CAD was higher in the ¼ group and reported an increased risk. The high number of patients compared to our study and the compatibility of our findings also support this study.

Hyemoon Chung et al. 226 measured Lp-PLA2 levels for the diagnosis of ACS with acute developmental syndrome and showed that the optimum cut-off was 15.41 IU/mL and was released for the diagnosis of ACS, and the specificity was 51.8% and 74%, respectively. In our study we found that plaque stability was improved at the Lp-PLA2 level [38].

Macrophages and regions rich in mast cells were detected in atherectomy samples. These cells can degrade the extracellular matrix by phagocytosis and the proteolytic enzymes they secrete. Enzymes such as plasminogen activators and MMP with collagenase, elastases, and gelatinase degrade cellular ESM components, including strimelizins. They are prone to rupturing by weakening the fibrous capsule. Then, Matrix metalloproteinase, especially MMP-9, facilitates the formation of plaque rupture and myocardial infarction. High MMP-9 levels indicate myocardial infarction and plaque rupture in unstable angina [39].

Our findings in this study determined that MMP-9 levels were higher in the group with the plaque and/ or stenosis and the Lp-PLA2 group than in the control group. This is consistent with the view that the presence of plaque rupture or stenosis is also associated with MMP-9 levels. At the same time, a solid positive correlation was found due to the cross-correlation between MMP-9 and Lp-PLA2 in this study. Therefore, evaluating MMP-9 and Lp-PLA2 levels together may provide much more valuable results in detecting the presence of plaque and/ or stenosis.

Consistent with this study, Alvarez et al. [38] investigated the relationship between serum MMP-2 and MMP-9 levels and symptomatic carotid stenosis in 2004.

A strong correlation was found between high serum MMP-9 concentration and the presence of macrophages in plaques (Spearman rho, 0.45; p=0.004). As a result of the logistic regression analysis, it was emphasized that a previous neurological event and serum MMP-9 levels above 607 ng/ml could be used as a predictive factor for unstable plaque.

Tooran Akbari et al. performed ROC curve analysis on MMP-9 levels and found that these factors have a high discriminatory power in detecting coronary artery disease, which is also consistent with our study. [40].

Bingli Liu et al. evaluated MMP9 as a biomarker for early diagnosis of arterial plaque, as serum MMP9 is an independent factor contributing to carotid artery plaque formation in patients with T2DM. Its sensitivity and specificity were 0.551 and 0.794, respectively, suggesting that tMMP9 may be a useful marker for predicting arterial plaque [41].

CRP did not show a strong correlation with any parameter. There was even a negative correlation with Lp-PLA2. However, the cause-effect relationship has not yet emerged.

Limitations

In order to make these parameters routine, these studies need to be developed with a larger number of patient groups. However, the parameters we evaluated in our study, such as Lp-PLA2, MMP-9 and sdLDL-C, require special equipment, techniques and kits in today's conditions, which limits their use in routine practice. In addition, the use of these parameters in routine practice requires financial resources.

CONCLUSIONS

Consequently, prevention of many risk factors in individuals at risk of coronary artery disease is recommended as the first step in protecting these patients. However, sdLDL-C, MMP- 9, and Lp-PLA2 levels must be associated with atherosclerotic plaques and/ or stenosis and plaques prone to rupture despite tender or calcified plaques. CT and/ or catheter angiography is the gold standard method for evaluating people with coronary heart disease. However, the nephrotoxic effect of contrast agents applied during angiography and the negative effects of radiation to which patients are exposed are also known. Alternative diagnostic tools are always needed to evaluate coronary arteries in people with renal failure and other chronic diseases.

Therefore, as emphasized in this study, it is thought that the evaluation of Lp-PLA2, MMP-9, and sdLDL-C levels, which are compared with the characteristics of atherosclerotic plaque structure, along with CT angiography findings can be used as an alternative to CT angiography in controlling patients at risk and patients who have had previous cardiological interventions. However, these studies need to be developed with a more substantial number of patient groups to make this important goal routine.

ABBREVIATIONS

ACS – acute coronary syndrome

CAD – coronary artery disease

CRP – C-reactive protein

CT – computed tomography

HDL – C- high-density lipoprotein cholesterol

LDL-C – low-density lipoprotein cholesterol

Lp-PLA2 – lipoprotein-associated phospholipase A2

MMP-9 – matrix metalloproteinase-9

sdLDL-C – small dense LDL-cholesterol

TC – total cholesterol

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None.

AUTHORS' CONTRIBUTION

NS – participated in the design of the study, data collection, data analysis, literature review, writing the original draft, reviewing it for important intellectual content, and searching for references.

SM – coordination of the study and participants, organization and planning of tasks, acquisition, analysis, and interpretation of data, participation in the design of the study, writing and reviewing the draft.

DBK – participated in conceptualization, methodology, formal analysis, preparation of the original draft, visualization, searching for and verifying references.

HI – acquisition, analysis, and interpretation of data; writing the original draft.

CONFLICT OF INTEREST

None to declare.

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REFERENCES

1. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA guidelines for coronary angiog raphy. A report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol. 1999;33:1756-824. DOI: 10.1016/S0735-1097(99)00126-6
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics-2011 update: a report from the American Heart Association. Circulation. 2011; 123: 18-209 DOI: 10.1161/CIR.0b013e3182009701
3. Rizzo M, Berneis K. Low-density lipoprotein size and cardiovascular risk assessment. QJM. 2006; 56: 967-976.
4. Eriksson EE, Xie X, Werr J, Thoren P, Lindbom L. Importance of primary capture and L-selectindependent secondary capture in leukocyte accumulation in inflammation and atherosclerosis in vivo. J Exp Med. 2001;194:205-18. DOI: 10.1084/jem.194.2.205
5. Smith JD, Trogan E, Ginsberg M, Grigaux C, Tian J. Decreased atherosclerosis in mice deficient in both macrophage colony-stimulating factor (op) and apolipoprotein E. Proc Natl Acad Sci U S A. 1995;92:8264-8. DOI: 10.1073/pnas.92.18.8264
6. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proc Natl Acad Sci U S A. 1995;92:3893-7. DOI: 10.1073/pnas.92.9.3893
7. Chen L, Chester MR, Redwood S, Huang J, Leatham E, Kaski JC. Angiographic stenosis progression and coronary events in patients with 'stabilized' unstable angina. Circulation. 1995;91:2319-24 DOI: 10.1161/01.CIR.91.9.2319
8. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997;336:1276-82 DOI: 10.1056/NEJM199705013361802
9. Fukuda D, Shimada K, Tanaka A, Kusuyama T, Yamashita H, Virmani R. Comparison of levels of serum matrix metalloproteinase-9 in patients with acute myocardial infarction versus unstable angina pectoris versus stable angina pectoris.Am J Cardiol. 2006 Jan 15;97 (2):175-80. DOI: 10.1016/j.amjcard.2005.08.020
10. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006; 354: 1264-1272. DOI: 10.1056/NEJMoa054013
11. Ai M, Otokozawa S, Asztalos BF, Ito Y, Nakajima K, White CC, et al. Small dense LDL cholesterol and coronary heart disease: results from the Framingham Offspring Study. Clin Chem. 2010; Jun;56(6):967-76. DOI: 10.1373/clinchem.2009.137489
12. Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bienek M, Waltenberger J, et al. C-reative protein in the arterial intima: rol of C-reative protein receptor-dependent monocyte recruitment in atherogenenesis. Arterioscler Thromb Vase Biol. 2000 ;20:2094-9. DOI: 10.1161/01.ATV.20.9.2094
13. Oei H-H S, van der Meer IM, Hofman A, Koudstaal PJ, Stijnen T, Breteler MMB, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke. The Rotterdam Study. Circulation. 2005;111:570 -575. DOI: 10.1161/01.CIR.0000154553.12214.CD
14. Stafforini DM, McIntyre TM, Carter ME, Prescott SM. Human plasma platelet-activating factor acetylhydrolase. Association with lipoprotein particles and role in the degredation of platelet-activating factor. J Biol Chem. 1987;262:4215- 4222. DOI: 10.1016/S0021-9258(18)61335-3
15. Gazi I, Lourida ES, Filippatos T, Tsimihodimos V, Elisaf M, Tselepis AD, et al. Lipoprotein-associated phospholipase A2 activity is a marker of small, dense LDL particles in human plasma. Clin Chem. 2005;51: 2264-2273. DOI: 10.1373/clinchem.2005.058404
16. Persson M, Nilsson J-A, Nelson JJ, Berglund G. The epidemiology of Lp-PLA2: distribution and correlation with cardiovascular risk factors in a population-based cohort. Atherosclerosis. 2007;190:388-396 DOI: 10.1016/j.atherosclerosis.2006.02.016
17. Budoff MJ, Achenbach S, Duerinckx A. Clinical utility of computed tomography and magnetic resonance techniques for noninvasive coronary angiography. J Am Coll Cardiol. 2003; 42:1867-78. DOI: 10.1016/j.jacc.2003.07.018
18. Achenbach S, Ropers D, Hoffmann U. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. J Am Coll Cardiol. 2004; 43: 842-7. DOI: 10.1016/j.jacc.2003.09.053
19. White CS, Kuo D. Chest pain in the emergency department: role of multidetector CT. Radiology. 2007; 245: 672-81. DOI: 10.1148/radiol.2453061481
20. Schuijf JD, Jukema JW, van der Wall EE, Bax JJ. Multi-slice computed tomography in the evaluation of patients with acute chest pain. Acute Card Care. 2007; 9: 214-21. DOI: 10.1080/17482940701589275
21. Ross R. Atherosclerosis is an inflammatory disease. Am Heart J. 1999; 138 (52): 19-20. DOI: 10.1016/S0002-8703(99)70266-8
22. Koenig W, Löwel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the framingham score : ımplications for future risk assessment: results from a large cohort study in Southern Germany. Circulation. 2004;109:1349-1353. DOI: 10.1161/01.CIR.0000120707.98922.E3
23. Kolodgie FD, Burke AP, Skorija KS, Ladich E, Kutys R, Makuria AT, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 2006; 26:2523-2529. DOI: 10.1161/01.ATV.0000244681.72738.bc
24. Schoenhagen P, McErlean ES, Nissen SE. The vulnerable coronary plaque. J Cardiovasc Nurs. 2000 Oct;15(1):1-12. DOI: 10.1097/00005082-200010000-00002
25. Nishikura T, Koba S, Yokota Y, Hirano T, Tsunoda F, Shoji M, et al. Elevated small dense low-density lipoprotein cholesterol as a predictor for future cardiovascular events in patients with stable coronary artery diseaseJ Atheroscler Thromb. 2014;21 (8):755-67. DOI: 10.5551/jat.23465
26. Kunutsor SK, Zaccardi F, Karppi J, Kurl S, Laukkanen JA. Is High Serum LDL/HDL Cholesterol Ratio an Emerging Risk Factor for Sudden Cardiac Death. Findings from the KIHD Study J Atheroscler Thromb. 2017 Jun 1;24 (6):600-608. DOI: 10.5551/jat.37184
27. Moriyama K, Takahashi E. Non-HDL Cholesterol is a More Superior Predictor of Small-Dense LDL Cholesterol than LDLCholesterol in Japanese Subjects with TG Levels <400 mg/dL. J Atheroscler Thromb. 2016 Sep 1;23 (9):1126-37. DOI: 10.5551/jat.33985

28. Robins SJ, Collins D, Nelson JJ, Bloomfield HE, Asztalos BF. Cardiovascular events with increased lipoprotein-associated phospholipase A (2) and low high-density lipoprotein-cholesterol: the Veterans Affairs HDL Intervention Trial.Arterioscler Thromb Vasc Biol. 2008 Jun;28 (6):1172-8. DOI: 10.1161/ATVBAHA.107.160739

29. Corson MA, Jones PH, Davidson MH. Review of the evidence for the clinical utility of lipoprotein-associated phospholipase A2 as a cardiovascular risk marker. Am J Cardiol. 2008;101:51-50. DOI: 10.1016/j.amjcard.2008.04.018

30. Lerman A, McConnell JP. Lipoprotein-associated phospholipase A2: A risk marker or a risk factor? Am J Cardiol. 2008;101:11-22. DOI: 10.1016/j.amjcard.2008.04.014

31. Ferri N, Paoletti R, Corsini A. Lipid-modified proteins as biomarkers for cardiovascular disease: a review. Biomarkers. 2005 Jul-Aug;10 (4):219-37. DOI: 10.1080/13547500500216660

32. Segers D, Helderman F, Cheng C, van Damme LC, Tempel D, Boersma E, et al. Gelatinolytic activity in atherosclerotic plaques is highly localized and is associated with both macrophages and smooth muscle cells in vivo. Circulation. 2007;115:609-16. DOI: 10.1161/CIRCULATIONAHA.106.636415

33. Chen Y, Fu Y, Wang S, Chen P, Pei Y, Zhang J, et al. Clinical significance of neutrophil gelatinase-associated lipocalin and sdLDL-C for coronary artery disease in patients with type 2 diabetes mellitus aged≥65 years. Cardiovasc Diabetol. 2022 Nov 17;21(1):252. DOI: 10.1186/s12933-022-01668-5

34. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003 Jan 28;107(3):499-511. DOI: 10.1161/01.CIR.0000052939.59093.45

35. Liu H, Yao Y, Wang Y, Ji L, Zhu K, Hu H. Association between high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2 and carotid atherosclerosis: A cross-sectional study. J Cell Mol Med. 2018 Oct;22(10):5145-5150. DOI: 10.1111/jcmm.13803

36. Schaloske RH, Dennis EA. The phospholipase A2 superfamily and its group numbering system. Biochim. Biophys. Acta. 2006; 1761: 1246-59 DOI: 10.1016/j.bbalip.2006.07.011

37. Daniels LB, Laughlin GA, Mark J, Bettencourt R, Wolfert RL, Barrett-Connor E. Lipoprotein -associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apperently healthy older population: the Rancho Bernardo study. J Am Coll Cardiol. 2008; 51: 913-919. DOI: 10.1016/j.jacc.2007.10.048

38. Hyemoon C, Hyuck Moon K, Jong-Youn K, Young Won Y, Rhee J, Choi EY, et al.Lipoprotein-Associated Phospholipase A2 Is Related to Plaque Stability and Is a Potential Biomarker for Acute Coronary Syndrome. Yonsei Med J 55(6):1507-1515, 2014. DOI: 10.3349/ymj.2014.55.6.1507

39. Maiolino G, Bisogni V, Rossitto G, Rossi GP. Lipoprotein-associated phospholipase A2 prognostic role in atherosclerotic complications.World J Cardiol. 2015 Oct 26;7 (10):609-20. DOI: 10.4330/wjc.v7.i10.609

40. Tooran A, Soudabeh F, Toktam Kazemi F, Reza F, Rahim R, Movahedi M, et al. Evaluation of MMP-9, IL-6, TNF-α levels and peripheral blood mononuclear cells genes expression of MMP-9 and TIMP-1 in Iranian patients with coronary artery disease. Cardiovasc Thorac Res. 2023, 15(4), 223-230. DOI: 10.34172/jcvtr.2023.31844

41. Liu B, Su L, Loo SJ, Gao Y, Khin E, Kong X, et al. Matrix metallopeptidase 9 contributes to the beginning of plaque and is a potential biomarker for the early identification of atherosclerosis in asymptomatic patients with diabetes. Front Endocrinol (Lausanne). 2024 Apr 10;15:1369369. DOI: 10.3389/fendo.2024.1369369.