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Comparison of inflammatory biomarkers for detection of coronary stenosis in patients with stable coronary artery disease

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Abstract. – BACKGROUND: The objective of the current study was to evaluate the role of various inflammatory biomarkers in detection of coronary stenosis in patients with stable coronary artery disease (CAD) and healthy people.

METHODS: A total of 111 patients with stable coronary artery disease, and 66 healthy subjects were enrolled in the study. Serum levels of lipoprotein-associated-phospholipase A2 (Lp-PLA_2), high-sensitivity C-reactive protein (hs-CRP), and myeloperoxidase (MPO) were measured to compare patient and control groups.

RESULTS: Baseline characteristics were similar between healthy and patient groups, with the exception of age. ANCOVA and log-transformed data of inflammatory biomarkers revealed that, Lp-PLA_2 ($p < 0,001$) and hs-CRP ($p < 0,05$) levels in all patient groups were significantly higher than in the control group. Conversely, there was no significant difference in MPO levels among groups.

CONCLUSIONS: In stable CAD patients, serum Lp-PLA_2 levels are more compatible than hs-CRP and MPO levels in the detection of coronary stenosis.

Key Words:
Atherosclerosis, Coronary artery disease, Lp-PLA_2, MPO, hsCRP.

Introduction

Atherosclerosis is a multifactorial disease, and inflammation plays an important role in atherogenesis and plaque vulnerability[1]. It has been established that vulnerable plaques are the underlying cause of most coronary events. It is important to identify patients at risk of coronary artery disease (CAD) for clinical diagnosis, treatment and prognosis. Because conventional risk factors do not explain the changes in atherosclerosis, efforts to identify vulnerable plaques have focused on developing novel biomarkers[2].

Lipoprotein-associated phospholipase A2 (Lp-PLA_2) is an enzyme that degrades oxidized phospholipids into low density lipoprotein cholesterol (LDL-C), leading to the formation of proinflammatory and cytotoxic products. Because of its high specificity for vascular inflammation, it is a novel biomarker and has been identified as a potential novel therapeutic target. Experimental studies have shown a direct causal link between Lp-PLA_2-mediated pathways and plaque inflammation and rupture. It is commonly seen in advanced rupture-prone and ruptured plaques[3].

C-reactive protein (CRP) is an acute phase reactant that is found in circulation. CRP is synthesized by the liver in response to factors released by adipocytes (TNF-alfa and other adipocytokines). It is a non-specific biomarker, and it can become elevated due to many non-cardiac inflammation. Because CRP cannot show where the inflammation is located in the body, other tests are needed to find the cause and location of the inflammation. Studies showed that higher than 2.4 mg/l high-sensitivity CRP (hs-CRP) levels have been associated with a doubling of risk for coronary events[4]. CRP should be measured as hs-CRP when assessing cardiovascular risk because it is designed for greater accuracy in measuring very low levels of CRP.

Myeloperoxidase (MPO) is a leukocyte-derived enzyme that is essential for immune system and inflammatory process. Several mechanisms may explain the proatherogenic effects of MPO,

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including LDL oxidation, inactivation of HDL, endothelial dysfunction due to a decrease of nitric oxide bioavailability, activation of metalloproteinase 7, and an increase in vascular cell apoptosis[5].

The aim of this study was to compare Lp-PLA2, MPO and hs-CRP levels in the detection of coronary stenosis in patients with CAD and healthy controls.

Patients and Methods

Study Population

A total of 224 patients (154 men and 70 women) suffering from chest discomfort (range: 35-85 years, average 57 years) were enrolled in the study. Out of these 224, 158 were scheduled for coronary angiography because of suspected CAD based on non-invasive assessment. Patients with symptoms of unstable CAD within the last month were excluded to avoid the influence of an acute coronary episode. Exclusion criteria included ongoing infections and autoimmune or other acute inflammatory conditions. Forty-seven patients were later excluded because of cancelled angiography, aforementioned illness or missed blood sampling. An angiographic analysis of the 111 subjects was performed by the investigators. The severity of coronary stenosis was estimated by visual determination. CAD was diagnosed if there was at least one lesion with > 50% stenosis in luminal diameter on coronary angiography according to the American College of Cardiology/American Heart Association lesion classification. Lesions were classified into the four groups according to the number of affected vessels: normal coronary angiogram or 1, 2 or 3 vessel diseases. A total of 66 healthy volunteers were used as the control group, and angiography was performed on 32% of them based on non-invasive diagnostic assessment.

Risk factors including high blood pressure, fasting blood glucose level, smoking and lipid status were assessed at the time of enrollment. Diabetes was defined as fasting serum glucose values ≥ 126 mg/dL on 2 or more occasions, or 2-hour serum glucose level > 200 mg/dL after an oral glucose tolerance test. Participants were accepted as hypertensive if they had a blood pressure ≥ 140/90 mmHg on two or more occasions or were already on antihypertensive therapy. If the patients had been given lipid-lowering therapy or had a history of total cholesterol levels > 240 mg/dL, they were accepted as hyperlipidemic. The research was approved by the local Ethics Committee, and all participants gave written informed consent before entering the study.

Laboratory Analysis

Blood samples were run after an overnight fasting of 12 h, and sera were separated by low-speed centrifugation for 15 min. Samples were immediately stored at -85°C for biomarkers. Levels of serum total cholesterol (TC) and serum triglycerides (TG) were estimated by enzymatic methods using an Abbot Architect C16000 autoanalyzer (Diamond Diagnostics Inc, Boston, MA, USA) with original reagents. HDL-C was measured by the dextran sulfate-Mg^{+2} precipitation method, whereas LDL-C was calculated by the Friedewald's formula. Apolipoprotein A-I (Apo A-I) and apoprotein B (Apo B) levels were assessed by immunonephelometry using Date Behring (BN II, Marburg, Germany) and its original reagent. The results are expressed in mg/dl of serum.

Biomarker Analysis

Lp-PLA_2 mass was determined in serum by a dual monoclonal antibody immunoassay standardized to the recombinant PAF-AH PLAC test (diaDexus Inc, San Francisco, CA, USA)[6]. The assay range is 1-1000 ng/mL, and the median value in healthy adults is 218 µg/L. Plasma hs-CRP levels were measured by an immunoturbidimetric method using a commercially available kit (Beckman Coulter, Krefeld, Germany) with the manufacturer's reagents. The detection limit for hs-CRP was 0.02 mg/L; intra- and inter-assay coefficients of variations were 5.2%. MPO concentrations were measured in plasma using a sandwich ELISA for human MPO according to the manufacturer's protocol (Hycult Biotechnology (Hycult Biotechnology (Hycult Biotech Inc, Uden, the Netherlands). The intra-assay coefficient of variance was < 10%. All plasma samples were analyzed in duplicate in the same run.

Statistical Analysis

Data are presented as the mean±SD for normally distributed continuous variables, as the median (IQR) for non-normally distributed continuous variables and as percentages for categorical variables. Normality was tested using the Kolmogorov-Smirnov test. hs-CRP and MPO were not normally distributed; therefore, these values were logarithmically transformed in order to approach normal distribution and obtain equal

variances. Analysis of variance (ANOVA) was used to evaluate unadjusted differences in continuous variables among the four groups. Jonckheere-Terpstra's test was applied to evaluate whether there were trends in the data with respect to severity of coronary artery disease. Comparisons between categorical variables were performed with a chi-square test or Fisher's exact test as appropriate. Analysis of variance with covariates (ANCOVA) was used to evaluate differences in inflammatory biomarker levels and biochemistry indices between groups after adjustment for all the variables that were significantly different among the groups. The simple logistic regression analysis was used to assess univariate associations between the Lp-PLA_2, hs-CRP, MPO and CAD status as a number of vessel diseases. In addition, a multiple logistic regression analysis was used to assess the independent adjusted relationship between these indices and CAD status with independent variables being those that were significantly different among the patient groups. Odd's ratios (OR) with 95% confidence intervals were calculated per one increase in standard deviation of inflammatory markers and the demographic indices and per one category variation in CAD severity. The specific relationship between vessel disease and inflammatory markers was assessed by Spearman's rank correlation. A p value < 0.05 was considered to indicate statistical significance; all tests were two-sided. The SPSS 16.0 statistical software package (SPSS Inc, Chicago, IL, USA) was used for all calculations.

Results

Participants were predominantly male and overweight, and some were taking medications for CAD, hypertension, dyslipidemia and diabetes. MPO measurements were not performed in eleven patients due to technical problems. Table I presents the results of unadjusted comparisons regarding baseline characteristics in four subgroups that were divided based on the angiographic findings involved in the study. The patients with diabetes mellitus and smoking were similar among groups. Total cholesterol, LDL-C, TC/HDL-C ≥4.5, hypertension, and male gender

Table I. Distribution of demographic features and lipid profiles in individuals with CAD in according to angiographic findings and without.

Parameters	Healthy control (n: 66)	1 vessel plugged (n: 31)	2 vessels plugged (n: 54)	3 vessels plugged (n: 26)
Age (year)	53 ± 12	60 ± 8[a]*	63 ± 10[b]***	60 ± 8[c]*
BMI (kg/m^2)	30 ± 5	30 ± 6	29 ± 4	29 ± 3
Waist circumference (cm)	106 ± 13	104 ± 12	102 ± 12	101 ± 10
Gensini Score	18 ± 19	32 ± 26	35 ± 43	33 ± 38
Gender, male, n (%)	39 (59)	16 (52)	39 (72)	23 (89)[c]**
Hypertension, n (%)	14 (30)	18 (58)[a]*	28 (52)	9 (35)
DM, n (%)	8 (12)	4 (13)	9 (17)	6 (23)
Smoking, n (%)	11 (17)	4 (13)	15 (28)	8 (31)
Dyslipidemia n (%)	1 (2)	6 (21)[a]*	4 (8)	2 (8)
TC/HDL-C ≥ 4.5	27 (41)	18 (67)	31 (63)	19 (73)[c]*
TG (mg/dL)	122 ± 55	144 ± 66	143 ± 84	130 ± 60
TC (mg/dL)	177 ± 28	200 ± 45[a]*	187 ± 37	175 ± 41
LDL-C (mg/dL)	111 ± 24	129 ± 35[a]*	121 ± 32	117 ± 33
HDL-C (mg/dL)	42 ± 10	41 ± 10	39 ± 12	32 ± 6[c]*******[f]*
TC/HDL-C	4.49 ± 1.29	4.99 ± 1.36	5.23 ± 1.84[b]*	5.62 ± 1.55[c]***
Apo AI (mg/dL)	142 ± 28	161 ± 35	147 ± 31	137 ± 23[c]*
Apo B (mg/dL)	98 ± 18	106 ± 33	102 ± 27	96 ± 28
Apo B/Apo AI	0.71 ± 0.18	0.67 ± 0.18	0.73 ± 0.25	0.72 ± 0.25

Data are presented mean ± SD for normally distributed continuous variables and median (IQR) for non-normally distributed continuous variables. Comparison of healthy control group vs (a) 1 vessel vs (b) 2 vessel vs (c) 3 vessel plugged; Comparison of patients with 1 vessel plugged vs (d) 2 vessel, vs (e) 3 vessel plugged and comparison of patients with 2 vessel plugged vs (f) 3 vessel plugged. *0.0 5 > p, **0.01 > p, ***0.005 > p.

Table II. Distribution of inflammatory biomarkers in individuals with CAD in according to angiographic findings and without.

Parameters	Healthy control (n: 66)	1 vessel plugged (n: 31)	2 vessels plugged (n: 54)	3 vessels plugged (n: 26)
Lp-PLA_2 (µg/L)	249 ± 118	365 ± 82[a]**	375 ± 92b**	331 ± 115[c]**
hs-CRP (mg/L)	2.6 (0.3-17)	5.1 (0.2-26)	9.6 (0.4-48)[b]**	11.6 (0.5-40)[c]*
MPO (µg/L)	32 (61-269)	79 (32-686)	109 (19-876)	87 (4-482)
Distribution in multivariable adjusted model[#]				
Log Lp-PLA_2 (ng/mL)	2.25 (2.19-2.32)	2.55 (2.51-2.59)[a]**	2.59 (2.56-2.61)[b]**	2.57 (2.52-2.61)[c]**
Log hs-CRP (µg/dL)	2.24 (2.10-2.38)	2.45 (2.25-2.66)[a]*	2.61 (2.47-2.76)+*	2.60 (2.41-2.80)[c]*
Log MPO (µg/L)	2.04 (1.97-2.11)	1.98 (1.85-2.11)	2.01 (1.90-2.13)	1.89 (1.70-208)

Data are presented mean ± SD for normally distributed continuous variables and median (IQR) for non-normally distributed continuous variables. [#]For all inflammatory markers, analyses were performed on the means of log-transformed values with 95 % confidence internal (Cl) and , the association between inflammatory biomarkers levels with severity of coronary artery disease after adjustment for baseline factors including age, sex, hypertension diabetes, smoking, BMI, waist circumference and TC/HDL-C ratio. Comparison of healthy control group vs (a) 1 vessel vs (b) 2 vessel vs (c) 3 vessel plugged *0.0 5 > *p*, **0.001 > *p*.

in patients with at least 1 vessel disease were higher than in the control group. The mean age was higher in patient groups, whereas waist circumference, body mass index and Gensini score were not significantly different. A significant decrease in HDL-C and apo AI levels was detected in patients with 3-vessel disease compared to those of the control group. However, plasma TG, apo B levels and the ratio of apo B/AI did not differ significantly among the study groups.

An unadjusted comparison (ANOVA) revealed that plasma Lp-PLA_2 levels for all groups were significantly higher than in the control group ($p < 0.001$), but hs-CRP levels were only higher in the 2-vessel disease group (Table II). Plasma MPO levels were lower in the control group compared to each vessel disease category, but this difference was not significant. In patient groups, inflammatory biomarker levels showed insignificant differences regardless of the number of vessels.

Taking into account the differences among groups (ANCOVA) and log-transformed data of inflammatory biomarkers, Lp-PLA_2 ($p < 0.001$) and hs-CRP ($p < 0.05$) levels in all patient groups remained significantly higher than in the control group. Conversely, there was no significant difference in MPO levels among groups, after adjusting for covariates including age, sex, hypertension, diabetes, smoking, BMI, waist circumference and TC/HDL-c ratio ($p > 0.05$) (Table II). Figure 1 demonstrates that there was a trend toward elevated plasma levels of Lp-PLA_2 and hs-CRP in patients with a higher number of vessel disease, with the exception of the 3-vessel disease group. Although the level of Lp-PLA_2 remained unchanged ($p < 0.001$) after covariate adjustment, the level of hs-CRP decreased ($p < 0.05$).

As seen in Table III, the results of univariate logistic regression analysis for each of the biomarkers showed that Lp-PLA_2 and hs-CRP parameters could discriminate CAD but not the severity of the disease. Adjusted multiple logistic regression analysis indicated that inflammatory biomarker levels continued to be independently associated with CAD presentation and confirmed a failure to project disparity in the number of diseased vessels.

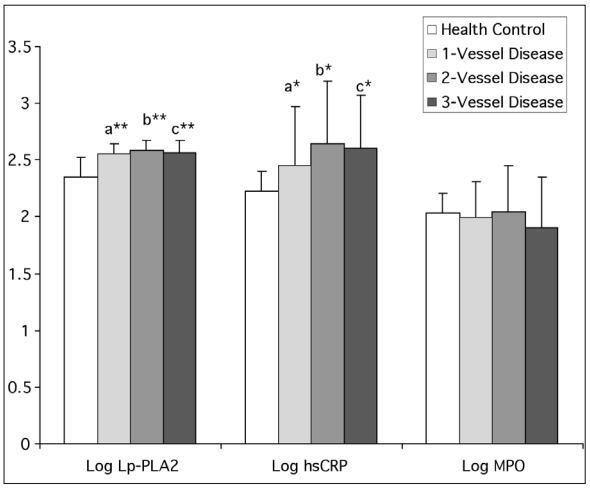

Figure 1. Mean (+SD) Log Lp-PLA_2, Log hs-CRP and Log MPO plasma levels in study group classified according *There is statistically significant difference ($p < 0.05$); **There is statistically significant difference ($p < 0.001$).

Table III. Prediction of CAD severity by univariate and multivariate logistic analysis for inflammatory marker levels in individual with case (n = 111) and control (n = 66) groups.

Variable	Odd's Ratio	% 95 CI	p
Lp-PLA_2	1.02	1.009-1.035	0.001
hs-CRP	19	0.100-3600	0.267
MPO	0.99	0.991-1.006	0.736
Multivariable adjusted model[#]			
Lp-PLA_2	74	8-720	0.002
hs-CRP	0.16	0.06-0.462	0.001
MPO	0.48	0.11-2.10	0.143

Ors indicate relative risk for a change in one standard deviation. [#]Adjusted for age, sex, hypertension diabetes, smoking, BMI, waist circumference and TC/HDL-C ratio.

Table IV summarizes the Spearman correlation coefficients for inflammatory biomarkers among the groups. In both 2-vessel disease and all patient groups, Lp-PLA_2 appeared to be positively associated with the variations of plasma hs-CRP, and the association was clearer in latter group ($p < 0.01$). This relationship was also demonstrated in patients with CAD as shown in Figure 2. Additionally, a positive correlation between plasma MPO and hs-CRP levels was observed in all patient groups.

Table IV. Spearman correlation coefficients for biomarkers in study groups.

Study groups	Lp-PLA_2	hs-CRP
Health control (n = 66)		
Lp-PLA_2	–	–
hs-CRP	0.182	–
MPO	0.146	-0.077
1-Vessel disease (n = 31)		
Lp-PLA_2	–	–
hs-CRP	0.276	–
MPO	-0.65	0.164
2-Vessel disease (n = 54)		
Lp-PLA_2	–	–
hs-CRP	0.285*	–
MPO	-0.090	0.254
3-Vessel disease (n = 26)		
Lp-PLA_2	–	–
hs-CRP	0.200	–
MPO	0.049	0.326
Total patients with CAD (n = 111)		
Lp-PLA_2	–	–
hs-CRP	0.275**	–
MPO	-0.049	0.244*

*There is statistically significant difference ($p < 0.05$); **There is statistically significant difference ($p < 0.01$).

Discussion

Despite considerable progress in treating CAD, it remains a major cause of mortality and morbidity across the world. Identifying those at risk is important for early diagnosis and treatment. Thus, investigators have focused on promptly identifying vulnerable plaques, which are responsible for most of the coronary events[7].

In our study, we assessed the value of a number of inflammatory biomarkers – namely, Lp-PLA2, hs-CRP, and MPO – in the detection of coronary stenosis among healthy people and established CAD patients. In addition, we analyzed the diagnostic values of various biomarkers in terms of CAD.

Male gender was predominant in this investigation. It was observed that CAD commonly occurred in the male cohort, especially in younger

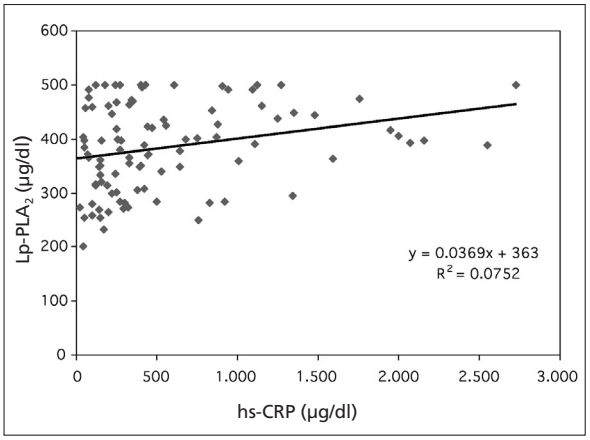

Figure 2. Mean (+SD) Log Lp-PLA_2, Log hs-CRP and Log MPO plasma levels in study group classified according *There is statistically significant difference ($p < 0.05$); **There is statistically significant difference ($p < 0.001$).

men. While the mean age was lower in the control group, smoking, diabetes and hypertension, which are known coronary risk factors, were similar between the control and patient groups. Food habits were also an important factor in terms of the development of CAD. TC/HDL-C ratio was significantly higher in patient groups than in the control due to very low HDL-C levels, especially in the 3-vessel disease group ($p <$ 000.5). A positive correlation between adipose tissue level (BMI, waist circumference) and hs-CRP was found. It was assumed that elevation of hs-CRP might be due to vascular inflammation.

Lp-PLA_2 is a vascular-specific biomarker. Many experimental and epidemiologic studies have shown that elevated Lp-PLA_2 levels are associated with an increased risk for initial coronary events, recurrent coronary events and stroke in secondary prevention[6,8]. The WOSCOPS study, which referred to a male cohort with hyperlipidemia, demonstrated an association between Lp-PLA_2 levels and coronary heart disease[9]. This association was observed only in patients with low cholesterol level in the ARIC study[10], whereas it was not an independent predictor of cardiovascular events in the Women's Health Study[11]. Conversely, Brikalis et al.[12] found increased Lp-PLA_2 levels in patients with established CAD and subsequent coronary events[12].

In our study, the Lp-PLA_2 level was significantly higher in all patients groups compared to the control. This association was correlated with the traditional risk factors, according to multiple logistic regression analysis ($p < 0.001$), but was not correlated with the number of affected vessels.

CRP, an acute phase reactant, may be a biomarker for proinflammatory milieu and a direct risk factor for coronary events[13]. Currié et al[4] concluded that CRP was a relatively moderate predictor of CAD. We observed significant positive correlation between hs-CRP and the CAD group, which was not associated with the risk factors for CAD or the number of affected numbers.

Another objective of this research was to assess the association between MPO levels and the severity of CAD. The increased MPO level is now recognized as a powerful prognostic determinant of myocardial infarction[5,14]. Although they relied on a small group of patients, Duzgunçinar et al[15] found a positive correlation between CAD severity and MPO levels assessed by Gensini scoring. However, a great deal of other studies revealed inconsistent results in terms of severity and prognosis between CAD and MPO levels[16-19]. Our findings agree with the aforementioned literature.

This study is limited by the heterogeneity of the participants, especially in the control group and in terms of the age of the patients.

Conclusions

The likelihood ratios of MPO and hsCRP for the diagnosis of premature coronary atherosclerosis were lower than Lp-PLA2. Lp-PLA2 is a more specific biomarker, and thus, it might be used for the diagnosis of premature atherosclerosis.

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