ORIGINAL RESEARCH

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The relationship between lipoprotein(a) and coronary artery disease, as well as its variable nature following myocardial infarction

Abstract

Purpose: The present study aimed to investigate the relationship between the severity of coronary artery disease (CAD) and level of Lipoprotein (LP)(a).

Methods: The study included 52 CAD patients and a control group consisting of 38 individuals. The patients were classified into three groups based on the clinical form of CAD (stable angina pectoris, SAP, unstable angina pectoris, UAP, and myocardial infarction, MI), and were further divided into three groups based on CAD severity (1-, 2- and 3-vessel). Serum Lp(a) levels were monitored 4, 8, and 24 h, 10 and 30 days following acute MI in 18 patients.

Results: Based on regression analysis, Lp(a) was not correlated with other lipoproteins or with risk factors of CAD, such as body mass index, smoking, family history, diabetes, age, gender, and hypertension ($r = 0.08-0.22$). 72% of the patients in the CAD group and 24% of the control group had an Lp(a) level $>30 \text{ mg dL}^{-1}$ ($P = 0.004$), and Lp(a) levels were higher in 3-vessel patients than in 2-vessel and 1-vessel CAD patients (86% *vs.* 68%, $P = 0.02$ and 86% *vs.* 62%, $P=0.01$, respectively). Serum Lp(a) levels were higher in the UAP and MI groups than in the SAP group ($48 \pm 44.7 \text{ mg dL}^{-1}$, $49 \pm 36.1 \text{ mg dL}^{-1}$ and $31.2 \pm 22.3 \text{ mg dL}^{-1}$, respectively, $P=0.02$). Lp(a) levels increased after acute MI, and reached peak levels 10 days post-MI (41% increase, $P=0.001$) and remained considerably elevated (18%) 30 days post-MI ($P=0.01$).

Conclusion: Serum Lp(a) was higher in the UAP and MI patients in comparison with the SAP patients, and was higher in 3-vessel CAD in comparison with 1- and 2-vessel CAD patients.

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Lipoprotein (Lp)(a) is a macromolecule with a structure similar to that of low-density lipoproteins (LDL-C), to which apolipoprotein(a) antigen is bound [1]. Epidemiological studies show that Lp(a) is an independent risk factor for the development of premature coronary artery disease (CAD) and cerebrovascular disease, and that, at high levels, it is correlated with atherosclerosis [2-6]. The atherogenic potential of Lp(a) is thought to be associated with inhibition of plasmin formation and fibrinolysis via competitive inhibition by plasminogen-like apo(a) [2]. Details of the metabolism, function, evolution and the regulatory mechanism of serum levels of Lp(a) are not yet known.

Several studies have clearly shown a correlation between lipoprotein lipid fractions and CAD [7-10]. The results of two studies on the relationship between Lp(a) levels and CAD report conflicting information [7,8]. The aim of the present study was to investigate the relationships between the severity of CAD and its clinical profile, quantitative measurements of lipoproteins and the risk factors for CAD. Myocardial infarction is well known to influence lipid concentrations [9] and the variable nature of Lp(a) following myocardial infarction (MI) is not clearly understood. The second part of this study aimed to investigate the variable nature of Lp(a) and determined the most appropriate time for Lp(a) measurement after MI.

Materials and Methods

The study included 52 patients (32 male and 20 female; mean age: 57 ± 6 years) diagnosed with CAD based on coronary angiography between 2001 and 2002. In all, 38 (24 male and 14 female) healthy individuals (mean age: 55 ± 8 years) with normal physical examination, electrocardiography and echocardiography results and no complaints at rest nor on exercise were included as the control group. The control group was selected based on clinical criteria that would put them at low risk of CAD. In addition they had lower incidence of hypertension and smoking.

Patients with a serious renal, hepatic, or thyroid disease were excluded from the study. The criteria for diagnosing MI was typical chest pain, a creatine kinase level twice that of normal, and the presence of ≥ 1 mm of ST segment elevation in two adjacent extremity leads and ≤ 2 mm elevation in two adjacent precordial leads. Unstable angina pectoris was defined as angina pectoris that occurred at rest or upon very mild physical exercise, or that had become longer and more severe within the previous 4 weeks.

Selective coronary angiography was performed on the patients. Coronary angiography results were evaluated by two independent researchers who were blinded to the serum Lp(a)

analyses. In coronary angiography, marked narrowing was defined as $>50\%$ reduction in the diameter of the left anterior descending (LAD), circumflex (Cx), or right coronary artery (RCA). To determine the severity of CAD, patients were classified as 1-vessel, 2-vessel, or 3-vessel CAD cases.

Blood samples were obtained from all the patients after a 12-h fasting period. Total cholesterol (TC) and triglyceride (TG) analyses were carried out with enzymatic methods using the cholesterol enzymatique color II reactive and triglycerides enzymatique trinder II reactive (Biotrol, Paris). High-density lipoproteins (HDL-C) quantification was performed with CHOLHDL (Mg-dextran sulfate) reactive (Sclavo, Sovicille, Italy) via enzymatic measurement of the remaining cholesterol in the supernatant following precipitation of very-low-density lipoprotein (VLDL) and LDL-C. The Friedewald formula was used to determine VLDL and LDL-C values: $LDL - C = [TC] - [HDL - C] - [TG/5 = VLDL]$ [10]. Blood samples obtained for serum Lp(a) measurement were separated from the serum by centrifugation for 30 min, and then were stored in a deep freezer at -80°C . Lp(a) values were determined using the radioimmunoassay technique and Pharmacia Diagnostics AB kits (Uppsala-Switzerland)—an immunoradiometric method that employs two different monoclonal antibodies. During incubation the apo(a) anti-apo(a) ^{125}I -antibodies and the solid phase react with anti-apo(a) antibodies bound to a microSepharose. The resulting antibody-antigen complex is added to the dissociation solution, centrifuged, and separated from the marker. The radioactivity measured in the pellet and the apolipoprotein concentrations are directly proportional. The range of the measurement is 16.8-840 U apo(a) L^{-1} . Apo(a) corresponds to approximately 1 mg L^{-1} of Lp(a).

In the second part of this study, 18 patients, aged 51-79 years, were diagnosed with acute MI based on typical chest pain that lasted more than 30 min, ECG findings, and changes in cardiac enzymes. To determine the variation in serum Lp(a) after MI, serum Lp(a) values were measured within the first 4 h of the onset of chest pain (range: 1.45-3.55 h; mean: 3.15 h), and at 8 and 24 h, and 10 and 30 days after the onset of chest pain. Statistical analysis was performed using SPSS v.11.0 (SPSS, Inc., Chicago). Continuous variables with normal distribution were presented as mean $\pm$ standard deviation. Median value was used in variables without normal distribution. Differences in the quantitative variables with and without normal distribution between the two groups were evaluated with Student's t-test and Mann-Whitney U test respectively. Differences in the qualitative variables were evaluated with the chi-square test. Stepwise logistic regression analysis was used to analyze the independent risk factors of CAD. Analysis of Vari-

TABLE 1. Clinical and demographic characteristics of the patients and controls.

	Controls (n = 38)	Patients (n = 52)	P
Age (years)	55.4 ± 8.1	57.5 ± 4.7	SI
Male	58.7 ± 7.3	60.8 ± 5.2	SI
Female	52.5 ± 3.4	55.3 ± 6.1	SI
Gender (female/male)	14/24	20/32	SI
Height (m)	1.64 ± 0.07	1.63 ± 0.09	SI
Weight (kg)	71.6 ± 8.4	70.8 ± 10.2	SI
BMI (kg m ⁻²)	27.1 ± 3.5	26.3 ± 4.1	SI
Family History (%)	3 (7)	9 (10.9)	SI
Smoking (%)	15 (4.2)	42 (80.7)	0.001
Hypertension (%)	3 (7.9)	12 (23.1)	0.04
Diabetes (%)	2 (5.2)	4 (7.6)	SI

SI: Statistically insignificant.

ance was used for assessing the effect of an explanatory categorical variable on a normally distributed continuous outcome variable. One-way analysis of variance was used to compare groups and multivariate analysis was used to evaluate the simultaneous responses of multiple dependent variables to a single independent variable. The following were included in the multivariate analysis: serum TC, LDL-C, the TC/HDL-C ratio, and Lp(a) levels. $P < 0.05$ was accepted as statistically significant for all the results.

Results

Demographic and clinical characteristics of the CAD patients and the control group are shown in Table 1. There were no differences between the CAD patients and the control group with

TABLE 2. Mean ± SD serum lipid, lipoprotein, and Lp(a) levels in the patients and controls.

	Controls (n = 38)	Patients (n = 52)	P
TC (mg dL ⁻¹)	192.5 ± 39	247.2 ± 21	0.03
TG (mg dL ⁻¹)	181 ± 86	217 ± 34	SI
LDL-C (mg dL ⁻¹)	103 ± 34	132.4 ± 28	0.004
HDL-C (mg dL ⁻¹)	39 ± 8.1	41 ± 9.3	SI
TC/HDL-C ratio	4.82 ± 1.6	5.94 ± 1.5	0.008
Lp(a) mg dL ⁻¹	14.3 (9.1-93.7)	42.8 (9.8-95.2)	0.002

SI: Statistically insignificant.

regard to age, gender, BMI and frequency of diabetes, whereas smoking and hypertension were more frequent in the CAD patients. Mean ± SD values for serum lipid, lipoproteins, and median value for Lp(a) in the study population are shown in Table 2. Based on analysis of variance, serum TC, LDL-C, the TC/HDL-C ratio, and Lp(a) levels were significantly higher in the CAD patients than in the control group. There were no significant differences in TG and HDL-C levels between the two groups. One-way analysis of variance showed that serum TC, LDL-C, the TC/HDL-C ratio, and Lp(a) levels were significantly associated with CAD; however, multi-variate analysis showed that only LDL-C and Lp(a) levels were significantly higher in patients with CAD. Regression analysis of the entire population showed no correlation between Lp(a) and other lipoproteins, TC or LDL-C ($r = 0.08-0.22$).

Hypertension, BMI, smoking, family history and diabetes had no influence on Lp(a) levels. Serum Lp(a) levels in the study population varied widely (Figure 1): 72% of the patients and 24% in the control group had Lp(a) levels >30 mg dL⁻¹

FIGURE 1. Distribution of serum Lp(a) frequency in the CAD patient and control groups.

FIGURE 2. Serum Lp(a) variation following MI.

*Variation from baseline: 41%, $P < 0.001$.

**Variation from baseline: 18%, $P < 0.01$.

TABLE 3. Lipid levels relative to the number of arteries with important lesions.

	Controls (n=38)	1-vessel (n=19)	2-vessel (n=18)	3-vessel (n=15)
TC (mg dL ⁻¹)	192.5 ± 3.9	246.3 ± 45	249.8 ± 32	244.6 ± 19
LDL-C (mg dL ⁻¹)	103 ± 34	132.3 ± 24	131.5 ± 44	134.8 ± 3.7
HDL-C (mg dL ⁻¹)	39 ± 8.1	37.5 ± 6.2	42.1 ± 9.2	40 ± 7.4
TC/HDL-C ratio	4.02 ± 1.6	5.72 ± 1.41	5.69 ± 1.47	5.94 ± 1.5
TG (mg dL ⁻¹)	181.4 ± 86	218.6 ± 6.5	217 ± 42	241.2 ± 74
Lp(a) (mg dL ⁻¹)	14.3 (9.1-93.7)	32.1 (9.8-65.4) ^I	41.7 (11.3-74.6) ^{II}	60.2 (14.5-95.2) ^{III}

I and III: P < 0.01; II and III: P < 0.02.

TABLE 4. Distribution of coronary arteries with a significant lesion according to patient subgroups.

		n	%
1-vessel CAD patients	LAD	6	11.5
	Cx	7	13.4
	RCA	6	11.5
2-vessel CAD patients	LAD+Cx	7	13.4
	LAD+RCA	5	9.5
	Cx + RCA	6	11.5
3-vessel CAD patients	(LAD + Cx + RCA)	15	28.8

TABLE 5. Serum lipid levels according to the clinical form of CAD.

	Controls (n = 38)	SAP patients (n = 18)	UAP patients (n = 14)	MI patients (n = 18)
TC (mg dL ⁻¹)	192.5 ± 39	247 ± 22	249 ± 18	242 ± 24
TG (mg dL ⁻¹)	181 ± 86	218 ± 31	212 ± 36	219 ± 33
LDL-C (mg dL ⁻¹)	103 ± 34	136 ± 34	138 ± 42	126 ± 38
HDL-C (mg dL ⁻¹)	39.4 ± 8.1	41 ± 6.2	42 ± 7.4	40 ± 8.9
TC/HDL-C ratio	4.8 ± 1.6	5.9 ± 1.3	6.0 ± 1.7	5.9 ± 1.4
Lp(a) (mg dL ⁻¹)	16.8 ± 14.2	31.2 ± 22.3 ^I	49 ± 36.1 ^{II}	48 ± 44.7 ^{III}

SAP: Stable angina pectoris; UAP: unstable angina pectoris; MI: myocardial infarction patients. I and II: P = 0.02; II and III: P 0.01

(P=0.004). Gender and age did not have a significant effect on serum Lp(a) levels.

The differences in TC, LDL-C, HDL-C, and TG levels, and the TC/HDL ratio between the two groups were not significant; however, serum Lp(a) levels were significantly higher in 3-vessel CAD patients than in 1- and 2-vessel CAD patients. Based on the analysis of the involvement of LAD, Cx, and RCA, 38% of the patients were diagnosed as 1-vessel CAD, whereas 34% and 28% were diagnosed as 2-vessel and 3-vessel CAD, respectively. In all, 66% of the 2-vessel patients had an important lesion in the RCA or Cx coronary arteries, along with an LAD lesion. The percentage of patients with values above that threshold was higher in 3-vessel CAD patients than in 2-vessel and 1-vessel CAD patients (P < 0.02).

The CAD patients were categorized into three groups as follows: stable angina pectoris (SAP) (34.6%), unstable angina pectoris (UAP) (26.9%), and MI patients (38.5%). Lipid levels in these groups are shown in Table 5. Serum Lp(a) levels in the

MI and unstable angina pectoris patients were higher than those in the stable angina pectoris patients. There was no difference between the groups with regard to lipid parameters.

Change in serum Lp(a) levels after acute MI is shown in Figure 2. While serum Lp(a) levels increased during the first 24 hours following MI, they reached peak levels on day 10; there was a 41% increase, as compared with the baseline values, which was statistically significant (P=0.001). While there was a decrease in the Lp(a) level at day 30 day, as compared to the values at day 10 day, it was still 18% higher than the baseline value (P=0.01).

Discussion

Current Lp(a) measurement methods enable quantitative evaluation. Lp(a) has a heterogeneous character, in terms of size and density [11]. The radioimmunoassay method used in the present study was sensitive, but required extensive laboratory work. Among normolipidemic individuals, Lp(a) levels

>30 mg dL⁻¹ were associated with a 1.75-fold increase in MI risk [12] and studies have shown that Lp(a) levels >30 mg dL⁻¹ are associated with severity of coronary artery disease [3,13]. In the present study the serum Lp(a) level was >30 mg dL⁻¹ in 72% of the CAD patients and in 24% of the control group ($P = 0.04$); gender did not affect the rate.

Although the relationships among CAD, TC, LDL-C, HDL-C and TG have been studied extensively, there are fewer studies on the correlations among serum Lp(a), and the presence and severity of CAD [14-16]. Albers *et al.* showed that high serum Lp(a) levels are important coronary risk factors in patients with a history of MI, particularly among younger patients [17]. In another study, in which 776 Swedish males were monitored for 6 years, the group comprised of fatal or non-fatal CAD patients had higher Lp(a) levels than the control group [18]. In our study, there was a statistically significant difference in the serum Lp(a) level between the CAD and non-CAD cases (42.8 (9.8-95.2) *vs.* 14.3 (9.1-93.7), $P=0.002$). Lp(a) was reported to have a risk value of 2.7 for CAD (95% CI: 1.72-6.4, $P=0.001$).

In the present study, the serum Lp(a) level does not correlate with the other lipoproteins; however, previous studies focusing on the relationship between Lp(a) and other lipoproteins have reported differing results. These conflicting results may be due to the fact that Lp(a) carries a small fraction of serum TC. Among the middle-aged or the elderly with a strong Lp(a) (+), TC concentrations were 5-10 mg dL⁻¹ higher than in people of the same age without a qualitative Lp(a) [19]. This suggests a relationship, though minor, between some mechanisms of Lp(a) anabolism and catabolism, and the mechanisms of LDL-C.

Although niacin lowers both LDL-C and Lp(a), other LDL-C-lowering drugs do not affect Lp(a) and this data supports that hypothesis that LDL and Lp(a) are metabolically independent of each other, and that the LDL receptor does not play a major role in Lp(a) regulation under physiological conditions. Patients with high levels of both LDL-C and Lp(a) were observed to have a 5-fold higher coronary risk [20]. In such cases, it remains unclear if both LDL-C and Lp(a) should be lowered, or if reducing only LDL-C would suffice to make Lp(a) less harmful. Although Lp(a) is similar to LDL in structure, the serum Lp(a) level is thought to be regulated independently. Lp(a) is removed via the LDL receptor pathway, but is bound more weakly than LDL; therefore, in the presence of very high LDL levels, the majority of Lp(a) is removed via pathways that are independent of the receptor and possibly more atherogenic.

Studies on hypertriglyceridemia and Lp(a) concentrations report varying results. This may have been due to apo(a) antigen-masking by TG-rich lipoproteins [2]. A study, which included a healthy normolipidemic population, showed that there was a weak, but significant relationship between Lp(a) and apo(B) levels [12]. Austin and Hokanson did not observe a relationship between Lp(a) and apo(B) levels when lipid concentrations were higher, which may have been due to the combined presence of apo(B) and apo(a) in the Lp(a). Nonetheless, apo(B) and apo(a) levels are independent of coronary risk. In contrast to other studies, Austin and Hokanson found a weak but important inverse correlation between Lp(a) and TG, which they attributed to the presence of apo(a) in lipoproteins containing various APO B100 molecules and more rapid catabolism of apo(a) if bound to TG-rich lipoproteins, as compared to regular Lp(a) [12]. While other studies reported no correlation between Lp(a), and TC, LDL-C, and HDL-C levels, one study reported a weak correlation between TG and Lp(a) [8].

In the current study, no correlation was observed between Lp(a) levels and the other CAD risk factors, such as BMI, hypertension, diabetes, family history, smoking, age and gender. Other studies, which investigated the relationship between Lp(a) and CAD risk factors, have reported weak correlations that cannot be verified [2,3]. While BMI is a strong indicator of other lipoproteins, as shown by previous studies, our study detected no significant correlation between Lp(a) and BMI. Studies focusing on the association between Lp(a), and smoking and diabetes have reported varying results [2,21]. In the current study, no relationship between those parameters was observed. In a recent meta-analysis, it was found that the RR for CAD per 3.5-fold higher Lp(a) level, adjusted for age and sex only, was 1.16 (95%CI, 1.11-1.22), and it was 1.13 (95%CI, 1.09-1.18) following further adjustment for systolic blood pressure, smoking, history of diabetes and total cholesterol [22].

The current study also investigated the association between the serum Lp(a) level and CAD severity. Lp(a) levels were higher in 3-vessel patients than in 1- and 2-vessel cases. Although this method, where coronary artery lesions were evaluated visually, is subjective, it is an efficient and commonly used clinical method. Novel quantitative angiographic methods have various problems and their efficacy has not been shown by studies investigating the relationship between CAD and CAD risk factors.

In a study in which the severity of CAD was graded based on the presence of atherosclerosis in the proximal, middle, and distal segments, a correlation was noted between CAD

severity, and TC and Lp(a), whereas no relationship was observed with TG [23]. Lp(a) is reported to be an important marker of atherosclerosis [24]. In the present study, more of the 3-vessel CAD cases had an Lp(a) level >30 mg dL⁻¹, as compared with the 1- and 2-vessel cases; however, the number of cases was not enough to allow for subgroup analyses. A significant correlation between the quantitative measurement of serum Lp(a) and angiographically-diagnosed CAD was also observed. This correlation was independent of other lipid parameters and CAD risk factors. Among the 3-vessel CAD patient subgroup in which CAD was angiographically more severe, Lp(a) elevation was more significant.

The results of studies on the relationship between lipoproteins and angiographically evaluated coronary atherosclerosis lack consistency [7,16]. Many studies reported important effects of TC, LDL-C, and HDL, whereas others reported the influence of TG. In the present study, TC, LDL-C, the TC/HDL-C ratio, and Lp(a) had an important effect on the differentiation of patient and control groups; Lp(a) was a better marker than others.

Regarding the classification of CAD relative to its clinical forms, TC, LDL-C, HDL-C, and TG values were similar in the UAP, MI and SAP patients, whereas Lp(a) values were higher in the UAP and MI patients. As the primary pathophysiological factor in the clinical profile of UAP and MI was elevated thrombus and plaque activity, Lp(a) may also play a role in this mechanism [2]. Apo(a) is very similar in structure to plasminogen; however, unlike plasminogen, it is not a zymogen and is not actively converted into fibrinolytic protease. *In vitro* studies have shown that Lp(a) reduces the plasminogen activation associated with streptokinase and tissue plasminogen activator. There is competition between Lp(a) and plasminogen with regard to binding sites on platelets, fibrinogen-fibrin and endothelial cells. The fact that Lp(a) has an antifibrinolytic effect and promotes thrombus formation may explain the observed difference in serum Lp(a) level between the SAP, UAP and MI cases.

Serum Lp(a) level varies significantly between populations if unaffected by such factors as age, gender, diet, cholestyramine and statins, but remains almost constant in each individual [21]. Lp(a) levels have been observed to changes in response to pregnancy, anabolic steroid therapy and surgical interventions [2]. Following acute MI, TC and LDL-C levels drop significantly, whereas TG levels remain the same; however, changes in serum Lp(a) following MI have not been studied [9]. In the present study, after a marginal increase over the first 24 hours following MI, Lp(a) levels increased significantly at 10 days after MI. The underlying reason behind this increase

may be increased synthesis, decreased removal, a combination of both, or variation in the distribution of Lp(a) particles over the intra- and extravascular spaces.

Following acute tissue damage and inflammation, acute phase reactants, such as fibrinogen, alpha-1 antitrypsin, and haptoglobin, increase. Hepatic Lp(a) production may also increase after MI. The role of Lp(a) in tissue damage and its prognostic importance after MI are not yet known. Moreover, there is a possibility that elevated Lp(a) is associated with recanalization of the related infarcted artery. Although this study has the limitation of having no pre-infarction Lp(a) value and no long-term post-MI value, Lp(a), measured within the first few hours of an acute MI, provides a useful baseline value.

In summary, serum Lp(a) levels increased slightly over the first 24 hours after acute MI, peaked by 10 d post MI, and began to decline by 30 d post MI, but remained higher than the baseline value. While some evidence indicates that Lp(a) may have a specific role in atherogenesis, the results of *in vitro* studies have been inconclusive. As our knowledge of Lp(a) increases, new questions arise about its physiological role and pathophysiological function.

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