ACUTE MYOCARDIAL INFARCTION RISK PREDICTED BY SERUM LEVELS OF LIPOPROTEIN (a) IN TURKISH POPULATION

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SUMMARY

Lipoprotein (a) [Lp(a)] is a macromolecular complex found in human plasma and is composed of 1 low density lipoprotein (LDL) particle to which 1 or more molecule of apolipoprotein (a) is covalently linked. Elevated levels of Lp(a) have been associated with acute myocardial infarction (AMI). In this study the serum levels of Lp(a) in patients with AMI compared with control subjects in Türkiye was determined. We determined serum levels of Lp(a) in 72 patients (47 men and 25 women) with clinically, electrocardiographically and biochemically documented AMI, and in 64 control subjects (28 men and 36 women) clinically free of cardiovascular, peripheral or cerebral arterial disease on the basis of history, physical examination and electrocardiographic criteria. Patients with AMI had higher Lp(a) levels than did control subjects (33.9 ± 23.9 vs. 14.1 ± 11.1 mg/dl, $p<0.0001$). The prevalence of Lp(a) excess (defined as >90th percentile of controls) was 55% in patients with AMI. Lp(a) levels were not correlated with other lipid and lipoprotein parameters. Also there was no correlation between serum Lp(a) levels and age and gender of subjects. Our data indicate that Lp(a) is a risk factor for AMI, independent of other lipid and lipoprotein parameters.

Key Words: Lipoprotein (a), Lp(a), Acute myocardial infarction, AMI, apolipoprotein (a)

INTRODUCTION

Lipoprotein (a) [Lp(a)] was first described by Berg in 1963 as a genetic variant of low density lipoprotein (LDL) which is inherited in an autosomal dominant mode (1). Lp(a) is a macromolecular complex found in human plasma and is composed of 1 LDL particle (apolipoprotein B-100) to which 1 or more molecule of apolipoprotein (a) [apo(a)], the specific marker of Lp(a) is covalently linked (1-4). Apo(a) is a glycoprotein that shares considerable homology to plasminogen (5,6). Thus lipoprotein (a) has the structural features of LDL and plasminogen that provides a link between atherosclerosis and thrombosis (2,4).

Coronary artery disease (CAD) is caused by the long-term deposit of blood lipids in coronary arteries which leads to atherosclerosis and necrosis of heart tissue (7). Acute myocardial infarction (AMI) is an acute manifestation of CAD. The risk factors for the development of CAD include increasing age, male sex, cigarette smoking, hypertension (>150/90 mm.Hg), diabetes mellitus, elevated LDL cholesterol and decreased high density lipoprotein (HDL) cholesterol (8). Clinical studies have shown that elevated levels of Lipoprotein (a) are also strongly associated with AMI (9-12).

In this study we examined Lp(a) levels and prevalence of Lp(a) in a group of patients with AMI compared with a control group clinically free of cardiovascular disease.

MATERIALS AND METHODS

Study population: The study group consisted of 72 hospitalized patients with clinically, electrocardiographically and biochemically evident AMI, 47 men and 25 women ages 34-80 years (54 ± 10 years, mean ± S.D.). The control group consisted of 64 subjects, 28 men and 36 women, ages 15-72 years (38 ± 14 years, mean ± S.D.). They were selected as being free of the clinical manifestations of cardiovascular, peripheral or cerebral arterial disease on the basis of history, physical examination and electrocardiographic criteria.

Blood sampling and analysis: Blood analysis performed included creatine kinase and its MB fraction, total cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and Lp(a).

Blood samples were drawn after a 12 hour fasting period in control subjects, and in the morning after admission in patient group.

Blood samples were obtained in tubes with no anticoagulant and centrifuged and the serum obtained stored at -70 C for subsequent analysis.

Creatine kinase blood levels and its MB fraction were measured with optimized reagents from RAICHEM. Total cholesterol and HDL-cholesterol blood levels were determined by "Cholesterol oxidase" method. The precipitating agent used for HDL-cholesterol was phosphotungstic acid with magnesium chloride.

Triglycerides were determined by "Glycerol kinase/glycerophosphate dehydrogenase" method. LDL cholesterol were estimated according to the formula (13):

LDL cholesterol= Total cholesterol - (HDL cholesterol + Triglycerides / 5)

To determine Lp(a) concentrations, an enzyme-linked immunosorbent assay was used. The assay utilizes affinity purified polyclonal antibodies raised against Lp(a).

Statistical analysis: Statistical analysis were performed with MICROSTAT software. Differences in mean values were evaluated by Student's test (unpaired). Correlations were determined by Pearson's correlation coefficient. A "p" value <0.05 was considered significant.

RESULTS

Plasma lipid and lipoprotein concentrations were measured in 64 cotrol subjects and 72 patients with AMI.

We compared lipid and lipoprotein concentrations in the control and AMI groups and found significant differences in Lp(a) levels (p<0.0001) between AMI group (33.9 ± 23.9 mg/dl) and control group (14.1 ± 11.1 mg/dl, mean ± S.D.) Also in AMI group total cholesterol (217 ± 44 vs. 183 ± 35 mg/dl, p<0.0001), triglyceride (183 ± 74 vs 118 ± 62 mg/dl, p<0.0001), and DL cholesterol levels (141 ± 46 vs 109 ± 34 mg/dl, p<0.0001) were higher and HDL cholesterol levels (39 ± 10 vs 50 ± 15 mg/dl, p<0.0001) were lover than control group (Table I).

When men and women were analyzed separately (Table II), Lp(a) levels in men with AMI (35.9 ± 26.9 mg/dl, mean ± S.D.) were higher than male control subjects (12.8 ± 10.9 mg/dl) and the difference was statistically significant (p<0.0001).

Again in men with AMI, total cholesterol (216 ± 51 vs 182 ± 34 mg/dl, p<0.01), triglycerides (186 ± 89 vs 133 ± 60 mg/dl, p<0.01) and LDL cholesterol levels (140 ± 53 vs 110 ± 35 mg/dl, p<0.01) were higher and HDL cholesterol levels were lower (39 ± 8 vs 46 ± 14 mg/dl, p<0.01) than male control subjects.

Lp(a) levels in women with AMI (30.2 ± 16.8 mg/dl, mean ± S.D.) were higher than female control subjects (15.2 ± 11.3 mg/dl) and the difference was significant (p<0.0001) (Table II).

Also in women with AMI, total cholesterol (219 ± 28 vs 184 ± 37 mg/dl, p<0.0001), triglyceride (176 ± 36 vs 106 ± 63 mg/dl, p<0.0001) and LDL cholesterol levels (143 ± 28 vs 109 ± 33 mg/dl, p<0.0001) were higher and HDL cholesterol levels (39 ± 13 vs 54 ± 15 mg/dl, p<0.001) were lower than female control subjects (Table II).

No statistically significant differences were observed in Lp(a) levels between men and women in the control group (12.8 ± 10.9 vs. 15.2 ± 11.3 mg/dl, mean ± S.D., p:NS) and in the AMI group (35.9 ± 26.9 vs 30.2 ± 16.8 mg/dl, mean ± S.D., p:NS).

The correlation coefficients between Lp(a) and lipid and lipoprotein variables are listed in Table III. For control subjects and cases no significant correlations were found between Lp(a) levels and other lipid variables. Also no correlation between Lp(a) levels and age were seen in control subjects (r:0.149, p>0.05) and cases (r:0.093, p>0.05).

Lp(a) frequency distribution curves of the control and AMI groups are highly skewed (Fig. 1). The prevalence of Lp(a) excess was defined as a Lp(a) level greater than 90th percentile of controls. This value was 28.3 mg/dl. In our study, 55% of our patients with AMI had Lp(a) excess.

Table I- Plasma lipid and lipoprotein concentrations in control and AMI group

	Controls	AMI	p Value
No. of subjects	64	72	
Lipoprotein (a)	14.1 ± 11.1	33.9 ± 23.9	<0.0001
Total cholesterol	183 ± 35	217 ± 44	<0.0001
Triglycerides	118 ± 62	183 ± 74	<0.0001
HDL cholesterol	50 ± 15	39 ± 10	<0.0001
LDL cholesterol	109 ± 34	141 ± 46	<0.0001

(Mean ± S.D., mg/dl) AMI: Acute myocardial infarction, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table II- Serum lipid and lipoprotein levels in men and women with AMI and in male and female control subjects

	Controls	AMI	p Value
	Men		
No. of subjects	28	47	
Lipoprotein (a)	12.8 ± 10.9	35.9 + 26.9	<0.0001
Total cholesterol	182 ± 34	216 ± 51	<0.01
Triglycerides	133 ± 60	186 ± 89	<0.01
HDL cholesterol	46 ± 14	39 ± 8	<0.01
LDL cholesterol	110 ± 35	140 ± 53	<0.01

(Mean ± S.D., mg/dl) AMI: Acute myocardial infarction, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table III- Pearson's Correlation Coefficient

	Variable lipoprotein (a)	
	Controls	AMI
No. of subjects	64	72
Ages of subjects	0.149	0.093
Total cholesterol	0.122	0.021
Triglycerides	-0.088	-0.062
HDL cholesterol	0.086	-0.281
LDL cholesterol	0.120	0.093

AMI : Acute myocardial infarction, HDL : High density lipoprotein, LDL: Low density lipoprotein

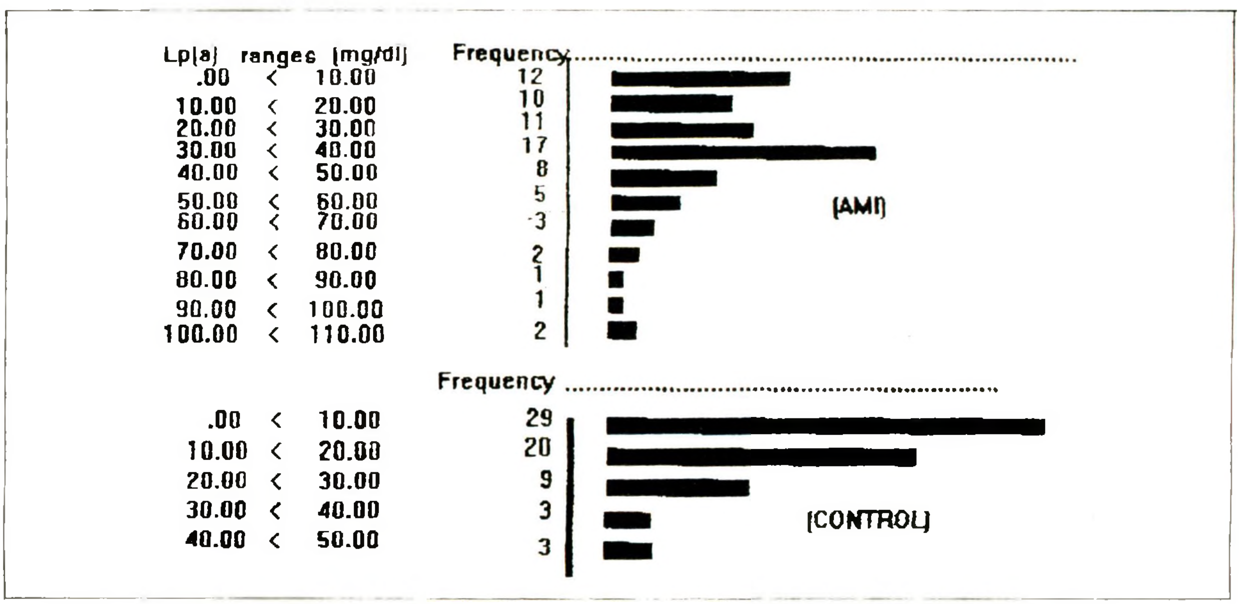

Fig. 1: Frequency distribution of lipoprotein (a) in acute myocardial infarction (AMI) and control groups

DISCUSSION

Lp(a) is a macromolecular complex consisting of 1 LDL particle to which is covalently linked 1 or more molecules of apolipoprotein (a), the specific glycoprotein marker of Lp(a) (1-4). The physiological role of Lp(a) is uncertain, but it has been recognized as a genetically determined lipoprotein associated with an increased prevalence of atherosclerotic vascular disease (2,3,14). The mechanism by which Lp(a) increases the development of atherosclerosis is complex and yet to be resolved. Lp(a) has been thought to have both thrombogenic and atherogenic potential due to its structural properties (2,3,14,15). Several in vitro studies have shown that Lp(a) with its strong homology to plasminogen can inhibit the streptokinase or tissue plasminogen activator (t-PA) mediated activation of plasminogen to plasmin (16-19)and it competes for the binding of plasminogen to its receptors on endothelial cell surfaces (16,20). These would lead to a thrombogenic state thought to occur at the endothelial surface. Thus prothrombotic action of Lp(a) was considered in the etiology of atherosclerosis.

On the other hand the atherosclerotic potential of Lp(a) was assumed to derive from its LDL like component and its capacity to deliver cholesterol to atherogenic sites (21). Lp(a) can traverse the arterial endothelium and accumulate in the intima. Here it goes under a series of structural changes involving the complexation of Lp(a) with glycosaminoglycans or proteoglycans and/or chemical modifications by oxygen free radicals (16,21). Modified Lp(a) would be taken up and degraded by intimal macrophages, causing them to transform into foam cells which are potential precursors of atherosclerotic plaque.

In this study the association between Lp(a) levels and AMI was documented in Turkish population. We have determined that patients with AMI have significantly higher plasma levels of Lp(a) than control subjects ($p<0.0001$) which is comparable with the findings of many investigators (23-27). We used a cut-off level for Lp(a) of 28.3 mg/dl that is >90th percentile levels in the control group and determined that 55% of our patients with AMI had Lp(a) excess. Similar threshold values have been reported in other studies (12,14,24). Thus Lp(a) levels above 28.3 mg/dl can be considered as a risk factor for AMI.

There was no significant correlation between Lp(a) levels and age and gender of subjects in the control and AMI group. This findings was comparable with the findings of Genest et al (27) and Murai et al (28).

Also we have found no correlation between serum Lp(a) levels and other lipid and lipoprotein variables. Also in the study of Hoefler et al (24), no significant correlation was found between Lp(a) levels and other lipid and lipoprotein levels. Thus the independence of Lp(a) from other lipid and lipoprotein concentrations was confirmed (12,26).

As a conclusion Lp(a) can be accepted as an independent risk factor for AMI. In subjects who are at high risk for AMI, the presence of high plasma levels of Lp(a) should encourage the clinician to look for and try to eliminate concurrent modifiable risk factors.

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