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Lipoprotein (a) and Apolipoprotein (a) Isoforms in Patients with Acute Myocardial Infarction

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Abstract: Problem statement: The objective of this study is to determine the relationship between plasma lipoprotein (a) levels and apolipoprotein (a) isoforms in a group of Jordanian patients with Acute Myocardial Infarction (AMI) **Approach:** A total of 90 patients with acute myocardial infarction were compared with 90 age-and sex-matched controls. Lipoprotein (a) levels were measured by ELIZA method and isoforms were identefied by high resolution sodium dodecyl sulfate/agarose gel electrophoresis with western blotting. **Results:** Plasma lipoprotein (a) levels were significantly elevated in patients with acute myocardial infarction as compared to controls (50.18 14.4 mg dL^{-1} Vs 33.1±10.5 mg dL^{-1}; $p<0.001$). S1 isoforms of apolipoprotein (a) was remarkable in addition of other isoforms in acute myocardial infarction than in controls. Apo (a) B isoform is associated significantly with LP (a)-high lipoprotein (a) level (63.1±22.55 mg dL^{-1}) **Conclusion:** Jordanian patients with acute myocardial infarction have higher plasma lipoprotein (a) as compared to controls. The common apo (a) isoform in Jordanian patients with acute myocardial infarction is the small apolipoprotein (a) S1, while the B isoform is associated with high level of plasma lipoprotein (a) level. The contribution of these apolipoprotein (a) isoforms to acute myocardial infarction needs further investigations.

Key words: Lipoprotein (a), myocardial infarction, coronary artery disease, apolipoprotein (a) isoforms, lipid profile

INTRODUCTION

Coronary artery disease is now a major public health in Jordan and is emerging as a major killer. Many conventional risk factors (i.e., smoking, hypertension, diabetes mellitus, hyperlipedemia) have been demonstrated to predict risk of coronary artery disease, not all coronary artery disease can be explained by these risk factors (Dominiczak, 2001). New emerging risk factors implicated in pathogenesis of coronary artery disease. Lipoprotein (a) is considered a new an independent risk factor for coronary artery disease (Kostner *et al*., 1981; Dahlen *et al*., 1986).

Lipoprotein (a) was identified in the plasma by Berg (1963). It is a modified form of LDL in which a large glycoprotein, Apo lipoprotein (a) is covalently bound to apo B by a disulfide bridge (Steyrer *et al*., 1994). The Apo (a) chains contains five cysteine rich domains known as Kringles (McLean *et al*., 1987). The fourth Kringle is homologous with the fibrin-binding domain of palsminogen, LP (a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells. This causes impairments in plasminogen activation, plasmin generation and fibrinolysis (Loscalzo *et al*., 1990). LP (a) also binds to macrophages via a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques (Zioncheck *et al*., 1991). The distribution of LP (a) varies between racial groups. It is normally distributed in African-American populations, however Caucasians, Eastern Asian and Asian Indian populations have LP (a) distributions that are skewed

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towards lower levels (Sandholzer *et al*., 1992). An association between LP (a) excess and ischemic heart disease was initially suggested by cross-sectional and retrospective epidemiological studies. Some studies suggested that LP (a) was an independent risk factor for ischemic heart disease (Bostom *et al*., 1994; Bostom *et al*., 1996), while others showed no significant association (Ridker *et al*., 1993; Cantin *et al*., 1998; Nishino *et al*., 2000). The purpose of this investigation was to determine the relationship between plasma lipoprotein (a) levels and the Apo (a) is forms in group of patients with acute myocardial infarction and normal persons.

MATERIALS AND METHODS

Ninety patients who satisfied the World Health Organization (WHO) criteria for myocardial infarction (WHO, 1997) were recruited from admission to the coronary care unit at Princes Basma Teaching Hospital. All patients enrolled were admitted to the hospital within 12 h of the onset of symptoms. The following patients were excluded from the study: Patients with chronic renal parenchyma disease or nephritic syndrome, concomitant liver disease and patients with disabling terminal disorders. Age and sex matched controls group with no history of ischemic heart disease or family history of premature ischemic heart disease were taken. Cases and controls filled in standard questionnaire about their personal histories, major risk factors, history of ischemic heart disease and provided blood samples for laboratory analysis. Venous blood samples were obtained after 12 h fasting within the first 24 h of myocardial infarction. Blood samples of the controls were taken after 12 h overnight fasting. Blood was transferred into EDTA tubes. Plasma was obtained by blood centrifuged at 1000 rpm for 15 min and samples were immediately separated into aliquot and stored at -2°C until analysis. Cholesterol, triglyceride and high density lipoprotein were quantitatively estimated by enzymatic colorimetric test-CHOD-PAP by commercially available kits provided by ARCOMEX. LP (a) was quantitatively estimated by Enzymatic Immunosorbent Assay (ELIZA). LP (a) phenotypes were determined by immunoblotting using LP (a) phenotyping reagent kit provided by progen, GMBH, Germany). Following reduction of the plasma specimens by the addition of mercaptoethanol, Tris-HCLand SDS, LP (a) isoforms were separated according to their molecular weight by SDS-PAGE or SDS polyacrylamide/agrose gel electrophoresis. The separated proteins were transferred to a nitrocellulose membrane. After blocking free reaction sites, the first antibody, i.e., a polyclonal anti-human LP (a) antibody from sheep bind to Apo (a) is forms. Excess first antibody was removed by washing. By applying the second antibody- an alkaline phosphatase-conjugated anti sheep IgG which binds to the first antibody and subsequent treatment with substrate, the band become visible.

Initially, Utermann identified six types of Apo (a) is forms and named them F, B, S1, S2, S3 and S4 based on their electrophoretic mobility. Later, these is forms were identified based on their kringle (IV) repeat number such as 19, 23, 27, 35 according to Kraft *et al*. (1996). These phenotypes can be interconverted into six different phenotypic group as F (with 11-13 repeats), B (14-16), S1 (17-19), S2 (20-22), S3 (23-25), S4 (>25).

Statistical analysis: All results are expressed as mean and standard deviation. Student t test was used to compare the means of the two groups. Spearman's correlation was used to determine the relationship between LP (a) and other variable. These statistical tests were performed using the Statistical Package for the Social Science (SPSS). The level of significant was $p<0.05$.

RESULTS

The baseline characteristics of patients and controls are summarized in Table 1. Prevalence of classical risk factors (smoking, hypertension and diabetes mellitus) are significantly higher in acute myocardial infarction than the controls. Lipid profiles are summarized in Table 2. Plasma total cholesterol, Low Density Lipoprotein (LDL), triglyceride and lipoprotein (a) levels were significantly elevated in patients (225.4±40.7, 161.4±33.8, 200.19±38.6 and 50.18±14.4 mg dL^{-1}, respectively; compared to controls. High density lipoprotein was significantly decreased in patients compared to controls (59.8±18.5 mg dL^{-1} vesus 87.65±20.6 mg dL^{-1}). The distribution of LP (a) in control subjects was positively skewed with a mean value of 33.11±10.5 mg dL^{-1}, while it is less skewed in patients of acute myocardial infarction.

Lipid and lipoprotein (a) levels in two age groups are shown in Table 3. LP (a) plasma level increases with age in both patients and controls. Mean plasma level of LP (a) was 42.96±17.8 mg dL^{-1} in patients while it was 26.18±13.1 mg dL^{-1} in controls group who are <50 year old and it was 54.95±23.9 mg dL^{-1} in patients and 38.84±18.6 mg dL^{-1} in controls >50 year old. The increase in LP (a) was sex independent in age <50, while it is sex dependent in >50 year. Plasma

levels of cholesterol, low density lipoprotein, triglycerides are significantly increased in both age groups in patients and controls, while HDL plasma level decreased significantly. The effect of age and sex with different major risk factors and lipoprotein (a) levels are shown in Table 4a and b. LP (a) level increased in patients <50 years not significantly in both sexes. The effects of age, diabetes and smoking risk factors increased plasma level of LP (a) in males >50 years old, while hypertension increased LP (a) level insignificantly in males and significantly in females >50 years old. The correlation between LP (a) and different risk factors are shown in Table 5; in control group there is a significant positive correlation between LP (a) and LDL-C (r = 0.25, p = 0.02) and CHL (r = 0.23, p = 0.03) and age (r = 0.28, p = 0.03) but not with TG and HDL-c. These relationships are different between males and females, LP (a) correlated significantly only with TG in male patients (r = 0.31, p = 0.033). LP (a) correlated significantly with age in male control (r = 0.47, p = 0.00) and in female patients(r = 0.54, p = 0.00).The frequency distribution of apo (a) isoforms are shown Table 6. Single band is the commonest phenotype with small isoforms with higher prevalence in patients than controls. The following apo (a) isoforms are elevated with higher percentages in myocardial infarction than control S1 (47.7 versus 41% in control), B-B (4.4 versus 0%), B-S1(2.2 versus 0%), B-S4(2.2 versus 0%) and S1-S4(2.2 versus 0%), disappearance of S1-S1(0 versus 4.4% in controls) and S1-S3(0 versus 2.2%) and decline of null isoform (6.6 versus 15.5%). The relationship between LP (a) isoforms and LP (a) concentration in patients and controls is given in Table 7. The LP (a) phenotype B is associated significantly with high LP (a) level (63.1±22.5 mg dL^{-1}).

Table 1: Baseline characteristics of myocardial infarction patients and controls in Jordan

Variable	Acute myocardial infarction patients (90)	Controls (90)
Age (years)	55 (±10.5)	53 (±9.5)
Sex (M/F)	72/18	72/18
Smoking	73 (83%)	33 (36.6%)
Diabetes mellitus	40 (44%)	8 (7.7%)
Hypertension	24 (26.6%)	6 (6.6%)

Table 2: Plasma levels of lipid profile and LP (a) in myocardial infarction patients and controls in Jordan

Lipid parameter	Patients	Controls	p-value
CHL (mg dL^{-1})	225.40±40.7	189.40±32.1	0.00
LDL-c (mg dL^{-1})	161.40±33.8	115.30±25.5	0.00
TG (mg dL^{-1})	200.19±38.6	99.14±24.1	0.00
HDL-c (mg dL^{-1})	59.80±18.5	87.65±20.6	0.00
LP (a) (mg dL^{-1})	50.18±14.4	33.11±10.5	0.00

CHL: Total cholesterol; LDL-c: Low density lipoprotein; TG: Triglyceride; HDL-c: High Density Lipoprotein; LP (a): Lipoprotein (a)

Table 3: Lipids profile and LP (a) plasma levels in <50 and >50 years old in acute myocardial infarction patients and control in Jordan

	Age <50 year			Age >50 year		
Variable	Patients	Controls	p	Patients	Controls	p
CHL (mg dL^{-1})	220.07 (±40.4)	185 (±30.9)	0.002	228.8 (±41.2)	192.1 (±33.2)	0.00
LDL-c (mg dL^{-1})	153.2 (±33.9)	110.9 (±20.1)	0.00	166.66 (±41.3)	118.7 (±23.6)	0.00
TG (mg dL^{-1})	201.37 (±46.2)	89.47 (±20.2)	0.00	199.93 (±42.0)	106 (±32.8)	0.00
HDL-c (mg dL^{-1})	64.21 (±23.9)	86.46 (±23.0)	0.00	57.13 (±21.9)	88.55 (±33.9)	0.00
LP(a) (mg dL^{-1})	42.69 (±17.8)	26.18 (±13.1)	0.00	54.95 (±23.9)	38.84 (±18.6)	0.00

Table 4a: LP (a) plasma levels (mg dL^{-1}) in myocardial infarction males and females patients who are<50 years old and other risk factors

	Male			Female		
Variables	Cases	Controls	p	Cases	Controls	p
Age (years)	40.50±18.9	29.57±11.8	0.04	44.47±17.2	22.62±13.7	0.0000
Diabetes mellitus	39.70±15.1	23.05±4.8	0.46	32.80±20.1	29.00±15.1	0.7340
Smoking	31.50±9.4	24.90±8.0	0.36	37.00±25.4	25.60±8.1	0.1000
Hypertension	36.17±13.6	24.86±8	0.21	47.5±17.4	29.6±13.7	0.4100

Table 4b: LP (a) plasma levels (mg dL^{-1}) in myocardial infarction males and females patients who are >50 years old and other risk factor

	Male			Female		
Variables	Cases	Controls	p	Cases	Controls	p
Age (years)	61.59±25	31.16±13.4	0.00	47.54±20.7	45.3±20.3	0.70
Diabetes	58.70±20.2	41.9±15.4	0.06	52.67±24.9	56.5±14.7	0.69
Smoking	65.06±25.2	41.8±17.2	0.07	63.58±13.1	47.08±26.3	0.43
Hypertension	46.90±17.4	33.26±12.5	0.21	57.50±17.4	39.60±13.7	0.05

Table 5: Correlation of different lipid parameters and ages with respect to LP (a) in myocardial infarction patients and control in Jordan

	Male				Female				Total			
	Patients		Controls		Patients		Controls		Patients		Controls	
Parameter	R	p	r	p	r	p	r	p	r	p	r	p
Age	-0.010	0.960	0.470	0.000	0.540	0.000	0.010	0.910	0.300	0.00	0.280	0.000
Apo (a)	-0.410	0.050	-0.200	0.350	-0.170	0.340	-0.410	0.050	-0.190	0.19	-0.240	0.100
HDL-c	-0.130	0.407	-0.570	0.700	0.019	0. 900	-0.300	0.050	-0.029	0.78	-0.030	0.220
LDL-c	0.040	0.790	0.130	0.380	-0.040	0.810	-0.010	0.960	0.250	0.20	0.250	0.480
TG	0.310	0.033	-0.002	0.980	0.200	0.170	0.150	0.296	-0.020	0.98	-0.020	0.520
CHL	0.004	0.790	0.100	0.500	0.027	0.070	-0.038	0.809	0.230	0.03	0.225	0.680

Table 6: Distribution of Apo (a) is forms in acute myocardial infarction patients and controls in Jordan

Phenotypes (%)	Patients (%)	Controls (%)
B	10 (11)	10 (11)
S1	43 (47.7)	37 (41)
S3	6 (6.6)	6 (6.6)
S4	12 (13.3)	13 (14.4)
>S4	6 (6.6)	4 (4.4)
Total single band	74 (82.2)	70 (77.7)
B-B	4 (4.4)	0
B-S1	2 (2.2)	0
B-S4	2 (2.2)	0
S1-S1	0	4 (4.4)
S1-S3	0	2 (2.2)
S1-S4	2 (2.2)	0
Total double band	10 (11.1)	6 (6.6)
Null	6 (6.6)	14 (15.5)
Total	90 (100)	90 (100)

Table 7: Apo(a) isoforms, kringle repeats and LP(a) plasma levels in myocardial infarction patients in Jordan

		LP (a) level mg dL^{-1}		
No. of kringle IV repeat	Apo (a) Isoforms	Patients	Controls	p
35	>S4	24.0±3	32.0±8.4	0.189
27	S4	31.0±6.6	27.0±8.8	0.429
23	S3	31.8±2.02	43.7±14.2	0.254
19	S1	32.5±9.2	40.8±15.1	0.080
14	B	63.1±22.5	40.7±14.9	0.050
<14	Null	30.0±9.6	20.0±11.1	0.210

DISCUSSION

In the current study, LP (a) has been shown to be significantly higher in patient with acute myocardial infarction than in control group. Several studies carried out worldwide have shown that LP (a) levels are higher in patients with coronary heart disease (Wald *et al*., 1994; Schwartzman *et al*., 1998), while others have shown no significant association (Juahiainen *et al*., 1991). In our study, the mean serum level of LP (a) concentration and distribution in Jordanian population was essentially similar to that reported in European, American white, Kuwaitis and some Asian population (Sandholzer *et al*., 1992; Akonji *et al*., 1999). In this study, the single band phenotype was the most common variety in the patients and controls (82.2 and 77.7% respectively). Other studies demonstrate different percentages of single band in different populations (67 in Kuwaiti, 53 in Koreans, 89% in Austrian (Kraft *et al*., 1988; Coudere *et al*., 1998). the smaller isoforms of LP (a) were the most dominant isoforms in patients and controls in our study (48,42% respectively). Lipoprotein (a) levels were significantly higher in the group with smaller isoforms than in group with large isoform. This confirms that individuals with smaller isoforms have higher LP (a) levels than those with larger isoforms as seen in the west (Seed *et al*., 1990; Utermann *et al*., 1987). The role of high LP (a) in atherosclerosis remains somewhat controversial. LP (a) may promote atherosclerosis by different mechanisms: enhance the LDL oxidation (Hansen *et al*., 1994), foam cell formation by binding to VLDL receptor found on the macrophage (Argraves *et al*., 1997) and decrease formation of plasmin may prevent activation of transforming growth factor-B, an inhibitor of vascular smooth muscle proliferation (Grainger *et al*., 1990). LP (a) excess may increase the incidence of acute coronary syndrome by impairment in plasminogen activation, plasmin generation, fibrinolysis and possible role in plaque rupture and coronary thrombosis (Loscalzo, 1990; Palabrica *et al*., 1995; Dangas *et al*., 1999; Stubbs *et al*., 1998).

CONCLUSION

Jordanian patients with acute myocardial infarction have higher plasma lipoprotein (a) as compared to controls. The common apo (a) isoform in Jordanian patients with acute myocardial infarction is the small apolipoprotein (a) S1, while the B isoform is associated with high level of plasma lipoprotein (a) level. The contribution of these apolipoprotein (a) isoforms to acute myocardial infarction needs further investigations.

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