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 identified 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, hyperlipidemia) 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 (Steyer et al., 1994). The Apo (a) chains contains five cysteine rich domains known as Kringle (McLean et al., 1987). The fourth Kringle is homologous with the fibrin-binding domain of plasminogen, 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...
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) in groups 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, ARCOMEX. LP (a) was quantitatively estimated by enzymatic colorimetric test-CHOD-PAP by commercially available kits provided by ARCOMEX. LP (a) phenotypes were determined by immunoblotting using LP (a) phenotyping reagent kit provided by progen, ARCOMEX. LP (a) was quantitatively estimated by enzymatic colorimetric test-CHOD-PAP by commercially available kits provided by ARCOMEX.

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 versus 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     |

Table 3: Baseline characteristics of myocardial infarction patients and controls in Jordan

| Lipid parameter | Patients | Controls | p-value |
|-----------------|----------|----------|---------|
| CHL (mg dL\(^{-1}\)) | 220.07 (±40.4) | 185 (±30.9) | 0.002 |
| LDL-c (mg dL\(^{-1}\)) | 153.2 (±33.9) | 110.9 (±20.1) | 0.00 |
| TG (mg dL\(^{-1}\)) | 201.37 (±46.2) | 89.47 (±20.2) | 0.00 |
| HDL-c (mg dL\(^{-1}\)) | 64.21 (±23.9) | 86.46 (±23.0) | 0.00 |
| LP (a) (mg dL\(^{-1}\)) | 42.69 (±17.8) | 26.18 (±13.1) | 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

| Variables          | Male Cases | Male Controls | Female Cases | Female Controls | p |
|--------------------|------------|---------------|--------------|-----------------|---|
| Age (years)        | 40.50±18.9 | 29.57±11.8    | 44.47±17.2   | 22.62±13.7      | 0.0000 |
| Diabetes mellitus  | 39.70±15.1 | 23.05±4.8     | 32.80±20.1   | 29.00±15.1      | 0.7340 |
| Smoking            | 31.50±9.4  | 24.90±8.0     | 37.00±25.4   | 25.60±8.1       | 0.1000 |
| Hypertension       | 36.17±13.6 | 24.86±8.0     | 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 factors

| Variables          | Male Cases | MaleControls | p |
|--------------------|------------|--------------|---|
| Age (years)        | 61.59±28.5 | 51.16±13.4   | 0.00 |
| Diabetes           | 58.70±20.2 | 41.±15.4     | 0.06 |
| Smoking            | 65.06±25.2 | 41.±17.2     | 0.07 |
| Hypertension       | 46.90±17.4 | 33.26±12.5   | 0.21 |

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

| Variable | Patients | Controls | p   |
|----------|----------|----------|-----|
| CHL (mg dL\(^{-1}\)) | 220.07 (±40.4) | 185 (±30.9) | 0.002 |
| LDL-c (mg dL\(^{-1}\)) | 153.2 (±33.9) | 110.9 (±20.1) | 0.00 |
| TG (mg dL\(^{-1}\)) | 201.37 (±46.2) | 89.47 (±20.2) | 0.00 |
| HDL-c (mg dL\(^{-1}\)) | 64.21 (±23.9) | 86.46 (±23.0) | 0.00 |
| LP (a) (mg dL\(^{-1}\)) | 42.69 (±17.8) | 26.18 (±13.1) | 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

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

| Variables | Male Cases | Male Controls | p |
|-----------|------------|--------------|---|
| Age (years) | 61.59±28.5 | 51.16±13.4   | 0.00 |
| Diabetes | 58.70±20.2 | 41.±15.4     | 0.06 |
| Smoking | 65.06±25.2 | 41.±17.2     | 0.07 |
| Hypertension | 46.90±17.4 | 33.26±12.5   | 0.21 |

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

| Parameter | Male | Female | Total |
|-----------|------|--------|-------|
| Age       |      |        |       |
| Apo (a)   |      |        |       |
| HDL-c     |      |        |       |
| LDL-c     |      |        |       |
| TG        |      |        |       |
| CHL       |      |        |       |

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

| Phenotypes (%) | Patients (%) | Controls (%) |
|----------------|--------------|--------------|
| B              |              |              |
| S1             |              |              |
| S3             |              |              |
| S4             |              |              |
| >S4            |              |              |
| 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

| No. of kringle IV repeat | Apo (a) | LP (a) level mg dL⁻¹ | 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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