# LIPOPROTEIN(A), APO(A) PHENOTYPES AND DYSLIPIDEMIA IN ACUTE CORONARY SYNDROMES

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*SUMMARY: Although several retrospective studies have shown a strong correlation between lipoproteins and atherosclerotic heart disease, the correlation is unclear in cases with coronary vasospasm. This study sought to examine dyslipidemia including lipoprotein(a) [Lp(a)] and Apo(a) phenotypes in coronary artery disease.*

*One hundred and fifteen patients with mean age of 58.7±13 years suffering from coronary artery disease were selected. They were divided into groups with stable angina pectoris (SA), unstable angina (USA), acute myocardial infarction (AMI). Control group consisted of 40 age and sex matched apparently healthy individuals. The lipids and lipoproteins including Lp(a) were measured using standard methods. Apo(a) phenotypes were evaluated by SDS-PAGE electrophoresis followed by immunoblotting.*

*In patients with coronary artery disease, high-density lipoprotein cholesterol (HDL-C) levels were significantly lower than those in control ($p<0.01$), but in SA its level was higher than those of USA and AMI ($p<0.05$). The levels of triglyceride and very low-density lipoprotein cholesterol (VLDL-C) were higher in SA and no significant differences were noticed in those of total cholesterol, but the concentrations of low-density lipoprotein cholesterol (LDL-C) in USA and AMI were significantly higher than those of SA and control groups. The ApoB concentration was markedly higher in USA group ($p<0.002$). The mean ± SD levels of total Lp(a) in USA and AMI groups were higher than those of SA and control groups ($p<0.001$). Comparing the frequencies of low molecular weight (LMW) and high molecular weight (HMW) Apo(a) phenotypes of patients with control group, high frequencies of LMW Apo(a) and high levels of Lp(a) were noticed in USA and AMI groups ($p<0.01$ in both cases).*

*Low serum HDL-C and high serum LDL-C and Lp(a) levels were characteristic in patients with USA and AMI. Comparing the frequencies of Apo(a) phenotypes in SA, USA and AMI with those of control it was concluded that Apo(a) phenotyping along with serum levels of Lp(a), HDL-C and LDL-C could be a useful risk predictors for the development of acute coronary syndromes and may be used in discrimination of different types of the coronary artery diseases.*

*Key Words : Acute coronary syndromes, dyslipidemia, lipoprotein(a), Apo(a), phenotypes.*

## INTRODUCTION

Atherosclerotic vascular disease is a major cause of death and morbidity in the most part of the world. Several retrospective studies have shown a strong independent correlation between Lp(a) and atherosclerotic disease (1). In the early 1970s, Lp(a) was characterized as a macromolecular complex assembled from LDL and a large

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glycoprotein called apolipoprotein(a) [Apo(a)]. The finding of a close structural homology between Apo(a) and plasminogen raised the question as to whether Lp(a) is atherogenic, thrombogenic or both, and stimulated intensive research in genetic, metabolism and function of this unique lipoprotein (2). Serum concentration of Lp(a) is mainly controlled by Apo(a) gene locus of chromosome 6 (3). Utermann detected six polymorphs which is different in size and a null variant by SDS-PAGE of Apo(a) (4). The size of the Apo(a) phenotypes (from lowest to highest apparent molecular weight) F, B, S1, S2, S3, S4 was inversely associated to serum levels of Lp(a) (5). The role of Lp(a) in atherosclerosis has not been clarified. Structural consideration suggest that Lp(a) could be atherogenic as well as thrombogenic (6).

The number of patients with unstable angina who require admission to monitored beds for hospital treatment is increasing and, in many countries, is higher than the number of patients admitted with AMI (7). Although these patients have similar pathophysiology, scientific data relating to the prevention of further CHD events has generally been limited to the patients with AMI (8). Since numerous studies show patients with USA and positive markers have high incidence of cardiac events in follow-up in this study, dyslipidemia, Lp(a) phenotypes were evaluated in acute coronary syndromes and SA. The results were compared with each other and with the control group.

## MATERIALS AND METHODS

The study was performed during one year period that began in January 2002. One hundred and fifteen patients with mean age of 58.7±13 years suffering from coronary artery disease were selected. The patients were divided into three groups, SA, USA, AMI according to the World Health Organization (WHO) criteria and compared to 40 age and sex matched apparently healthy individuals. The characteristics of the 3 groups of the patients and the control group including age, sex, blood pressure, diabetes mellitus, BMI were evaluated. Venous blood samples were taken from the anticubital vein at fasting state, and serum was separated by centrifugation within 1 hour of collection. The levels of total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, ApoB and Lp(a) were measured by standard methods in Cobas Mira autoanalyzer (9-13). The Apo(a) phenotypes were determined by a high resolution SDS-Agarose gel electrophoresis followed by immunoblotting (14). All the studied subjects were divided into three groups according to their Apo(a) phenotypes; individuals with LMW isoforms like F, B, S1 and S2, HMW isoforms like S3 and S4 and null types without detectable isoforms.

Chi-square test, group paired t-test, analysis of variance were used as appropriated. The results expressed as mean±SD. P value of $< 0.05$ was considered statistically significant. The data were analyzed by SPSS software.

## RESULTS

Of the 155 participants in the study, 40 patients had SA, 38 patients had USA, 40 patients had AMI and the rest were normal individuals of the control group. The clinical characteristics of the four studied groups are listed in Table 1. Mean age, gender distributions and BMI were almost similar in all groups. The prevalence of hypertension was higher in AMI and USA group, but in SA group it was lower than those of the both groups, but still higher than that of control group.

The percentage of smokers was significantly higher in AMI and USA groups, but there were no significant differences between control and SA groups. The BMI did not differ markedly between the control, AMI, USA and SA groups.

Table 1: The clinical characteristics of patients and control groups.

| | Normal subjects | AMI | USA | SA |
|---|---|---|---|---|
| Age (year) | 58 ± 13 | 56 ± 12 | 59 ± 11 | 62 ± 10 |
| Male/Female | 30/10 | 31/9 | 29/9 | 31/10 |
| Hypertension | 12 | 33 | 35 | 24 |
| Smoking | 17 | 48 | 25 | 15 |
| BMI ($kg/m^2$) | 27 ± 4.1 | 28 ± 3.5 | 27 ± 5.1 | 28 ± 4.8 |

Table 2: The levels of lipids and lipoproteins in patients and control groups.

| Parameters (mg/dL) | Groups | | | |
|---|---|---|---|---|
| | Control | SA | USA | AMI |
| Total cholesterol | 200 ± 18 | 215 ± 12 | 224 ± 22 | 231 ± 15 |
| Triglyceride | 195 ± 23 | 260 ± 38 | 218 ± 25 | 212 ± 21 |
| HDL-C | 48 ± 12 | 38 ± 8.5 | 30 ± 7 | 31 ± 5.5 |
| LDL-C | 113 ± 8.5 | 129 ± 11 | 156 ± 15 | 158 ± 21 |
| VLDL-C | 39 ± 4.5 | 52 ± 7.5 | 44 ± 3 | 42.5 ± 2 |
| ApoB | 111 ± 10 | 120 ± 16 | 134 ± 18 | 119 ± 8 |

Serum total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C and ApoB levels in each group are shown in Table 2. The serum total cholesterol levels in SA, USA and AMI groups were all somewhat higher as compared with the control group ($p>0.05$), although no significant difference was found between SA and USA groups. The levels of triglyceride and VLDL-C in SA group were significantly higher than those of control and the other patient groups ($p<0.001$). Comparing with control group marked reduction in the levels of HDL-C was noticed in all three groups of the patients ($p<0.001$ for each). High levels of LDL-C were noticed in USA and AMI groups ($p<0.05$), but no differences were observed between those of control and SA groups ($p>0.05$). The serum ApoB levels in SA, USA and AMI groups were higher than that of control group, but the differences were meaningful in the cases of SA and USA groups ($p<0.05$ in both cases).

Frequency of Apo(a) phenotypes and Lp(a) levels according to Apo(a) phenotypes in the patients and control groups are shown in Table 3. The mean levels of serum Lp(a) in patients with acute coronary syndromes were higher than that of control ($p<0.05$ in all cases). Significant differences were also observed between the total levels of Lp(a) in three groups of the patients and in the SA group the levels were much lower than those of USA and AMI groups ($p<0.05$ in both cases).

The frequency of LMW Apo(a) phenotypes in all the patients groups was significantly higher than those of control group ($p<0.05$ in all cases)

Interestingly, the patients with LMW Apo(a) phenotypes had increased Lp(a) concentration than those with HMW ($p<0.005$). No statistically significant differences in Lp(a) values were noticed between patients and control in null phenotypes.

## DISCUSSION

In the present study significantly lower levels of HDL-C were noticed in AMI, USA and SA groups. Similar results have been reported by others (15). A positive correlation between HDL-C and acetylcholine-induced coronary vasore activity or vasodilatation in both angiographically smooth and diseased coronary segments has been reported (16). Zeiker *et al.* reported that coronary arterial segments from patients with elevated serum HDL-C levels demonstrated a significantly blunted constrictor response to both stimuli (acetylcholine and cold pressor test) compared with segments from patients with low HDL levels, suggesting that HDL exerts a beneficial effect on abnormal vascular activity. HDL aside from its several potential antiatherogenic actions including reverse cholesterol transport (18), an increase in prostacyclin production (19) and promotion of regenerated endothelial proliferation (20) has an antioxidant effect (22) preventing LDL oxidation.

Increased oxidative susceptibility concomitant with vitamin E deficiency has been recently demonstrated in LDL from patients with active variant angina whose serum LDL level was not elevated (23).

High levels of LDL-C were observed in USA and AMI groups, but the level of ApoB was only significantly high in USA group. The concentrations of triglyceride and VLDL-C were also higher in the USA group. The composition of LDL is related to a number of factors such as the concentration of LDL-C, HDL-C, triglyceride, age, physical activity and also determined by genetic factors (24, 25). It has been demonstrated that reduction in HDL could be related to a reciprocal increase in IDL or smaller, dense LDL(26). Some workers generally accepted that a decrease of cholesterol/ApoB ratio in LDL reflect the presence of smaller dense LDL which is more difficulty cleared and more

Table 3: Total Lp(a) levels frequency of Apo(a) phenotypes and Lp(a) according to Apo(a) phenotypes in patient and control groups.

| Groups | Total Lp(a) (mg/dL) | Phenotypes | | | | | |
|---|---|---|---|---|---|---|---|
| | | Null (%) | Lp(a) (mg/dL) | LMW (%) | Lp(a) (mg/dL) | HMW (%) | Lp(a) (mg/dL) |
| Control | 22.5 ± 9.2 | 1.5 | 2.7 ± 2.2 | 18 | 27.5 ± 11.2 | 81 | 17.5 ± 7.2 |
| SA | 31.5 ± 10.5 | 2.5 | 3.3 ± 2.5 | 53.2 | 43.3 ± 10 | 46.8 | 20 ± 8.1 |
| USA | 46.3 ± 9.2 | 3.2 | 2.2 ± 1.8 | 58.1 | 57 ± 11 | 41.9 | 36.2 ± 5.2 |
| AMI | 43.8 ± 8.3 | 1 | 1.1 | 60.3 | 54 ± 9.1 | 39.7 | 33 ± 12 |

atherogenic (27). In the present study high levels of LDL-C and ApoB in USA group may be related to formation of small dense LDL particles.

In the present study we evaluated serum lipids and lipoproteins with emphasis on Lp(a) and Apo(a) phenotypes in three groups of patients and the control group. Concordant to the results of Kinlay *et al.* and other studies (28, 29), our study clearly showed that the levels of Lp(a) in patients are higher than those of the other groups. Although, this association has not been confirmed by some studies (30, 31), our results are similar to the results of numerous investigations (32), demonstrating that Lp(a) concentration is elevated in patients with acute coronary syndromes. We observed that Lp(a) levels increase in all groups of patients with LMW and HMW Apo(a) phenotypes compared to those of control group, but the increase of Lp(a) levels in patients with LMW phenotypes were higher than those patients with HMW phenotypes. Moreover in both the control and the patient groups the LMW phenotypes were associated with higher Lp(a) levels than HMW phenotypes, but patients with LMW phenotypes had higher Lp(a), concentrations compared to that of control subjects.

In summary, the decrease of HDL-C and elevation of LDL-C and Lp(a) were the characteristic lipoprotein disorders observed in patients with acute coronary syndromes. The changes were most significant in the case of USA group, although these lipoprotein disorders may not trigger events of acute coronary syndromes, they probably play an important role in the atherosclerotic and thrombogenic changes of coronary artery disease. It is concluded that marked reduction of HDL-C and significant elevation of LDL-C and Lp(a) in patients with AMI and USA may help to discriminate those groups of patients from the SA group.

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