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The Association between Serum Lipoprotein (a) and Other Cardiac Risk Factors with the Severity of Coronary Artery Disease

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ABSTRACT

Several meta-analyses have provided support for an association between lipoprotein (a) [Lp (a)] and coronary disease, but the correlation of Lp (a) and other coronary risk factors with severity of coronary artery disease (CAD) are ambiguous. In this case control study, plasma Lp (a) concentration, lipid profile, diabetes, hypertension, smoking were evaluated in 108 patients with and without CAD (Case: 55 and Control: 53) who were admitted at heart center in Shahid Beheshti hospital of Zanjan in 2009. Also patients were classified into two risk groups according to their major risk factors; low risk (with two or few risk factors) and high risk (with three and more risk factors). The collected data was analyzed with using chi square, independent sample t-test, fisher's exact test, Mann-Whitney test, Kruskal Wallis test and Pearson's correlation coefficient. The mean concentration of Lp (a) in the case and control groups were 60±11 mg/dL and 32±3 mg/dL, respectively (P=0.054). 41.8% of the case group and 22.6% of the control group have abnormal level of Lp (a) (≥30 mg/dL) (P=0.03). Mean lipoprotein (a) was also higher in three vessels disease compared control group (46±41 vs. 31±23) and maximum level of lipoprotein (a) in control group was 92 mg/dL and in three vessels disease was 520 mg/dL. Between other cardiac risk factors, diabetes was more frequent in case than control groups (29.1% vs 5.7%) and had a significant relationship with severity of coronary disease (P=0.001). The main findings of this study were that mean Lp(a) levels were higher in the three vessels group compared to control and diabetes had significant relationship with the severity of coronary disease.

1. Introduction

Coronary artery disease (CAD) is a multifactor disorder with more than two hundred known risk factors. Three risk factors groups associated with increased risk factor for CAD includes classical, predisposing and conditional risk factors.[1] The classical risk factors including sex, age, smoking, hypertension, cholesterol, and diabetes mellitus have the major role in the pathogenesis of the atherogenesis. The predisposing risk factors including family history of premature CAD, obesity, physical inactivity, and psychosocial factors worsen the independent risk factors. Conditional risk

factors including homocysteine, triglyceride, lipoprotein (a), prothorombic factors and inflammatory markers are linked with increased risk for CAD, but mechanisms which show their causative, independent and quantitative contributions to CAD have not been determinted.[1] Changes in lipid metabolism have an important role in the progression of atherosclerosis[2] and the laboratory determination of lipoproteins is very important in diagnosis and treatment of this condition.[3] Epidemiological investigations of blood concentration of lipoprotein(a) and coronary heart disease have resulted in conflicting results, some studies showed strongly positive association while others reported no association at all.[4-6] Also the coronary risk factors are not independent of one another, have direct or indirect relationships, therefore, determining the influence of each risk factor and the network of multiple risk factors is very important to prevent the incidence of cardiovascular events.[7] It has been therefore hypothesized that assessment of lipoprotein (a), may improve the prediction of cardiovascular risk factors. The current case control study was undertaken to clarify the relationship between Lp (a) and other risk factors with the extent of coronary disease.

2. Materials and Methods

We performed a case control study of baseline characteristics of all patients referred to coronary angiography center in Zanjan at Beheshti hospital from Sep 2008 to Dec 2009. In this study 108 consent subjects of both sexes underwent diagnostic coronary angiography. Of subjects 55 were cases and 53 were controls. Patients with a prior history (up to three month) of acute coronary syndrome (ACS); who using oral anticoagulants, estrogens or hypolipidemic agents and patients suffering from other disorder that interference with this study such as renal, hepatic, coagulation disorders, and auto-immune disease, cancer and patients with triglyceride levels above 400 mg/dL were excluded from the study.

2.1. Patients group

In the present study we included patients who had one or more stenosis of at least 50% of the vessels diameter on any of main coronary arteries. Angiographic finding were classified according to the segmental assortment (CASS: Coronary artery surgery study).[8] The assessment of stenosis severity was done in a visual method. Angiograms were assessed by an experienced cardiologist who was unaware of the patients Lp(a) levels and other risk profiles. The severity of coronary artery involvement was graded according to the following findings: 1- Normal coronary, with no coronary lesion or lesions<10% stenosis. 2-one vessels disease (1VD): The lesion>50%stenosis in one coronary artery or one of it's main branches 3- two vessels disease (2VD), the lesion>50%stenosis in two coronary arteries 4- three vessels disease (3VD), the lesion>50% stenosis in three coronary arteries.[8]

2.2. Controls- subjects

Who had normal coronary on angiography and sex-age matched with case group. All subjects completed a detailed questionnaire providing information on personal data, demographic data, and history of angina, previous myocardial infarction (MI), hypertension and smoking.

2.3. Parameter definition

Major risk factors for CAD were determined. A sustained blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic and/or the use of antihypertensive drugs at the time of investigation were defined as hypertension. Hypercholestrolemia was defined as plasma total cholesterol level≥200 mg/dL. Diabetes mellitus was considered to be present if there was fasting blood sugar≥126mg/dL or if the patients was using insulin or an oral hypoglycemic agent or reported a history of diabetes mellitus. High Lp(a) was fined as plasma Lp(a) ≥30 mg/dL. Smoking was defined as the use of one cigarette daily at least for one year. For the ACS variable it was considered when the individuals presented with acute myocardial infarction or unstable angina. Patients were classified into two risk groups according to their major risk factors; low risk (with two or fewer risk factors) and high risk (with three and more risk factor).

2.4. Biochemical and angiographic measurements

After 12 hrs overnight fast the day before coronary angiography venous blood was obtained. Serum was prepared by centrifugation at 1000g, at 4°c up to 30 min after collection. Total cholesterol and triglyceride concentration were determined enzymatically with colorimetric methods (Pars Azmun Co. Iran) and by automatic analyzer (Selectra II Analyzer, Netherland). For measurement of Lp (a) levels plasma samples were kept at -70°c for three months. Then total Lp(a) levels were quantified using immonoturbidometery method (pars azmun Co. Iran) by automatic analyzer (Selectra II Analyzer, Netherland).[9,10] All angiography producers were done by Philips Integris H5000. Catheters (Judkins, left and right) were from Cordis Corporation (US).

2.5. Statistical analysis

Primary analysis compared Lp (a) levels in the case and the control groups. Secondary analysis evaluated the relationship of Lp (a) with classical cardiovascular risk factors and extent of coronary disease. All analysis were performed using independent sample t-test and chi square, Fisher's exact test and Kruskal Wallis test and Pearson's correlation coefficient . P-value<0.05 was considered as significant level.

2.6. Ethic

The study protocol was approved by the ethics committee of Zanjan university of Medical sciences.

3. Results

Initially 108 patients enrolled in this study. Forty nine percent (27 cases) of the case group and 53% (28 cases) of the control group were male. No significant statistical differences were found between sex and age of the patients in two groups (P=0.167 and 0.254, respectively). Demographic and clinical parameters of the subjects are shown at Table 1.

Table 1- Demographic parameters of case and control groups

Parameters	Control %(n)	Case %(n)	P-Value
Patients	(53)	(55)	
Mean age	54.73±8.09	57±7.64	0.16
age≥50	50.9(27)	61.8(34)	0.20
Lipoprotein (a)≥30mg/dL	22.6(12)	41.8(23)	0.03
Cigarette smoking	24.5(13)	29.1(16)	0.59
Hypertension*	17.0(9)	18.2(34)	0.30
Hypercholesterolemia¶	32.1(17)	45.5(25)	0.22
Hypertriglyceridemia §	13.2(7)	14.5(8)	0.84
Diabetes †	5.7(3)	29.1(16)	0.001

*. Blood pressure ≥140/90
¶. Cholesterol ≥200mg/dL
§. Triglyceride ≥200 mg/dL
†. Fasting blood sugar ≥126 mg/dL
Data are means ± SD or %(n)

The mean age of patients with CAD was higher than the control group (57±7.64 vs. 54.73±8.09) respectively. The majority of risk factors leading to CAD were higher in the group with three vessel disease compared to the control (Table 2). The median Lp(a) levels were higher in the high risk patients compared to low risk patients (48.4±68 vs 40±33) respectively and this difference was not significant statistically. We considered 30 mg/dL as a cut-off point for normal level of Lp(a) in serum, the frequency of abnormal Lp(a) serum concentration was higher in the high risk group compared to the low risk group (74% vs. 25%). Lipoprotein (a)≥30 mg/dL was higher in three vessels disease compared control group (40% vs. 22.6%) (Table 2).

Table 2- Comparison of cardiovascular risk factors in three vessels and control groups.

Parameters	Control n (%)	Three vessels n (%)	p-value
Male	28(52.8)	12(60)	0.58
age≥50	39(73.6)	17(85)	0.30
lipoprotein (a)≥30mg/dL	12(22.6)	8(40)	0.14
Cigarette smoking	13(24.5)	9(45)	0.09
Hypertension*	9(17)	4(20)	0.8
Hypercholesterolemia¶	17(32.1)	9(45)	0.30
Hypertriglyceridemia §	7(13.2)	2(10)	0.71
Diabetes †	3(5.7)	8(40)	0.001

*. Blood pressure ≥140/90
¶. Cholesterol ≥200mg/dL
§. Triglyceride ≥200 mg/dL
†. Fasting blood sugar ≥126 mg/dL

The Median of lipoprotein (a) was also higher in three vessels disease compared control group (28.7 vs 24.2 P=0.24). Mean lipoprotein (a) was also higher in three vessels disease compared control group (46±41 vs 31±23) and maximum level of lipoprotein (a) in control group was 92 mg/dL and in three vessels disease was 520 mg/dL. The median concentration level of lipoprotein (a) in the case and control groups were 32 and 24.2 mg/dL respectively (P= 0.054). The mean concentration of lipoprotein (a) in the case and control groups were 60±11 mg/dL and 32±3mg/dL respectively (P= 0.054). In the case group 17(31%) had one vessel disease, 18(33%) had two vessels disease and 20(36%) had three vessels disease. The results showed that in all patients 72.2% had two and more than two risk factors (high risk group). Of evaluated cardiovascular risk factor, only cholesterol concentration had significant correlation with the lipoprotein (a) levels (r=0.19, P=0.047). Between other cardiac risk factors, diabetes was more frequent in the case than the control groups (29.1% vs 5.7%) and had a significant relationship with severity of the coronary disease (P=0.001).

4. Discussion and conclusion

Many researchers are trying to developm laboratory tests to identifying patients at higher risk of developing CAD thus this is the object of many studies. It is possible to judge the value of determining a certain parameter with the laboratory test to prevent the disease, found its extent or check the efficacy of the management adopted. This case control study assessed a population of mild to high risk, since all individuals had been referred for coronary angiography to assess chest pain. The main

finding of this study was that mean Lp(a) levels were higher in the three vessels group compared to the control. The positive correlation between Lp(a) and CAD established on coronary angiography was demonstrated by Gapta et al[11] in the Indian population, also by Labeur et al[12] in the Belgian population and also in Brazilian population by Maranhao et al,[13] demonstrated the association between elevated serum levels of Lp (a) and the extent of CAD.

A correlation has been observed between Lp(a) and cholesterol concentration.[12] In this study a significant difference between the prevalence of high levels of Lp(a) and the severity and extent of CAD was not identified. On the other hand, some studies did not show an association between Lp (a) serum levels and CAD[14]. others reported a valid predictive value to the sub-population of Lp(a) with high fibrin affinity.[15] Moliterno et al showed no corelation between plasma Lp(a) concentration and the precence or absence of CAD in Africa-Americans.[16] Determination of definite cut-off point for Lp(a) is difficult. Frolkis,[17] Willeit et al (18), Buldassarre et al (19) and Jurgens et al (20) regarede 32 mg/dL, 30 mg/dL , >24 mg/dL and >20 mg/dL as cut-off points for high Lp(a) concentration respectively. Since the relationship between Lp (a) serum concentration and coronary atherosclerosis was determined significant at levels over 30 mg/dL in our study, we considered Lp (a) ≥30 mg/dL as cut-off point for our population study. Veeranna et al, [21] showed between traditional cardiac risk factor only diabetes mellitus emerged as an independent predictor of obstructive coronary artery disease burden, that was similar to our results, that diabetes was more frequent in case than control groups (29.1% vs 5.7%) and had a significant relationship with the severity of coronary disease (P=0.001). The limitation of our study was the very small sample size, so we propose larger study in the future.

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Ethical issues

The study was approved by the Ethical Committee of the University.

Conflict of interests

No conflict of interest to be declared.

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