IS LIPOPROTEIN (A) A PREDICTOR OF CORONARY ARTERY DISEASE SEVERITY?

Tayyebeh Miandoabi[(1)], Masoumeh Sadeghi[(2)], Hasan Shemirani[(3)]

Abstract

INTRODUCTION: Studies on the association between the plasma concentration of lipoprotein (a) and coronary heart disease (CHD) have reported conflicting findings.

METHOD AND MATERIALS: The objective of the present study was to evaluate the association between serum levels of lipoprotein (a) and ischemic heart disease as well as other cardiovascular risk factors in a population-based study. Lipoprotein (a) serum was measured in 142 patients with chronic stable angina undergoing clinically indicated coronary angiography. Lipid profile, fasting blood glucose, anthropometric and clinical parameters were analyzed.

RESULTS: Lipoprotein (a) levels were significantly associated with coronary artery stenosis in men, but not in women. Also, an direct association between mean levels of lipoprotein (a) and coronary artery stenosis in men younger than 55 years old and an inverse association in men older than 55 years old were observed.

CONCLUSION: Multivariate analysis revealed that lipoprotein (a) was considered an independent predictor for severity of CAD in men, especially in younger ages.

Keywords: Lipoprotein (a), cardiovascular risk factors, Ischemic heart disease, coronary angiography.

***ARYA Atherosclerosis Journal* 2008, 4(2): 49-52**

Date of submission: 2 Jan 2008, ***Date of acceptance:*** 26 Feb 2008

Introduction

About 17 million people die annually as a consequence of cardiovascular diseases, particularly heart attacks and stroke.[1] While various conventional risk factors such as male gender, advanced age, high blood pressure, diabetes mellitus and obesity are known for CVD, they can not explain all cardiovascular incidences.[2] In this particular context, additional clarification on the role of emerging risk factors such as hyper triglyceridemia, certain subclasses of LDL- C, homocysteine and lipoprotein (Lp) (a), a large protein attached to an LDL particle are necessary.[3] Epidemiological studies on coronary heart disease (CHD) and blood pressure have shown conflicting results, ranging from a strongly positive association to no association at all.[4-6] In spite this, Lp (a) physiologic function has not been completely understood,[7] its clinical importance in fibrinolytic and atherothro-mbotic processes has already been described.[8,9] In fact, the mechanism by which Lp (a) contributes to atherosclerosis is poorly understood, but it appears to be related to its lipoproteic structure that includes a lipid component similar to LDL and two major proteins: apolipoprotein (a) [Apo (a)] and apolipoprotein B100.[8] The LDL-resembled lipid component induced accumulation of cholesterol in the atheroma,[9] whereas the possible inhibitory effect of Lp (a) on Fibrionolysis may be explained by a competitive structural similarity between Apo (a) and plasminogen, overall contributing as a prothrombotic factor in activation of athero thrombosis.[7-9] Additionally, Lp (a) has been associated with high blood pressure,[10] diabetes mellitus[11,12] and dyslipidemia.[13,14]

According to some authors, obesity, another important risk factor for CVD, may also be correlated with altered Lp (a).[15-17] The purpose of the present study is to evaluate whether the serum levels of Lp (a) are associated with ischemic heart disease (CAD) as well as other cardiovascular risk factors in a population-based study. It is a local cross sectional study of the patients with stable angina.

1) MD, Cardiology Resident, Isfahan University of Medical Sciences, Isfahan, Iran.
2) MD, Assistant Professor, Cardiologist, Isfahan Cardiovascular Research Centre, Isfahan, Iran.
E-mail: sadeghimasoumeh@gmail.com
3) MD, Assistant Professor, Cardiologist, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding author: *Masoumeh Sadeghi*

Materials and Methods

This was a cross sectional study on 142 patients who were randomly selected using simple sampling method. We designed the current study on the basis of a previous study in which we had enrolled a total of 142 consecutive patients with chronic stable angina, 40-60 years of age, who were undergoing clinically indicated coronary angiography at the Shahid Chamran Hospital, Isfahan University of Medical Sciences, from 2005 to 2006. Patients underwent an initial evaluation that included collection of demographic data, past medical history, physical activity, psychosocial symptoms and unknown risk factors. The exclusion criteria included prior administration of station, acute coronary syndrome (ACS) and renal failure. Renal Failure was defined with GFR < 60 m1/min/1.73m^2. Venous sampling was obtained in fasting state (after 10-12h) before angiography and placed in tubes containing EDTA and frozen at -70°C until the analysis was performed. Fasting blood sugar (FBS), triglyceride (TG), cholesterol (chol), low density of cholesterol (LDL) and high density of cholesterol (HDL) were measured in blood samples. Hypercholesterolemia, high LDL-C level, hypertriglyceridemia and hyperglycemia were defined at least 200 mg/dl, 129 mg/dl, 150mg/dl and 110mg/dl, respectively. A low level of HDL was considered < 40mg/dl. Two blood pressure measurements were carried out in seated position upon interval of 5 min, using an aneroid manometer. Blood pressure range was classified in accordance with WHO-ISH guideline.[18] Body mass index (BMI) was calculated in kg/m2 according to the World Health Organization (WHO) criteria.[19] Lp (a) determinations were performed at Cardiovascular Research Center of Isfahan. Lp (a) was measured with Eliza method and other particles were measured with direct methods. After sampling, angiography was performed with Judkinz method.

Angiographic analyses:

1 The maximal stenosis in each of 27 segments of coronary arteries was assessed by three cardiologists who were unaware of risk factors. The angiographic data were reported baseed on the number of coronary arteries including stenotic (one, two or three vessels), location of lesion in proximal, mid portion and distal of artery, and severity of lesion: mild < 50%, moderate between 50% to 75% and severe stenosis > 75%.

Analysis variance test (t-test, one way and logistic model) was used to estimate statistical difference between means of Lp (a), anthropometric data and BMI, biochemistries, plus clinical parameters. P value < 0.05 was considered significant. The analysis was carried out using SPSS 13.

Results

The total sample (n = 142) was composed of 60 (42.3%) women and 82 (57.7%) men, with mean age of (57.82 ± 10.2 years), (56.76 ± 8.61) and (59.32 ± 11.16), respectively. Table 1 presents the univariate analysis of Lp (a) levels in comparison to demographic and behavior variables.

Table 1. Lp (a) levels in accordance to demographic and behavior variables

Variables	n	Mean ± SD	P value
Gender			0.417
Male	82	46.23 ± 36.881	
Female	60	40.84 ± 40.390	
Age			
<55	62	44.32 ± 43.757	0.745
>55	80	42.19 ± 34.94	
Smoking			
Non-smoking	97	43.43 ± 37.388	0.904
Smoker	37	44.35 ± 44.357	

No significant difference was found between Lp (a) serum levels among male and female (table 1). Age was also not significantly associated with Lp (a) levels (44.32 ± 43.75 in age < 55 versus 42.19 ± 34.94 in age > 55). There was no significant difference concerning smoking. (Non smokers 43.43 ± 37.38 versus smokers, 43.35 ± 44.35, P = 0.904). Table 2 shows correlation between Lp (a) and biochemical variables. Univariate analysis of mean Lp (a) levels (43.12 ± 38.90) were similar in patients with moderate (49.37 ± 36.67) and high LDL-C (51.85 ± 42.53). Both Lp (a) levels at moderate and high LDL-C were not significantly higher than individuals within the normal range of LDL-C (38.68 ± 36.32, P = 0.206). The mean LP

Table 2. Lp (a) levels in accordance to Biochemistry variables.

Variables	n	Mean ± SD	P value
LDL-C mg/dl			
≤ 129	87	38.68 ± 38.317	0.206
130-159	27	49.37 ± 36.667	
≥ 160	27	51.85 ± 42.526	
Total	141	43.25 ± 39.012	
Total cholesterol			
< 200	67	36 ± 37.5	0.07
200-239	51	52.57 ± 40.35	
≥ 240	24	42.22 ± 367	
Total	142	43.12 ± 38.9	
HDL-C			
> 60	7	50.14 ± 15.443	0.775
40-60	65	44.58 ± 34.259	
< 40	70	41.06 ± 44.406	
total	142	43.12 ± 38.903	
Triglyceride			
< 150	59	48.82 ± 33.788	0.133
150-199	33	48.18 ± 49.579	
> 200	50	34.34 ± 35.694	
Total	142	43.12 ± 38.903	
Fasting glucose			
<110	85	48.81 ± 42.089	0.84
110-126	14	28093 ± 24.014	
>126	43	36.49 ± 34.378	
total	142	43.12 ± 38.903	

Table 3. Lp (a) levels in accordance to anthropometric variables.

Variables	n	Mean ± SD	P value
Body mass index	Kg/m^2		
< 18.5	4	51±35.318	0.509
18.5-24.9	31	51.39±34.423	
25-29.9	14	39.14±41.536	
>30	33	43.33±33.488	
Total	142	43.12±38.903	

(a) levels of patients with moderate and high total cholesterol (52.27 ± 40.35 and 42.22 ± 36.7, respectively) were not significantly higher than patients with normal total cholesterol (36 ± 37.5, P = 0.07). No significant association between Lp (a) levels and HDL-C (P = 0.775), TG (P = 0.133) and FPG (P = 0.84) were found. As table 3 shows, no association were observed between Lp (a) and BMI (P = 0.509). Regarding the clinical variables, Lp (a) didn't significantly alter as a consequence of changes in the systolic (P = 0.745) and diastolic blood pressure (P = 0.678) (Table 4). An association were observed between mean of Lp (a) and numbers of coronary artery stenosis in men (P = 0.04) but not in women (P = 0.98). Also, there was an association between age and number of coronary artery stenosis in men both younder or older than 55 years old. In less than 55 years old patients, the higher Lp (a) was, the number of coronary artery stenosis were more (P = 0.03), but in patients older than 55 years old, the higher Lp (a) was, there was more chances of single vessel to be increased (P = 0.04).

Table 4. Lp (a) levels in accordance to clinical variables.

Variables	n	Mean ± SD	P value
Systolic Bp(mmHg)			0.745
< 130	120	43.3±38.36	
130-139	4	42.1±39.40	
140-159	10	46.3±40.57	
160-179	6	45.17±54.712	
>180	1	1.00	
Total	141	43.30±38.984	
Diastolic Bp (mmHg)			0.678
<85	130	42.9±39.312	
90-99	11	48. ±36.255	
Total	141	43.30±38.984	

Discussion

In this cross sectional study, Lp(a) mean levels (43.12 ± 38.90) were greater than those observed in France by Boyer et al [13] and in Brazil by Ana-Paula et al.[20] This study showed that Lp(a) levels were not significantly associated with age, LDL-C, Total cholesterol and BMI. Unlike our study, others reported

significant correlation between Lp(a) and age, LDL, total cholesterol and BMI.[13,20] The discrepancies between our data and the results of these other studies may be due to smaller sample in our study than those. Another reason may be greater mean Lp(a) levels in our study than others. In our study, positive association between number of coronary artery disease with Lp(a) levels was observed in men, but not in women. But in men aged ≥ 55 years, high levels of Lp(a) was associated with single vessel and in men aged < 55 year, higher levels of Lp(a) was associated with multivessel disease. This data suggest that in ages younger than 55 years, higher levels of Lp(a) are more serious predictor for severity of coronary artery disease, than older ages. Similar to the study of Ana Paul et al [20] in Brazil, in general, no significant association trend was observed between all obesity-related indices and Lp(a) levels. In spite of the various influences that the smoking habit may exert on lipid metabolism, a positive association between smoking and Lp(a) levels was not verified either in this study or elsewhere.[20,21] With respect to blood pressure, we have not demonstrated any association between systolic or diastolic component of arteries blood pressure and Lp(a) levels. Similar to Ana Paul et al [20], ex-

amining, concentration of Lp(a) did not show any difference between hypertensive and non hypertensive individuals.

Although, there was no association between Lp(a) and Framingham risk factors in our study, our multivariate analysis found that Lp (a) was considered an independent predictor for severity of IHD in men, especially in younger ages. Also, recently published data indicated that elevated Lp (a) increases the risk for myocardial and angina, especially in men with high LDL-C levels.[22] Paradoxically, a recently published study considered Lp(a) an independent predictor of stroke, death from vascular disease and any other cause of death in older men.[23] However, larger trial with greater samples are required to accurately find the association between Lp (a) and severity of CAD.

References

1. OPAS (organizacion Panamericana de la salud). Tendencias demograficas y de mortalidad en la regio'n de las Ame'rica, 1980-2000. Bol Epidemiol 2002; 23 (3): 1-4.
2. Armaganijan D, Batlouni M. Impacto dos fatores de risco tradicionais. Rev Soc cardiol Estado de são Paulo 2000; 10(6): 686-93.
3. Harjai KJ. Potential new cardiovascular risk Factors: left ventricular hypertrophy, homo cysteine, lipoprotein (a), triglycerides, oxidative stress and fibrinogen. Ann Intern Med 1999; 131: 376-86.
4. Gwe wich v, Mittleman M. Lipoprotein (a) in coronary heart disease: is a risk factor after all? JAMA. 1994; 271: 1025-1026.
5. Barnathan ES. Has lipoprotein little (a) shrunk? JAMA 1993; 27 2224-2225.
6. Marcovina SM, Koschinsky ML. Lipoprotein (a) as a risk factor of coronary artery disease. Am J cardiol. 1998: 82 57u-66u.
7. Kosschinsky ML, Marcouina SM. Structure- function relationships in apolipoprotein (a) insights into lipoprotein (a) assembly and Pathog enicity. Curr opin lipidol 2004;15:167-74.
8. Koschinsky ML, Marcovina SM. Evaluation of lipoprotien(a) as a prothrombotic factor: progress from bench to bedside. Curr opin lipidol 2003: 14(4):361-6.
9. Angles-cano E. Structural basis for the pathophysiology of lipoprotein (a) in the athero- thrombotic process. Braz J med Biol Res 1997; 30: 1271-80.
10. Catalano M, Perilli E, Carzaniga G, et al. Lp(a) in hypertensive patients. J hum Hypertens 1998; 12:83-9.
11. Gazzaruso C, Bruno R, Pujia A, et al. Lipoprotein (a) , apolipoprotein (a) polymorphism and coronary atherosclerotic severity in types diabetic patients. Int J Cardiol 2006; 108(3): 354-8.
12. Habib ss. Aslam M. Lipids and lipoprotein (a) concentrations in Pakistani Patients patients with types diabetes mellitus. Diab obes Metab 2004; 6:338-43.
13. Boyer H, Gennes JL, Truffert J, et al. Lp(a) levels in different types of dyslipidenia in the French population. Atherosclerosis 1990;85: 61-9.
14. wang J, Zhang C, chen D, liux, Feng x. lipoprotein (a) and its immune complexes indyslipidemic subjects. Clin Biochem 2004; 37-3.
15. Lamon- Fava s, Wilson P, Schaefer EJ. Impact of body mass index on coronary heart disease risk factors in men and women. Arterioscler Thromb vasc Biol 1996; 16:1509-15.
16. Chein K-L lee Y-T, Sung F-C, etal , lipoprotein (a) level in the Population in Taiwan: relation ship to sociodemographic and atherosclerotic risk factors. Atherosclerosis 1999; 143: 267-73.
17. Akanji A, Al-Shayji, kumar P. Metabolic and anthropometric determinants of serum Lp(a) concentrations and apo (a) poly morphism in a healthy Arab Population. Int J obes 1999;23:855-62.
18. World Health Organization. Who Expert Committee on Physical Status: The use and interpretation of anthopowet physical status. Geneva: world Health organization; 1995 [Who Technical Report Series, vol.854] .
19. Guide lines Subcominittee 1999 world Health Organization: international Siciety of hypertension guidelines for the management of hyper tension. J Hypertens 17:151, 1999.
20. Ana Paula carlos candido, silvania Ferreira, Angelica Alves Lima, Etal, Lipoptein (a) as a risk factor associated with ischemic heart disease: ouno Preto study. Atherosclorosis 191 (2007) 454-459.
21. Sanz EJ, Cazuro AM, Bellido AL, Martin IML. Cigarette consumption and Lipoprotein (a) concentratios. Clin chem. 1996; 42: 479.
22. LUC G, Bard JM, Ar veiler D, et al. Lipoprotein (a) as a predictor of coronary heart desease; The PRIME study, Athero sclerosis 2002; 163: 377-84.
23. Ariyo AA, Thach c, Tracy R. Lp(a) Lipoprotein, vascular disease, and mortality in elderly. N Eng I Med 2003; 349:2108.