LIPOPROTEIN (a) LEVELS AND CORONARY ARTERY DISEASE IN IRANIAN PATIENTS. IS THERE A LINK?

H. Rezvan[*1], F. Rahimi[2] and H. Darvish[3]

1) I. B.T.O Research Center, IBRF Research and Development, Tehran, Iran
2) Department of Pathology, Taleghani Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3) Reference Laboratory, Ministry of Health, Tehran, Iran

Abstract- Lipoprotein(a), an LDL variant, has been claimed to have a role in atherogenesis and therefore coronary artery disease (CAD). However, its production and atherogenecity seems to vary among ethnic groups. In order to study the possible correlation between levels of Lp(a) and CAD in Iranian patients who suffered myocardial infarction (MI), a case-control study was carried out on 120 MI patients and 120 matched healthy subjects. Levels of Lp(a) were significantly higher in the MI patients than the control group ($P < 0.0001$), which demonstrates a possible correlation between levels of Lp(a) and CAD. Estimation of Lp (a) may be helpful in evaluating the risk of CAD, particularly in those patients with borderline levels of triglycerides and cholesterol.
Acta Medica Iranica, 42(4): 263-266; 2004

Key words: Lipoprotein (a), coronary artery disease, serum lipoprotiens, triglycerides, cholesterol

INTRODUCTION

Atherosclerosis is an inflammatory disease, which has been attributed mainly to elevated cholesterol levels (1), however, it seems that pathogenesis of atherosclerosis involves much more than that. Despite changes in lifestyle and use of new pharmacologic approaches to lower cholesterol levels (2-4), cardiovascular disease continues to be the principle cause of death in United States, Europe and the Eastern Mediterranean region (5).

Although hypercholesterolemia is main risk factor in approximately 50 percent of patients with coronary artery disease (CAD) (6), several other factors such as hyperhomocysteinemia (6,7), levels of DHEAS (8), and lipoprotein (a) [Lp(a)] levels (9,10) may have a role in atherogenesis and are under study. Lp(a) is a plasma particle, an LDL variant, identified by Berg in 1963 (11), production of which is largely a genetic trait. It has been called the "enigmatic particle", because its pathogenic mechanism is unclear and its concentration and atherogenecity vary among ethnic groups (12-14). In Iran, Lp(a) has not been evaluated extensively; therefore, this study was designed in order to achieve an insight into the probable role of Lp(a) in inducing CAD and therefore finding new ways to prevent CAD in our population.

Received: 24 Jun. 2002, Revised: 28 Sep. 2003, Accepted: 13 Oct. 2003

***Corresponding Author:**
H. Rezvan, I. B. T. O Research Center, IBRF Research and Development, Tehran, Iran
Tel: +98 21 8268344, 8278341-3, Fax: +98 21
E-mail: hourirezvan@yahoo.com

MATERIALS AND METHODS

The design of the investigation was based on a case-control study. The selected population consisted of men and women aged 45-60 (53±6.44) who were diagnosed with myocardial infarction in the CCU of one of the major general hospitals in Tehran, in a one year period from 1997 to 1998. The control group was a matched population who were normal according to physical examinations. Both groups were informed and entered the study voluntarily.

Lp(a) estimation was carried out by electrophoresis on agarose gel using "Ultrasensitive Hydragel Lipo+Lpa" plates from Sebia, France. The bands were observed and the peak areas were calculated using a "Preference" scanner, France.

HDL and LDL were also estimated by agarose gel electrophoresis using plates from Sebia (France). Determination of cholesterol and triglecride(TG) was carried out on Corning-550 Express, autoanalyser (USA) using enzymatic kits from Zeest Chimie, Iran.

RESULTS

The results obtained for the levels of Lp(a) in patients diagnosed with MI and the healthy control group is demonstrated in table 1. It is apparent that levels of Lp(a) are generally higher in men than women and that Lp(a) levels are significantly higher in the MI patients than control group ($P< 0.0001$).

Lipid profiles of the two groups are tabulated in table 2. It can be seen that, except for HDL-C, other parameters are significantly higher in the case group. It should be noted that the wide standard deviation observed for the Lp (a) level in the control group was due to the fact that several zero values existed in this group.

DISCUSSION

According to the recent lipid guidelines by American Association of Clinical Endocrinology (AACE) (6), our data indicate that mean levels of TG in the control group were around "no-risk" values (150 mg/dl), whereas total cholesterol levels were in the acceptable range (< 200 mg/dl). Our data indicated that, as expected, the levels of TG were significantly higher in our MI patients than normal control group. However it should be noted that the mean values of these lipid parameters in our patients were in the borderline range (TG, 150-200 mg/dl; Cholesterol, 200-239 mg/dl) according to the recent guidelines by AACE, and that only 35% of our MI patients had lipid values within the high-risk serum concentration (TG > 200, cholesterol > 240), indicating that a normal value for TG and cholesterol does not necessarily indicate "No-risk", and that other risk factors should be considered. Interestingly Lp (a) levels were also higher in MI patients.

The structural heterogeneity of Lp(a) as a consequence of the apo(a) size heterogeneity has important implication for the accurate measurement of Lp(a) in human plasma (15). Repeated antigenic determinants are present in variable numbers in different Lp(a) particles, and the immunoreactivity of the antibodies directed to these repeated epitopes can vary. As a consequence, immunoussays using polyclonal or monoclonal antibodies tend to underestimate or overestimate the apo(a) concentration according to structural size.

Table 1. Lp(a) levels in MI patients and normal control group *

	Lp(a) level (%)		
Study Group	**Male**	**Female**	**Total**
Patients (n = 120)	1.54±0.52 (n = 66)	0.9 ±0.23 (n = 54)	1.25±0.4
Controls (n = 120)	0.13 ±0.46 (n = 62)	0.04 ±0.23 (n = 58)	0.08±0.3

*Data are given as mean(±SD).

Table 2. Lipid profiles in MI patients and normal control group*

Study Group	**Lp(a) (%)**	**TG (mg/dl)**	**Cholesterol(mg/dl)**	**LDL-C (%)**	**HDL-C(%)**
Patients (n=40)	1.25±0.41	154.87±73.4	202.58±48.3	62. 86±1 1.1	25.63±7.5
Contro1(n = 120)	0.08±0.36	117.65±30.4	192.77±30.2	54.86 ±6.4	23.72±16.6
P Value †	0.00001	0.0001	0.01	0.0001	0.25

* Data are given as mean(±SD).

†Data were compared using *t* test. In order to confirm the statistical results the data we also studied using *t* in a multicomparison *t* test with a = 0.01 and (1- a /2m) using "Bonferroni-Dunn" methods; significant difference was confirmed between the patients and control group in all parameters except for HDL.

At present, Lp(a) measurements are not standardized and most of the Lp(a) assays have not been evaluated further for apo(a) size sensitivity. As a result, Lp(a) values reported in clinical studies are difficult to compare (12,15). In the present study, being one of the first which has been carried out in Iranian population, it was decided to employ electrophoresis on ultrasensitive agarose gel capable of separating Lp(a) in order to avoid the above mentioned complications related to immunoassays. In a recent report from Iran, studying a group of patients with angina pectoris, no significant difference was observed for the Lp(a) levels in the two groups under study (16). This controversy may be attributable both to the fact that the case groups in the two studies were not the same, as well as the possibility of the difference in techniques, since immunoassay was used in the latter study. However, because Lp(a) values can vary among ethnic groups, reference values need to be population based. Furthermore, such values may also be racially specific. For example, African Americans in general have significantly higher Lp(a) concentrations than Caucasians (13,17), but do not manifest a higher incidence of CAD. This preliminary study in our population is an indication that Lp(a) estimation may be helpful in estimation of CAD risk, in particular amongst those who present borderline values for cholesterol and TG. However, obviously much further work need to be carried out, especially with respect to standardization of techniques in order do make comparisons of data from various groups more meaningful. In fact, as an international effort in this respect, an IFCC committee has been set to work toward standardizing Lp(a) estimations (12).

Acknowledgement

The authors would like to extend their gratitude to Dr. F. Azordegan for his valuable advice and help on statistical analysis. Special thanks are extended to the Day General Hospital Laboratory for the generous support of this study.

REFERENCES

1. [No authors listed]. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation. 1994; 89(3):1333-445.

2. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333(20): 1301-1307.

3. [No authors listed]. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) Lancet. 1994 ;344(8934):1383-9.

4. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997;337(19):1360-9.

5. Ala'din Alwan. Prevention and control of cardiovascular disease. 1st ed. World Health Organisation EMRO; 1995.

6. AACE Lipid Guidelines Committee. The American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. Endocr Pract. 2000; 6(2):162-213.

7. Alpert MA. Homocyst(e)ine, atherosclerosis and thrombosis. South Med J. 1999; 91(1): 858-865.

8. Aminian B, Ostovan MA, Omrani GH. Correlation between DHEA-S and coronary artery disease. Arch Iranian Med. 2001; 3: 170-173.

9. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol. 1998; 82(12A):57U -66U.

10. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PW, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. JAMA. 1996;276(7):544-8.

11. Berg K. A new serum type system in man - the Lp system. Acta Pathol Microbiol Scand. 1963;59: 369-382.

12. Rifai,N, Bachorik PS, Albers J. Lipids, Lipoproteins and apolipoproteins. In: Burtis CA, Ashwood ER, Tietz NW, editors. Tietz text book of clinical chemistry. 3rd ed. Philadelphia: W. B. Saunders company; 1999. p. 809-861.

13 Sorrentino MJ, Vielhauer C, Eisenbart JD, Fless GM, Scanu AM, Feldman T. Plasma lipoprotein (a) protein concentration and coronary artery disease in black patients compared with white patients. Am J Med. 1992; 93(6):658-62.

14. Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS. Racial (black-white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children. Bogalusa Heart Study. Circulation. 1991; 84(1):160-167.

15. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). Clin Chem. 1995; 41(2):246-255.

16. Meraji S, Abuja PM, Hayn M, Kostner GM, Morris R, Oraii S, Tatzber F, Wonisch W, Zechner R, Gey KF. Relationship between classic risk factors, plasma antioxidants and indicators of oxidant stress in angina pectoris in Tehran. Atherosclerosis. 2000; 150(2): 403-412.

17. Marcovina SM, Zhang ZH, Gaur VP, Albers JJ. Identification of 34 apolipoprotein (a) isoforms: differential expression of apolipoprotein (a) alleles betwee American blacks and whites. Biochem Biophys Res Commun. 1993; 191(3): 1192-1196.