A PILOT STUDY FOR ASSESSING THE Lp(a) LEVELS IN MARMARA REGION

(Received 30 April, 1997)

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ABSTRACT

Objective: The aim of this study was to determine Lp(a) levels of healthy people and assess the risk of coronary atherosclerosis in terms of lipid values and Lp(a).

Methods: Lp(a) was measured by an Elisa method, while other lipid parameters were assayed enzymatically with an autoanalyzer.

Results: Mean levels, standard deviation, and median of Lp(a) were found to be 23.9±26.3 mg/dl, 14.3 mg/dl respectively. Five and 95 percentile values for Lp(a) were found to be 0 and 82.2 mg/dl. Twenty-four percent of our study group had Lp(a) value above 30 mg/dl. Lp(a) frequency distribution of our group is skewed to the left.

Conclusion: Mean value for Lp(a) of our pilot study group is quite high when compared to other populations and we plan to screen a much larger group.

Key Words: Lp(a), atherosclerosis, risk factors, MI

INTRODUCTION

Lp(a) is a LDL like lipoprotein that contains an additional apolipoprotein, apo (a) linked to apo B100 via a disulphide bridge. Lp(a) differs from LDL by a larger particle size (diameter 255A), by a higher protein density (1.07), by protein and carbohydrate composition, and by electrophoretic mobility. Lp(a) is present in all density intervals between 1.0-1.21 g/ml.(1). If Lp(a) containing plasma is subjected to density gradient ultracentrifugation, approximately 90% of Lp(a) is found as a distinct band between LDL and HDL_2 (2). Lp(a) is found in only higher primates except for hedgehog. Animal experiments are made in cynomolgus monkeys that are very similar to humans and transgenic animals that express human apo(a) (3).

The hypothesis that Lp(a) contributes to atherosclerosis by prothrombotic and proatherogenic mechanisms has been based on the similarity between apo(a) and plasminogen and Lp(a) and LDL. Lp(a) has the size of the most atherogenic particle (IDL) and thus may be selectively filtered from plasma by arterial intimal layers. Lp(a) easily self aggregates and can easily stick to surfaces which may also add to its atherogenicity. Lp(a) interacts with glycosaminoglycans and with proteoglycans. Lp(a)-proteoglycan complexes can be avidly taken up by the scavenger receptors on macrophages. Like LDL, Lp(a) is also oxidized and ox-Lp(a) is taken up by macrophages and causes cholesterol ester accumulation. Lp(a) is more atherogenic for smooth muscle cells (SMC) compared to LDL by inhibiting TGFß which is an inhibitor of SMC growth (4,5). Brown and Goldstein have suggested that Lp(a) could play a role in wound healing by binding to fibrin clot and supplying cholesterol for cell growth (6). Lp(a) is suggested to be the late member in the chain of responses to cellular damage. There are also studies showing that Lp(a) is a surrogate for ascorbate and it is associated with disease when levels of ascorbate are low (7,8). Various case-control studies and researches done with transgenic mice have shown Lp(a) as an independent risk factor for atherosclerosis and proven the above hypothesis (9,10). Elevated levels are associated with a risk of vein graft stenosis and atherosclerotic disease of the lower extremities (11). However some prospective studies have failed to show an association between coronary heart disease and Lp(a) (12).

MATERIALS AND METHODS

Venous blood was taken from 132 healthly individuals aged between 16 and 77. A person was considered healthy if he was not diabetic, hypertensive, did not have overt health problems and did not use medication. The average age of our group was 38.7. Experimental protocol has been approved by the Ethical Committee. Plasma total cholesterol, triglycerides, HDL-cholesterol as well as Lp(a) were

measured in blood samples taken after 12 h of fasting. Aliquots of plasma were stored at -40 C for Lp(a) measurement. Total cholesterol and triglycerides were measured enzymatically (Randox) with a Technicon RA-XT autoanalyzer. HDL-cholesterol was determined after precipitation of apo B containing particles with phosphotungstic acid. LDL-cholesterol was calculated according to Friedewald formula for those with triglyceride values of less than 400 mg/dl (13). Lp(a) was analyzed with a commercial available enzyme-linked immunosorbent assay (ELISA); the Biopool Tint Elize kit.

RESULTS

Mean Lp(a) values were 23.9±26.3 mg/dl and the median values were 14.3 mg/dl. Mean plasma total cholesterol, triglycerides, HDL-cholesterol, LDL cholesterol, and corrected LDL-cholesterol results were given in Table I. Twenty-four percent of the group had Lp(a) levels above 30 mg/dl. Lp(a) frequency distribution was skewed to the left like other ethnic groups (Fig. 1). The skewness and kurtosis were found to be 1.697 and 2.72 respectively. The mean values for the blood lipids were in exceptable ranges but the mean value for HDL- cholesterol was in the border.

No correlation was found with the Spearman correlation test between Lp(a) and age, smoking or any other lipid parameter except for LDL- cholesterol (Table II); hence this study once more verifies that Lp(a) is an independent entity not influenced by most of the variables.

Table I. LIPID VALUES (Mean values in mg/dl)

	n=132
Lp(a)	23.9±26.3
Total Cholesterol	172.4±47.5
Triglycerides	143.9±90.6
HDL-Cholesterol	36.0±10.2
LDL-Cholesterol	106.1±37.8

Table II. CORRELATION ANALYSIS (Spearman)

	r	p
Lp(a) -Glucose	-0.1279	0.246
Lp(a) -Cholesterol	0.1698	0.058
Lp(a) -Triglyceride	-0.0550	0.544
Lp(a) -LDL Cholesterol	0.1950	0.033*
Lp(a) -C LDL Cholesterol	-0.0320	0.773
Lp(a) -HDL Cholesterol	0.1295	0.150
Lp(a) -LDL Chol/LDL Cholesterol	0.0660	0.556
Lp(a) -Cholesterol/HDL Cholesterol	-0.0463	0.672
Lp(a) -Age	-0.0020	0.983
Lp(a) -Smoking	-0.0788	0.544

*Significant

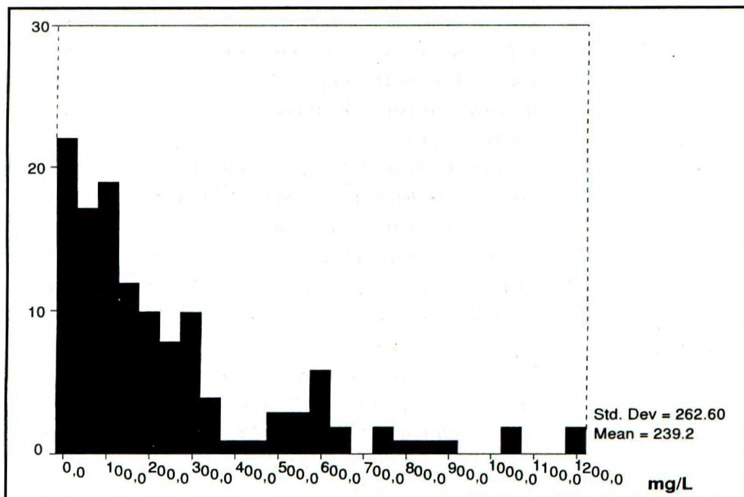

Fig. 1: Frequency distributions of Lp(a) concentrations

DISCUSSION

Lp(a) serum concentrations are considered to be influenced little by factors other than apo(a) gene. It is important to know the factors affecting plasma Lp(a) levels. It is known that familial hypercholesterolemia, lipoprotein lipase deficiency, abetalipoproteinemia and apo A-IV and apo E as well as hepatic and renal disease affect Lp(a) levels. Walek et al have demonstrated an inverse correlation between Lp(a) serum concentration and triglycerides in hypertriglyceridemia (14).

Plasma Lp(a) levels are relatively constant throughout life but tend to increase in postmenopausal women (15). Lp(a) levels change dramatically in pregnancy and anabolic steroids are very effective in lowering Lp(a) levels (16). Oral contraceptives increase Lp(a) levels (17). Hypothyroid state is correlated with increased Lp(a) (18).

Liver damage and alcohol consumption greatly reduce plasma Lp(a) even when other plasma lipoproteins are not altered (19). Patients suffering from cholestasis show very low or no Lp(a). which after treatment rises to normal levels by 2-3 weeks (19).

Lp (a) acts like an acute phase reactant by transiently increasing after myocardial infarction and surgical operations. Dahlen et al showed that although Lp(a) increased in 11 of 22 patients studied during the first week after MI, Lp(a) levels did not change in those with Lp(a) levels less than 1 mg/dl (20).

Lp(a) levels are not efficiently reduced by diet or routinely employed medications (21). The most effective method to lower elevated levels is LDL-apheresis or plasmapheresis. Combination of drugs like nacin + neomycin or colestipol + niacin that reduce plasma Lp(a) levels are especially effective in highest plasma concentrations while N-acetylcysteine has controversial effects (22-24).

Only polyunsaturated fatty acid (e.g. eicosapentaenoic acid) rich diets that interfere with protein secretion from liver, and drugs that lower lipoprotein synthesis directly (nicotinic acid) are capable of reducing plasma Lp(a) levels (25).

Ovaries take up significantly higher amounts of Lp(a) compared to LDL, this preferential Lp(a) uptake is also seen in kidney. Patients with nephropaty have elevated levels of plasma Lp(a). These factors must be taken into considerations in screening people for Lp(a).

Although our study group is small in number to reflect the Turkish population, the mean Lp(a) value is quite high when normal reference intervals are taken into consideration. Örem et al found a mean Lp(a) value of 21.3 mg/dl in a study covering 248 healthy volunteers (127 males and 121 females) in Kayseri region, Turkey (26). In Turkish Heart Study the mean Lp (a) level was found to be 12 to 14.1 mg/dl in five different regions in Turkey (27). In each region 89 to 263 subjects were included in the study.

Mean Lp(a) values seem to differ among different ethnic groups and geographic regions; Chinese having the lowest and the Sudanese having the highest values (26). Lp(a) values of our group does not show a normal distrubution but is skewed to the left like that of other populations. Median values are used in the evaluation of parameters like Lp(a) that show a skewed distribution and have standard deviation higher than the mean value. Because Lp(a) is an independent risk factor for coronary artery disease and is quite impossible to lower with diet and exercise, it is very beneficial for each individual to know his Lp(a) plasma level and take necessary preventive actions to lower other controllable risk factors.

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