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Increased plasma level of lipoprotein(a) and homocysteine is a marker of increased cardiovascular risk

Povećana razina lipoproteina(a) u plazmi i homocisteina pokazatelj je povećanog kardiovaskularnog rizika

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Summary

Introduction. Recent molecular research regards Lp(a) as the "third cholesterol" which should be treated in the same way like the total and LDL-cholesterol in reduction of total cardiovascular risk. Although early data on the relationship between elevated blood homocysteine concentrations and CAD and stroke have been somewhat inconsistent, hyperhomocystinemia has been suggested as an indicator of an increased risk of cardiovascular disease. In light of this, our study objective was to provide answers to the following questions: 1. Is serum Lp(a) concentration a risk factor for coronary artery disease in Croatian population; 2. What are the frequencies of various apo(a) isoforms in elevated serum Lp(a) concentrations; 3. Is there a relation between elevated serum homocysteine and Lp(a) concentration; 4. Investigate the relation of Lp(a) to other lipid disorders and other cardiovascular risk factors.

Methods. This study was performed in Dubrava University Hospital in Zagreb, Croatia. 87 patients participated with no known preliminary coronary or peripheral vascular disease. The patient groups were stratified according to increased and normal Lp(a) levels measured from serum. Extensive medical history was obtained, blood biochemistry was evaluated and all patients underwent exercise stress testing.

Results. In the group with increased concentration of Lp(a) in serum (> 0.30 g/L) there were 53 patients (average age 55 years, 32 males and 21 females), and normal concentration of Lp(a) in serum (< 0.30 g/L) was found in 34 patients (average age 52 years, 20 males and 14 females). The patients with increased Lp(a) levels were significantly older than the patients with normal Lp(a) levels ($p = 0.020$). The average concentration of Lp(a) in patients with negative exercise stress testing results was 0.38g/L, and in those with positive exercise stress testing results it was 0.51 g/L, with this difference among groups being significant ($p = 0.049$). The correlation of homocysteine and Lp(a) levels was statistically significant ($r = 0.57$, $p < 0.01$). Frequencies of phenotype Lp(a) were determined with the predominance of S4 phenotype (in 34 patients, 39.10%).

Conclusions. Lp(a) concentration is a statistically significant risk factor for coronary artery disease. Homocysteine and Lp(a) seem to interact to increase the risk of CAD. No significant association was observed between Lp(a) levels and conventional risk factors for CAD.

Key words: lipoprotein (a), homocysteine , biomarker, cardiovascular risk

Sažetak

Uvod. Nedavna molekularna istraživanja smatraju Lp (a) "trećim kolesterolom" koji se treba tretirati na isti način kao i ukupni i LDL-kolesterol u smanjenju ukupnog kardiovaskularnog rizika. Iako su rani podaci o odnosu između povišenih koncentracija homocisteina u krvi i KBS i moždanog udara bili nekonzistentni, hiperhomocistinemija je predložena kao pokazatelj povećanog rizika od kardiovaskularnih bolesti. U tom

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smislu, cilj našeg istraživanja bio je dati odgovore na sljedeća pitanja: 1. da li je serumska koncentracija Lp (a) čimbenik rizika za koronarnu bolest srca u hrvatskoj populaciji; 2. koje su frekvencije različitih apo (a) izoformi u povišenim koncentracijama Lp (a) u serumu; 3. postoji li veza između povišene koncentracije homocisteina u serumu i koncentracije Lp (a); 4. istražiti odnos Lp (a) prema drugim poremećajima lipida i drugim kardiovaskularnim čimbenicima rizika.

Metode. Istraživanje je provedeno u KB Dubrava u Zagrebu. U istraživanju je sudjelovalo 87 bolesnika bez poznatih preliminarnih koronarnih ili perifernih vaskularnih bolesti. Skupine bolesnika stratificirane su prema povećanoj i normalnoj razini Lp (a) izmjerene iz seruma. Dobivena je opsežna medicinska povijest, napravljena biokemijska analiza krvi i svi bolesnici su podvrgnuti testu opterećenja.

Rezultati. U skupini s povišenom koncentracijom Lp (a) u serumu (> 0,30 g/L) bilo je 53 bolesnika (prosječna dob 55 godina, 32 muškarca i 21 žena), a normalna koncentracija Lp (a) u serumu (< 0,30) g/L) nađena je u 34 bolesnika (prosječna dob 52 godine, 20 muškaraca i 14 žena). Bolesnici s povišenim razinama Lp (a) bili su značajno stariji od bolesnika s normalnim razinama Lp (a) (p = 0,020). Prosječna koncentracija Lp (a) u bolesnika s negativnim rezultatima testa opterećenja bila je 0,38 g/L, a kod osoba s pozitivnim rezultatima testa opterećenja 0,51 g / L, pri čemu je ta razlika bila značajna (p = 0,049). Povezanosti razina homocisteina i Lp (a) bile su statistički značajne (r = 0,57, p < 0,01). Učestalost fenotipa Lp (a) određena je s prevladavajućim fenotipom S4 (u 34 bolesnika, 39,10%).

Zaključci. Koncentracija Lp (a) statistički je značajan čimbenik rizika za koronarnu bolest srca. Čini se da homocistein i Lp (a) djeluju kako bi povećali rizik KBS. Nije uočena značajna povezanost između razina Lp (a) i klasičnih čimbenika rizika za KBS.

Ključne riječi: lipoprotein (a), homocistein, biomarker, kardiovaskularni rizik

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Introduction

Atherosclerosis is responsible for almost all cases of coronary artery disease (CAD). This insidious process begins with fatty streaks that are first seen in adolescence; these lesions progress into plaques in early adulthood, and culminate in thrombotic occlusions and coronary events in middle age and later life. A variety of factors, often synchronous, is associated with an increased risk for development of atherosclerotic plaques in coronary arteries. The conventional risk factors for premature CAD include smoking, hyperlipidaemia, hypertension, diabetes and a positive family history for CAD. However, many patients have precocious atherosclerosis without having any of these conventional risk factors. Identification of other markers that increase the risk of CAD may improve our understanding of the pathophysiologic mechanisms of the disorder and allow the development of new preventive and therapeutic measures.

Lipid abnormalities play a critical role in the development of atherosclerosis. However, the role of lipoprotein (a) [Lp(a)] remains controversial. Lp(a) is a specialized form of low-density lipoprotein (LDL) that is assembled in an extracellular compartment from apolipoprotein (a) and LDL.[1] Lp(a) can bind to macrophages via a high-affinity receptor, possibly promoting foam cell formation and localization of Lp(a) at atherosclerotic plaques.[2] Available literature contains somewhat contradictory data on the significance and influence of Lp(a) levels on cardiovascular risk. Recent molecular research regards Lp(a) as the "third cholesterol" which should be treated in the same way as total and LDL in reduction of total cardiovascular risk.

Elevated plasma homocysteine level has received greater attention in the last few years as an important risk factor for vascular disease, including atherosclerosis. Although early data on the relationship between elevated blood homocysteine concentrations and CAD and stroke have been somewhat inconsistent, hyperhomocystinemia has been suggested as an indicator of an increased risk of cardiovascular disease.[3,4] The study by Harpel et al. suggested that moderate elevations in blood homocysteine could significantly increase the affinity of Lp(a) for fibrin and perhaps other thrombogenic surfaces and thus be an important link in thrombosis and atherogenesis.[5]

In light of this, our study objective was to provide answers to the following questions: 1. Is serum Lp(a) concentration a risk factor for coronary artery disease in the Croatian population; 2. What are the frequencies of various apo(a) isoforms in elevated serum Lp(a) concentrations; 3. Is there a relation between elevated serum homocysteine and Lp(a) concentration; 4. What is the relation of Lp(a) to other lipid disorders and other risk factors; 5. could elevated serum Lp(a) concentration be a predictor of atherosclerosis progression rate?

Methods

Extensive medical history was obtained from patients presenting at the internal medicine medical office on a regular visit due to arterial hypertension, a common condition which increases the risk for a variety of cardiovascular diseases, aged 50 to 60, of both genders and without documented cardiovascular disease. Medical history focused on the presence of family history of atherosclerotic disease, smoking status, nutrition (continental or Mediterranean), lifestyle, presence/lack of physical activity and possible cardiac or circulatory difficulties. Exclusion criteria were documented cardiovascular diseases such as coronary artery disease, stroke, heart failure, atrial fibrillation and peripheral vascular disease, intake of medications that alter the metabolism of lipoproteins, such as hypolipemics, oral contraceptives, immunosuppressives and beta-blockers.

Blood biochemistry samples were obtained from 12-hours fasting precubital vein blood.

Serum Lp(a) level was assessed in 87 patients selected by immunoturbidimetric test that contained policlonal Lp(a) antibodies. The cut-off level for higher risk for atherosclerosis development was 0.30 g/L or more. Apo(a) isoform was assessed by sodium-dodecyl-sulfate (SDS) polyacrylamide gel electrophoresis with monoclonal antibodies immunoblotting technique.

Selected patients underwent full physical examination, ECG and exercise stress testing by Bruce protocol. The presence of positive exercise stress testing was used as an indicator of cardiovascular risk presence. Brachial arterial blood pressure was assessed on both arms by standardized mercury (Hg) sphygmomanometer, in supine position after five minutes rest. Patients with levels of 140/90 mm Hg and higher, and those taking antihypertensives were considered as hypertensive. The body mass index (BMI) was calculated as a ratio of body mass in kilograms and second power of body height in meters. The normal range was considered as from 18.5 to 24.9. Triglycerides level was assessed by the photometric method with normal ranges for men and women < 1.7 mmol/L. Cholesterol was assessed by the CHOD-PAP method. Normal values were considered as < 4.5 mmol/L. High-density lipoprotein (HDL) was assessed by same method after detergent extraction of LDL and very-low-density lipoprotein (VLDL), with reference values for men and women > 1.0 mmol/L and > 1.2 mmol/L respectively. LDL was assessed directly from serum with Tr-53101 reagens, with reference values for men and women < 2.5 mmol/L. Apo (a-1) and Apo (b) were assessed by the immunoturbidimetric method. Reference values for Apo (a-1) were for 0.73 to 1.69 g/L, and for Apo (b) from 0.58 to 1.38 g/L. Homocysteine serum concentration was assessed by fluorescence polarization immunoassay. Normal value was considered lower than 12 μmol/L. Fibrinogen was assessed quantitatively by the modified BEHRING method. Normal values were from 1.8 to 3.5 g/L.

Statistical analysis was preformed on a computer with statistical software SPSS (Statistical Package for social science, SPSS for Windows 7.5, SPSS Inc. Chicago, USA). Distribution of serum lipoprotein (a) and homocysteine concentrations were described as median and interval numeric data, and nominal data was described with frequency.

Numeric data was compared with the Mann-Whitney test and Pearson correlation coefficient. Distributions of nominal values were compared with χ^2 and proportion tests. In all performed tests, the observed significance level was $p < 0.05$ and considered statistically significant.

Results

In total, 87 patients were included in the study, of which 53 had Lp(a) > 0.30 g/L, and 34 had Lp(a) < 0.30 g/L. There was no significant difference among those two groups in regards to age, gender, body height, body mass, presence of positive family history for CAD, smoking, hypertension and nutrition.

When comparing patients with Lp(a) concentration higher than 0.30 g/L and those with Lp(a) concentration lower than 0.30 g/L, the first group had significantly higher levels of homocysteine in serum, as showed in Table 1. The correlation of homocysteine and Lp(a) levels was significant ($r = 0.57$, $p < 0.01$).

Lp(a) phenotype frequencies were determined (Table 2), with clear predominance of S4 phenotype (in 34 patients, 39.10%). Its frequency in subjects with negative exercise stress testing was up to 50.00%, and was significantly higher than in those with positive exercise stress testing (21.20%). No significant differences were found in frequencies of other phenotypes (S1, S1S2, S2, S2S3, S2S4, S3, S3S4, S4 and S5) when comparing groups by results of exercise stress testing.

The group with low molecular mass apo(a) phenotype (S0, S1, S2, S1S2, S2S3, S2S4) had significantly higher homocysteine levels than the group with high apo(a) molecular mass phenotype (S3, S4, S3S4), 13.15 (6.3 – 32.7) μmol/L and 11.2 (5.4 – 18.4) μmol/L, respectively, with this difference between groups being significant ($p = 0.026$). The tendency for higher Lp(a) levels in group with phenotype apo(a) of low molecular mass was observed (Table 3).

Table 1 Average values and standard deviations of lipids, fibrinogen, homocysteine and glucose in blood serum in all patients, in groups with normal and elevated Lp(a) levels
Tablica 1. Prosječne vrijednosti i standardna odstupanja lipida, fibrinogena, homocisteina i glukoze u krvnom serumu kod svih bolesnika, u skupinama s normalnom i povišenom razinom Lp (a)

	All patients (N = 87) *Svi pacijenti*	Lp(a) < 0.30 g/L (N = 34)	Lp(a) > 0.30 g/L (N = 53)	χ^2	P
Triglycerides (mmol/L)	1.89 (0.40 – 8.50)	2.01 (0.58 – 7.03)	1.64 (0.40 – 8.50)	-1.55	0.120
Cholesterol (mmol/L)	5.40 (0.40 – 8.50)	5.27 (3.70 – 7.30)	5.49 (2.20 – 10.35)	-0.6	0.548
HDL (mmol/L)	0.93 (0.27 – 1.81)	0.92 (0.42 – 1.81)	0.96 (0.27 – 1.64)	-0.45	0.651
LDL (mmol/L)	3.45 (0.54 – 7.86)	3.38 (0.72 – 7.86)	3.57 (0.54 – 5.38)	-0.02	0.983
Fibrinogen (g/L)	3.00 (1.10 – 5.30)	2.80 (1.10 – 5.20)	3.00 (1.14 – 5.30)	-0.84	0.398
Homocysteine (umol/L)	11.55 (5.40 – 32.70)	9.55 (5.40 – 16.90)	12.85 (6.30 – 32.70)	-3.87	<0.001
Blood glucose (mmol/L) *Glukoza u krvi*	5.20 (4.00 – 12.90)	4.95 (4.10 – 10.90)	5.40 (4.00 – 12.90)	-0.65	0.101

Table 2 Lp(a) phenotype frequencies and their relation to exercise stress testing result
Tablica 2. Frekvencije fenotipa (a) i njihova veza s rezultatom ispitivanja testiranja otpornosti na stres

Phenotype	All patients (N = 87) *Svi pacijenti*	Positive EST* (N = 33)	Negative ESTR* (N = 54)	χ^2	P
S1	4 (4.6%)	2 (6.15%)	2 (3.7%)	0.01	0.993
S1S2	5 (5.7%)	2(6.1%)	3 (5.6%)	0.14	0.708
S2	9 (10.3%)	3 (9.1%)	6 (11.1%)	0.01	0.945
S2S3	6 (6.9%)	5 (15.2%)	1 (1.9%)	3.73	0.055
S2S4	3 (3.4%)	3 (9.1%)	0	2.75	0.099
S3	11 (12.6%)	5 (15.2%)	6 (11.1%)	0.05	0.827
S3S4	9 (10.3%)	4 (12.1%)	5 (9.3%)	0.01	0.959
S4	34 (39.1%)	7 (21.2%)	27 (50.0%)	5.97	0.016
S0	6 (6.9%)	2 (6.1%)	4 (7.4%)	0.04	0.847

* exercise stress testing result
* *vježbe testiranja otpornosti na stres*

Table 3 Average values of Lp (a) in regards to apo (a) phenotype
Tablica 3. Prosječne vrijednosti Lp(a) u odnosu na apo (a) fenotip

	S1 (N = 4)	S1S2 (N = 5)	S2 (N = 9)	S2S3 (N = 6)	S2S4 (N = 3)	S3 (N = 11)	S3S4 (N = 9)	S4 (N = 34)	S0 (N = 6)
Lp(a) (mmol/L)	0.12	0.99	0.77	0.68	0.58	0.55	0.43	0.31	0.26

In the group with positive exercise stress testing result fasting blood glucose and Lp(a) levels were significantly higher than in the group with negative exercise stress testing, as shown in Table 4.

Table 4 Concentration of Lp(a) and fasting blood glucose in regards to exercise stress testing results
Tablica 4. Koncentracija Lp (a) i glukoze u krvi nakon posta u odnosu na rezultate vježbe testiranja otpornosti na stres

	Negative ESTR* (N = 54)	Positive ESTR* (N = 33)	χ^2	P
Lp(a) (g/L)	0.38 (0.21 – 1.40)	0.51 (0.23 – 1.40)	-1.86	0.049
Glucose (mmol/L)	5.20 (4.0 – 10.9)	5.9 (4.30 – 12.90)	-2.57	0.012

* exercise stress testing result
* *vježbe testiranja otpornosti na stres*

Discussion

Many clinical studies of CAD, cerebrovascular disease and peripheral artery disease have been undertaken to assess the association of Lp(a) with disease.[6,7,8] In this cross-sectional study designed to determine the association of Lp(a) and CAD, it was found that serum Lp(a) concentration is a statistically important risk factor for coronary artery disease in the Croatian population. These results are consistent with the data from literature on Lp(a) as a risk factor for atherosclerosis, but are unique in the aspect of relating elevated levels of Lp(a) with positive stress exercise testing as a marker of CAD in asymptomatic individuals. The study by Uterman et al. showed that Lp(a) phenotypes S1 and S2 are associated with high and phenotypes S3 and S4 with low Lp(a) concentrations.[9] In this study we noticed the tendency for higher Lp(a) levels in the group with phenotype apo(a) of low molecular mass. The simplest explanation for this ought to be that the same genes are involved in determining both electrophoretic Lp(a) phenotypes and Lp(a) lipoprotein concentrations in plasma. Our group noted the predominance of S4 phenotype (in 34 patients, 39.10%) and its frequency in subjects with negative exercise stress testing that was up to 50.00%, and was significantly higher that in those with positive exercise stress testing (21.20%).

A high homocysteine level may act in concert with a high Lp(a) level to promote atherosclerosis and or vascular disease. The existence of this link was also described in several other studies. Harpel et al[5] initially suggested that homocysteine promoted the binding of Lp(a) to plasmin-modified fibrin. This could potentially lead to more atherogenesis and atherothrombosis associated with elevations of both homocysteine and Lp(a). It is now known that Lp(a) is composed of apo(a) linked to an apolipoproteine(B)-100-LDL [apo(B)-100–LDL] particle by a single disulfide bond. Thiols, such as homocysteine, are known to dissociate apo(a) from the Lp(a) complex, leading to the exposure of an additional lysine-binding site on apo(a). This additional lysine-binding site may increase the affinity of apo(a) for plasmin-modified fibrin, thus impeding fibrinolysis.[10] Our findings support the hypothesis that homocysteine and Lp(a) interact to increase the risk of CAD.

The link between Lp(a) concentration and well established risk factors for premature CAD (smoking, hyperlipidaemia, hypertension, diabetes and presence of positive family history for CAD) has been evaluated. No significant association trend was observed between obesity and Lp(a) levels. In spite of the various hypotheses that the smoking habit may exert on the lipid metabolism, there was no positive association between tobacco use and Lp(a) levels neither in this study nor in other studies.[11] Considering that the selection of patients was very carefully performed to avoid other influences on Lp(a) concentrations inconsistent with the presence of the smoking habit, studies of a larger number of very carefully selected cases are required. With respect to blood pressure, it has not been demonstrated that there is any association between the systolic or diastolic component of arterial blood pressure and Lp(a) levels. Those observations have been confirmed by a study examining hypertensive and non hypertensive individuals which also did not observe differences in the concentration of Lp(a). The study by Cândido et al. found that Lp(a) levels were significantly associated with the presence of ischemic heart disease.[12] In relation to other cardiovascular risk factors, it was verified that Lp(a) levels were statistically associated with age, total cholesterol, LDL-cholesterol and percentage of body fat determined by bioelectric impedance, but not arterial hypertension. In contrast, Catalano et al. reported significantly elevated levels of plasma Lp (a) in 123 Caucasian essential arterial hypertensive patients (47 men and 76 women).[13]

Although our study confirmed a significant relation between fasting blood glucose level and exercise stress testing results, no correlation was demonstrated when comparing serum glucose level in the group with high Lp(a) level and normal Lp(a) level. This could be explained by our hypothesis that Lp(a) is an independent risk factor for CAD. Answers whether relation exists are still contradictory. The study by Khare et al. showed that Lp(a) levels were elevated in

diabetes, especially type 2, when compared with the non-diabetic subjects or type 1.[14] Other studies confirmed that impaired glucose tolerance was not related with Lp(a) levels.[12]

This study hasn't found a correlation between Lp(a) concentrations and the presence of dyslipidemia, which may suggest that Lp(a) level is not influenced by other dyslipidemic conditions. Contrary to this study, a similar study performed by Boyer et al. observed a significant difference between the median Lp(a) level of the normolipidemic group and of the dyslipidemic group as a whole. Median Lp(a) levels in the 4 dyslipidemic groups did not differ significantly.[15] Another study by Bartens et al. indicates that plasma Lp(a) concentrations are elevated in hyperlipidaemia if patients have high cholesterol levels, whereas Lp(a) is normal to low in patients with elevated triglycerides.[16] Further analysis of this contradictory data is necessary in a larger prospective study.

Although this study confirmed that serum Lp(a) concentration is a risk factor for coronary artery disease in the Croatian population, our hypothesis that elevated serum Lp(a) concentration could be a predictor of atherosclerosis progression rate couldn't have been tested in this cross – sectional study due to limitations of this study design. The study by Hartmann et al. suggested an increasing significance of Lp(a) in predicting cardiovascular risk.[17] A large randomized prospective study is required to address this question and to determine the existence of positive correlation between Lp(a) levels and plaque progression.

Conclusion

This study confirmed that serum Lp(a) concentration is a statistically significant risk factor for coronary artery disease in the Croatian population. No significant association was observed between Lp(a) levels and conventional risk factors for CAD. This finding is important because it shows that elevated lipoprotein Lp(a) is associated with CAD and it adds to the poll of evidence that Lp(a) should be treated in the same way as total and LDL in reduction of total cardiovascular risk. A high tendency exists for higher Lp(a) levels in the group with phenotype apo(a) of low molecular mass, which is indicative that size, as well as amount, is important - that the smaller the Lp(a) particle, the higher the risk of heart disease.

Our findings support the hypothesis that homocysteine and Lp(a) interact to increase the risk of CAD and levels of each marker positively correlate with one another.

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