ORIGINAL ARTICLE

Correlation of lipoprotein (a) concentration with the extent of coronary artery disease in patients on lipid lowering therapy

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Abstract

OBJECTIVES: Lipoprotein (a) [Lp(a)], together with other serum lipoproteins have an important role in the pathogenesis of coronary heart disease. The objective of the study was to assess the association between plasma levels of Lp(a) with the extent of angiographically defined coronary artery disease (CAD).

PATIENTS AND METHODS: A total of 518 consecutive patients (66 % males) underwent coronary angiography in connection with lipids and lipoprotein determinations between 1st January and 31st May 2010. Most of the patients were treated with lipid lowering therapy (77 % statins). Modified angiographic Gensini Score (GS) and adjusted angiographic score (AS) were used to reflect the extent of coronary atherosclerosis.

RESULTS: Both GS and AS angiographic scores correlated significantly with age, male gender, statin therapy and inversely with left ventricular ejection fraction (p<0.05–0.01 for all). The results showed significant inverse correlation of HDL cholesterol levels with GS and AS (r=–0.16, p<0.001), and apolipoprotein A levels with GS and AS (r=–0.20, p<0.0001) and a positive correlation of Lp(a) levels with angiographic score (r=0.13, p<0.01) and with adjusted angiographic score (r=0.16, p<0.01). Regression analysis showed only Lp(a) concentration was an independent lipid factor that correlated with the extent of CAD.

CONCLUSION: Only Lp(a) levels correlated with the extent of coronary artery disease as assessed with coronary angiography in patients treated with lipid lowering therapy.

Abbreviations:

AS	- adjusted angiography score
Apo A	- apolipoprotein A I
Apo B	- apolipoprotein B 100
bpm	- beats per minute
CAD	- coronary artery disease
DBP	- diastolic blood pressure
DM	- type 2 diabetes mellitus
GS	- Gensini angiography score
HDL	- high-density lipoprotein
HN	- hypertension
HR	- resting heart rate
LDL	- low-density lipoprotein
Lp(a)	- lipoprotein (a)
LV EF	- left ventricle ejection fiction
SBP	- systolic blood pressure

INTRODUCTION

Lipoprotein (a) [Lp(a)], together with other blood lipids and lipoproteins have an important role in the pathogenesis of coronary heart disease. Concentration of Lp(a) is an independent risk factor for coronary artery disease (CAD) (Dahlen *et al.* 1986, Marcovina *et al.* 1996, Morrisett 2000). Lp(a) consists of a low density lipoprotein (LDL) particle linked with a specific apolipoprotein(a) [apo(a)] glycoprotein, which is structurally similar to plasminogen. This similarity accounts for some of the unique characteristics of Lp(a), such as its prothrombogenic effect and the ability to impair thrombolysis (Ganne *et al.* 1999, Soulat *et al.* 1999).

Several studies have established the positive correlation between serum LDL cholesterol levels, serum triglyceride levels and the severity of coronary atherosclerosis and the negative correlation thereof with serum HDL cholesterol levels. On the other hand, the effect of elevated serum levels of Lp(a) on the extent of coronary artery disease [CAD] remains largely disputed. Nevertheless, there has been an ongoing debate concerning the correlation between Lp(a) serum levels and the actual extent and severity of CAD based on angiographic assessment. Some studies have demonstrated a significant correlation, but others have not (Budde *et al.* 1994, Wilson *et al.* 1999, Nguyen *et al.* 1997). Particularly interesting are findings suggesting that Lp(a) is more strongly associated with the presence of CAD in women compared to men (Frohlich *et al.* 2004).

Various scoring systems for CAD extent and severity and different selection criteria for participating patients were used in these studies, which makes reaching a consensus all the more difficult.

The objective of the study was to assess the association between serum levels of Lp(a) and other blood lipids with the extent of angiographically defined CAD in the non-selected patients cohort from a real life setting who were referred for a coronary angiography.

MATERIAL AND METHODS

Patients were recruited amongst individuals undergoing selective coronary angiography for evaluation of suspected ischemic heart disease. A total number of 518 consecutive patients (66% males) underwent coronary angiography in connection with blood lipids and lipoproteins determinations between 1st January and 31st May 2010 at the Cardiovascular Center, Na Homolce Hospital. Most of the patients were receiving lipid-lowering therapy or were on a low-lipid diet. All subjects were at high risk of cardiovascular event and 288 (56%) of patients had history of coronary artery disease. Patients with acute coronary syndromes (acute myocardial infarction, unstable angina pectoris) were not included.

Coronary angiograms were obtained by the standard techniques with multiple aspects and recorded and independently reviewed by experienced interventional cardiologists. The angiograms were defined as to the number of vessels involved (0, 1, 2 or 3) and as to the severity of lesions, namely greater or smaller than 50% lumen obstruction. A modified angiographic Gensini Score (GS) and adjusted angiographic score (AS) were used to reflect the extent of coronary atherosclerosis.

Blood lipids and lipoproteins were determined from the venous blood samples obtained on the day of coronary angiography in the morning after overnight fasting at the Department of clinical biochemistry, haematology and immunology, Na Homolce Hospital. Biochemical analyses were realized on the analyser Unicel DxC 800 (Beckman Coulter company, Germany).

Concentration of total cholesterol, LDL cholesterol, HDL cholesterol was measured in plasma using homogenous elimination determination with a specific detergent. Plasma concentrations of triglycerides were determined by enzymatic colorimetric test (method GPO-PAP).

Concentrations of apolipoprotein AI, apolipoprotein B100 and lipoprotein (a) were measured in serum by immunoassay – nephelometry. Glucose concentration in plasma was determined by Glucose Oxidase Method (oxygen consumption measured with method by Clark).

Vital signs were obtained following patients´ hospital admission after 10 minutes rest in the sitting position, while heart rate was recorded from 12-leads electrocardiography in the supine position.

Left ventricle ejection fraction was measured by dual mode echocardiography on a GE Vivid 7 Ultrasound Machine with 5S 2.2 5.0 MHz, High Resolution Adult Cardiac Phased Array Sector using area-length method.

Lipid-lowering therapy information was obtained from patients´ medical history. Statin therapy was used in 397 (77 %) patients as a monotherapy. No other lipid-lowering drug class was used. The dose of statins was recalculated to equivalent atorvastatin dose according to a method based on a study by Law (Law *et al.* 2003). Mean statin dose of the patients treated with lipid-lowering therapy was 24 mg (1–80 mg range). Antiplatelet therapy was used in 296 (57%) patients and 34 patients (7%) were receiving anticoagulation therapy.

Mean age of the subjects was 66 years (range 30–89), mean body mass index was 29.41 kg/m^2 . Other characteristics, including laboratory results, are shown in the Table 1. For the statistical analysis, the two sample t-test with unequal variances, Spearman´s correlation coefficient and stepwise logistic regression were used. Correlations were calculated in the total patients cohort (n=518) and separately in the subgroup of subjects treated with lipid-lowering therapy (n= 397, 77%).

RESULTS

Both GS and AS angiographic scores correlated significantly with age, male gender, statin therapy and inversely with left ventricular ejection fraction

(p<0.01–0.05 for all). The results showed a significant inverse correlation of HDL cholesterol levels with GS and AS (r=–0.16, p<0.001), and apolipoprotein A levels with GS and AS (r=–0.21, p<0.0001) and a positive correlation of Lp(a) level with angiographic score (r=0.13, p<0.01) and with adjusted angiographic score (r=0.16, p<0.01).

The significant correlation was found both in the total patients population (n=518), and in the subgroup of subjects treated with lipid-lowering therapy (n=397) (Table 2).

Stepwise logistic regression showed that only Lp(a) concentration was an independent lipid factor correlating with the extent of CAD defined as an adjusted angiographic score (partial correlation 0.1786, p=0.002).

We compared lipid profile and other parameters between the group of patients without coronary artery disease (GS=0: CAD$^-$, n=172) and with (GS>0, CAD$^+$, n=346) coronary artery disease. Among (CAD$^-$) 56% (n=96) of patients were taking statin therapy, while 87% (n=301) in (CAD$^+$) were using lipid-lowering therapy. The difference in lipid profile and other parameters in patients with and without coronary artery disease are shown in the table (Table 3).

We compared lipid profile and correlation of lipid and lipoprotein levels with angiography scores between male and female patients. The mean Lp(a) concentration was 307.3 mg/l in men and 282.8 mg/l and the difference was not statisticaly significant. The differences of other blood lipids concentrations between men and women were not significant too. We found no significant differences in correlation of lipid and lipoprotein levels with angiography scores between male and female patients.

Tab. 1. Patients characteristics – categorical and continuous variables

Parameter	Number/ Mean	Proportion/ SD	Min	Max
Male gender	342	66 %		
HN	199	39 %		
DM	141	27 %		
Glucose >5.6 <7.0 mmol/l	218	42 %		
Smokers	199	39 %		
Statin	397	77 %		
Atorvastatin	313	66 %		
SBP mmHg	142.08	16.64	90	210
DBP mmHg	83.04	9.73	50	123
HR bpm	70.76	14.33	43	138
LV EF %	57.89	14.63	15	91
Glucose mmol/l	6.66	2.13	3.27	20.45
Cholesterol mmol/l	4.52	1.05	2.2	9.04
LDL chol mmol/l	2.66	0.88	0.74	5.69
HDL chol mmol/l	1.09	0.35	0.34	3.19
Triglycerides mmol/l	1.50	1.06	0.3	11.26
Apo B g/l	1.09	0.90	0.39	2.81
Apo A g/l	1.46	0.23	0.77	2.62
Lp(a) mg/l	282.01	334.01	18	1780

Statin – number of patients receiving statin therapy
Min – minimum value; Max – maximum value

Tab. 2. Results – correlation of clinical and lipid parameters with angiography scores in the subgroup of subjects treated with statins (n=397).

Parameter	GS *r*	GS *p*-value	AS *r*	AS *p*-value
Age	0.156	0.0004	0.153	0.0006
Male gender	0.197	<0.0001	0.194	<0.0001
LV EF	–0.260	0.154	–0.270	0.014
HR	–0.097	0.030	–0.093	0.037
Statin dose	0.21	<0.0001	0.212	<0.0001
Cholesterol	–0.130	0.0023	–0.140	0.0016
LDL chol	–0.140	0.0016	–0.146	0.001
HDL chol	–0.157	<0.001	–0.151	<0.001
Apo A	–0.261	<0.0001	–0.196	<0.0001
Apo B	–0.024	0.630	–0.025	0.608
Lp(a)	0.134	0.007	0.159	0.002
Glucose	0.12	0.007	0.109	0.014

r – Spearmann´s correlation coefficient; *p* – level of significance

Tab. 3. Difference in lipid and other parameters in patients with and without angiographicaly proven coronary artery disease.

Parameter	CAD(–) (n=172)		CAD (+) (n=346)		*p*-value
	Mean	SD	Mean	SD	
Cholesterol mmol/l	4.69	0.85	4.43	1.19	0.003
LDL chol mmol/l	2.81	0.63	2.59	0.82	0.004
HDL chol mmol/l	1.14	0.11	1.08	0.13	0.034
Triglycerides mmol/l	1.39	0.70	1.52	1.24	0.07
Apo B g/l	0.92	0.05	0.88	0.06	0.04
Apo A g/l	1.52	0.05	1.44	0.05	0.0002
Lp(a) mg/l	246	765	301	129	0.09
Glucose mmol/l	6.27	3.08	6.77	4.88	0.003
Statin dose	9.82	11.69	22.68	18.03	0.003

DISCUSSION

In 518 patients referred for coronary angiography, HDL cholesterol and apolipoprotein A level (inverse correlation) and Lp(a) concentration correlated with the extent of coronary artery disease as assessed with angiography scores. These correlations were significant also in the subgroup of patients treated with statin therapy (n=397), and the stepwise logistic regression showed that Lp(a) level was the only important and significant lipid parameter associated with the extent of CAD.

Prospective studies demonstrated a clear association between Lp(a) and the risk of coronary artery disease (Danesh *et al.* 2000). There were several studies investigating the relation of Lp(a) with the severity of CAD. The study by Dangas *et al.* (1999) was the first to report an association between Lp(a) and totally occluded coronary arteries and association of Lp(a) with the clinical syndrome of unstable angina. The simple scoring system for coronary angiograhic findings was used in that study (non-obstructive, obstructive disease, occlusions). In our study, patients with unstable angina pectoris (acute coronary syndromes) were not included. We used a more precise scoring system, which was previously described in a study by Hamsten *et al.* (1986). In a study by Tarchalski *et al.* (2003), a modified angiograhic Gensini Score was used to reflect the extent of coronary atherosclerosis. That study was one of many others showing a significant inverse correlation of HDL cholesterol levels with the extent of CAD. Unfortunately, Lp(a) levels were not determined in that study. Another study by Zampoulakis *et al.* (2000) showed association of Lp(a) and the number of diseased coronary vessels. Furthermore, it showed that elevated Lp(a) predisposed to the extent of CAD and total occlusion but not to the severity of lesions. A similar investigation was performed by Gupta *et al.* (1996), who reported difference in Lp(a) levels between subjects with normal coronaries and subjects with mild, moderate and severe CAD, when the severity of CAD was defined as a number of involved vessels and severity of artery narrowing.

We also compared lipid profile and other parameters between group of patients with angiographically defined CAD (+) and without CAD (–) artery disease. Our results are somewhat different from previous observations, where Lp(a) level was significantly higher in patients with CAD (+) compared to those without CAD (–) (Frohlich *et al.* 2004).

We found no significant differences of blood lipids and lipoprotein levels and correlation of lipids and lipoprotein levels with angiography scores between male and female patients too.

As expected, other lipid and lipoprotein levels (including cholesterol, LDL chol, HDL chol, and apolipoprotein A and B) were significantly lower in CAD (+) compared to CAD (–). Only mean glucose concentration and triglyceride levels were higher in CAD (+) subjects. This finding might be explained by the proportion of subjects treated with lipid lowering therapy with statins in these subgroups: more patients (87%) in CAD (+) were treated with statins than in CAD (–) (56%) and had significantly different statin dose. The difference in the treatment is difficult to explain. This finding might be caused by different approaches to the therapy among referring physicians. It is possible that subjects considered to be at a higher risk of a cardiovascular event were using higher doses.

We conclude, that Lp(a) concentration was an independent lipid factor that correlated with the extent of CAD as assessed with coronary angiography scores in subjects treated with the most effective lipid-lowering therapy – statins. It is well known, that compared with other blood lipids (e.g. LDL cholesterol), Lp(a) is relatively refractory to life-style and drug interventions. There are limited and variable data on the effects of statins and fibrates on Lp(a) levels. Only studies with niacin reported Lp(a) level reduction by 30–40% in a dose dependent manner. Randomized, controlled trials designed to detect selective reduction of Lp(a) concentrations to reduce the risk of cardiovascular disease are needed (Nordestgaard *et al.* 2010).

REFERENCES

1 Budde T, Fechtrup C, Bosenberg E, Vielhauer C, Enberges A, Schulte H, *et al.* (1994) Plasma Lp(a) levels correlate with number, severity, and length-extension of coronary lesions in male patients undergoing coronary arteriography for clinically suspected coronary atherosclerosis. Arterioscler Thromb.**14**: 1730–1736.

2 Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM (1986) Association of levels of lipoprotein Lp(a), plasma lipids and other lipoproteins with coronary artery dinase, documented by angiogramy. Circulation. **74**: 758–765.

3 Danesh J, Collins R, Peto R (2000) Lipoprotein(a) and coronary heart disease meta-analysis of prospective studies. Circulation. **102**: 1082–1085.

4 Dangas G, Ambrose JA, D´Agate DJ, Shao JH, Chockalingham S, Levine D, *et al.* (1999) Correlation of serum lipoprotein(a) with the angiographic and clinical presentation of coronary artery disease. Am J Cardiol. **83**: 583–585.

5 Frohlich J, Dobiášová M, Adler L, Francis M (2004) Gender differences in plasma levels of lipoprotein (a) in patiens with angiographically proven coronary artery disease. Physiol Res. **53**: 481–486.

6 Ganne F, Vasse M, Beadeux JL, Peynet J, Francois A, Paysant J, *et al.* (1999) Increased expression of u-PA and u-PAR on monocytes by LDL and Lp(a) lipoproteins: consequences for plasmin generation and monocyte adhesion. Thromb Haemost. **81**: 594–600.

7 Gupta R, Vasisht S, Bahl VK, Wasir HS (1996) Correlation of lipoprotein (a) to angiographically defined coronary artery disease in Indians. Int J Cardiol. **57**: 265–270.

8 Hamsten A, Walldius G, Szamosi A, Dahlen G, de Faire U (1986) Relationship of angiographically defined coronary artery disease to serum lipoproteins and apolipoproteins in young survivors of myocardial infarction Circulation. **73**: 1097–1110.

9 Law MR, Wald NJ, Rudnicka AR (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systemic review and metaanalysis. BMJ. **326**: 1423–1430.

10 Marcovina SM, Albers JJ, Wijsman E, Zhang ZH, Chapman NH, Kennedy H. (1996) Differences in Lp(a) concentrations and apo(a) polymorphisms between Black and White Americans. J Lipid Res. **37**: 2569–2585.

11 Morrisett JD (2000) The role of lipoprotein(a) in atherosclerosis. Curr Atheroscler Rep **2**: 243–250.
12 Nguyen TT, Ellefson RD, Hodge DO, Kent RB, Kottke TE, Abu-Lebdeh HS (1997) Predictive value of electrophoretically detected lipoprotein (a) for coronary heart disease and cerebrovascular disease in a community-based cohort of 9936 men and women. Circulation. **96:** 1390–1397.
13 Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, et al., for the European Atherosclerosis Society Consensus Panel (2010) Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. **31**: 2844–2853.
14 Soulat T, Loyau S, Baudouin V, Durlach V, Gillery P, Garnotel R, *et al.* (1999) Evidence that modifications of Lp(a) in vivo inhibit plasmin formation on fibrin: a study with individual plasmas presenting natural variations of Lp(a). Thromb Haemost. **82**: 121–127.
15 Tarchalski J, Guzik P, Wysocki H (2003) Correlation between the extent of coronary atherosclerosis and lipid profile. Mol Cell Biochem. **246**: 25–30.
16 Wilson SH, Celermajer DS, Nakagomi A, Wyndham RN, Janu MR, Ben Freedman S, *et al.* (1999) Vascular risk factors correlate to the extent as well as the severity of coronary atherosclerosis. Coron Artery Dis. **10**: 449– 453.
17 Zampoulakis JD, Kyriakousi AA, Polaris KA, Karaminas NT, Palermos ID, Chimonas ET, *et al.* (2000) Lipoprotein(a) is related to the extent of lesions in the coronary vasculature and to unstable coronary syndromes. Clin Cardiol. **295**: 895–900.