RELATION BETWEEN LIPOPROTEIN(a), FIBRINOGEN AND CAROTID INTIMA-MEDIA THICKNESS IN ESSENTIAL HYPERTENSIVE PATIENTS

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Abstract. Recent studies have indicated that lipoprotein(a) [Lp(a)] and fibrinogen are novel risk factors for systemic atherosclerosis. The main objective of this study was to evaluate the level of Lp(a) and fibrinogen in patients with essential hypertension. The study comprised 20 patients with arterial hypertension and dyslipidemia, 20 patients with arterial hypertension without dyslipidemia and 16 age- and sex-matched control subjects. In all patients, the plasma total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol, TC/HDL-cholesterol ratio, LDL-cholesterol/HDL-cholesterol ratio, Lp(a) and fibrinogen levels were evaluated. Using B-mode ultrasonography, we evaluated carotid intima-media thickness (IMT). We found significant higher Lp(a) levels in hypertensive patients with or without comparative with the control group. The most elevated concentrations of fibrinogen were found in a hypertensive group with dyslipidemia comparative with a hypertensive group without dyslipidemia and with the control group. We found a strong positive correlation between Lp(a) and IMT ($p < 0.001$), and a moderate positive correlation between Lp(a) and fibrinogen ($p < 0.001$) and between fibrinogen and IMT ($p < 0.001$). The measurement of IMT could represent a simple and noninvasive method to monitor hypertensive subjects, with higher levels of Lp(a) and fibrinogen, indifferently of the status of traditionally dyslipidemic risk factors.

Key words: hypertension, lipoprotein(a), fibrinogen.

INTRODUCTION

Several novel risk factors have been proposed as potential criteria for improved detection of subclinical atherosclerosis. In particular, clinical interest has focused on emerging lipid parameters such as lipoprotein(a) and on inflammatory biomarkers such as fibrinogen [12, 18, 20, 24].

Structural homologies between Lp(a) and low-density lipoprotein cholesterol (LDL-cholesterol), apolipoprotein B, and plasminogen increase the possibility that

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like fibrinogen, Lp(a) could potentially be involved in atherosclerosis and thrombosis [1]. Lp(a) levels are known to exhibit significant inter-individual variation and are strictly under genetic control [1, 9]. Elevated serum Lp(a) levels are associated with an increased risk of cardiovascular disease and renal failure in hypertensive patients, but only if LDL-cholesterol levels are also high [6]. As Lp(a) levels are genetically determined, screening for Lp(a) levels in asymptomatic individuals has been suggested to identify the subjects at risk.

Misbalance of atherogenic lipoproteins, low levels of high-density lipoprotein cholesterol (HDL-cholesterol), high levels of LDL-cholesterol, high levels of total cholesterol (TC), all risk factors of atherosclerosis, may injure the arterial wall and elicit an inflammatory response. Atherogenesis represents a low-grade chronic inflammation. When atherogenesis is accelerated by multiple risk factors, it is possible that the inflammatory response within the arterial wall is sufficiently severe to elicit increased levels of acute phase reactants, such as fibrinogen [3, 4, 23].

Recent guidelines have emphasized the importance of non-HDL-cholesterol as a predictor of cardiovascular risk [10], while others have strongly advocated the use of specific lipid ratios such as TC to HDL-cholesterol, or LDL-cholesterol to HDL-cholesterol [16, 19].

The development of the B-mode ultrasound technique has made it possible to noninvasively study the atherosclerotic process. Intima-media thickness (IMT) of the carotid artery has been used as a noninvasive indicator for the atherosclerotic process in the coronary arteries [11].

There are very limited case-control studies determining association between Lp(a) excess and essential hypertension.

The present study examined if there is a correlation between Lp(a), fibrinogen and carotid IMT in hypertensive patients with or without dyslipidemia, with no clinical signs of associated pathologies or organ damage.

MATERIALS AND METHODS

Our study consisted of a group of 20 patients with arterial hypertension and dyslipidemia (male 25%, mean age 56 ± 3.44 years), a group of 20 patients with arterial hypertension without dyslipidemia (male 45%, mean age 54 ± 4.71 years), and a control group of 16 healthy subjects (male 31%, mean age 55 ± 4.17 years), with no clinical signs of associated pathologies or organ damage, hospitalized in the IVth Medical Clinic of the "Victor Babeş" University of Medicine and Pharmacy, Timişoara, in a two year period.

Blood pressure values were measured in the upper arm of seated patients using a standard sphygmomanometer following the recommendations of the 2007 European Society of Hypertension / European Society of Cardiology guidelines [10].

Concentrations of TC, HDL-cholesterol, triglycerides (TG) and serum creatinine levels were measured with enzymatic methods on an automated clinical chemistry analyzer (Dimension RxL Max, Siemens Healthcare Diagnostics) using original reagents from Siemens Healthcare Diagnostics.

The LDL-cholesterol concentration was calculated using Friedewalds' equation: LDL-cholesterol (mg/dL) = [TC (mg/dL) – TG (mg/dL) / 5] – HDL-cholesterol (mg/dL) [15]. Plasma non-HDL-cholesterol was calculated by subtraction of HDL-cholesterol from TC.

Estimated creatinine clearance was evaluated using the Cockcroft-Gault formula [6].

The plasma fibrinogen concentration was determined with a nephelometric assay (ACL 1000 coagulation analyzer, Instrumentation Laboratory) using original reagents from Siemens Healthcare Diagnostics.

Lp(a) values were determined by a commercially available sandwich ELISA (Mercodia AB, Uppsala, Sweden).

Dyslipidemia was stated considering values for specific parameters given in the current European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice [10].

ASSESSMENT OF VASCULAR FUNCTION

IMT was measured by high-resolution B-mode ultrasonography with an ultrasonographic apparatus with linear transducer of 7.5 MHz (Model ProSound SSD-4000, Aloka Co., Ltd., Tokyo, Japan). It was measured in both carotid arteries, on the distal straight 1 cm of the common carotid arteries, the carotid bifurcations, and the proximal 1 cm of the internal carotid arteries. The carotid IMT was determined as the average of 12 measurements (both sides, 6 measurements every side, the thickness of the near and the far wall of each of the three segments). According to literature, the presence of carotid IMT > 0.9 mm was defined as thickened IMT [13].

The study was performed in compliance with the guidelines of the local Ethics Committee of the Hospital and with the Helsinki Declaration of 1975, as revised in 2000.

STATISTICAL ANALYSIS

Statistics instruments were EPI Info 6 and Excel Microsoft Office 2003.

Continuous variables were expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. The correlations between Lp(a), fibrinogen and all the remaining parameters studied were checked using Pearson's correlation test. The χ^2 test was used for the non-parametric variables. Statistical significance was defined as two-sided $p < 0.05$.

RESULTS

The baseline characteristics of the subjects from the three groups are summarized in Table 1.The three groups were similar in terms of age, sex, family history of cardiovascular disease, smoking habits, and body mass index (BMI), while the average of systolic and diastolic blood pressure values was higher in hypertensive patients with or without dyslipidemia comparative with the control group. There was no difference between the groups in terms of serum creatinine levels and creatinine clearance values.

Table 1

Clinical and biochemical characteristics in the study groups (mean ± SD)

Characteristics	Control group	Hypertensive group without dyslipidemia	Hypertensive group with dyslipidemia
Patients (*n*)	16	20	20
Age (y)	55 ± 4.17	54 ± 4.71	56 ± 3.44
Sex M/F (%)	31/69	45/55	25/75
FH (+) (%)	43	45	35
Smokers (%)	31	24	45
BMI (kg/m^2)	22.85±1.85	22.93 ± 2.06	23.88 ± 1.15
Systolic BP (mmHg)	120 ± 7.27	165 ± 4.99	165± 5.5
Diastolic BP (mmHg)	77 ± 7.96	103 ± 4.83	102 ± 3.40
Creatinine (mg/dL)	0.85 ± 0.15	0.85 ± 0.18	0.87 ± 0.17
Creatinine clearance (mL/min)	85 ± 17.41	84 ± 5.48	80 ± 13.61
Fibrinogen (mg/L)	196 ± 39.00	260 ± 62.40	279 ± 71.32
IMT (mm)	0.68 ± 0.06	0.79 ± 0.16	0.85 ± 0.19

Legend: FH = family history of cardiovascular disease, BMI = body mass index, BP = blood pressure

The most elevated concentrations of fibrinogen were found in the hypertensive group with dyslipidemia (279 ± 71.32 mg/L) even if they were not statistically higher comparative to the hypertensive group without dyslipidemia (260 ± 62.40 mg/L, $p = 0.19$). On the opposite the fibrinogen concentration of both groups of hypertensive patients was statistically higher than of the control group (196 ± 39.00 mg/L, $p < 0.001$).

The mean IMT values were significantly higher in the group with arterial hypertension with dyslipidemia (0.85 ± 0.19 mm) than in the group without dyslipidemia (0.79 ± 0.16 mm, $p = 0.01$). We also observed a statistically significant difference between the mean IMT values at patients with arterial hypertension without dyslipidemia than in the control group ($p = 0.006$).

Table 2 describes serum lipid and lipoprotein profiles of the patients in the studied groups.

Table 2

Serum lipid and lipoprotein profiles in the study groups (mean ± SD)

Characteristics	Control group (n = 16)	Hypertensive group without dyslipidemia (n = 20)	Hypertensive group with dyslipidemia (n = 20)
TC (mg/dL)	177 ± 8.88	179 ± 8.66	234 ± 50.78
Triglycerides (mg/dL)	115 ± 21.80	128 ± 23.08	169 ± 14.68
LDL-cholesterol (mg/dL)	107 ± 6.77	105 ± 6.88	165 ± 47.55
HDL-cholesterol (mg/dL)	46 ± 4.15	48 ± 5.69	34 ± 5.12
Non HDL-cholesterol (mg/dL)	131 ± 8.02	131 ± 9.15	188 ± 51.72
TC/HDL–cholesterol ratio	3.84 ± 0.30	3.70 ± 0.42	6.60 ± 1.29
LDL-cholesterol/HDL – cholesterol ratio	2.34 ± 0.22	2.20 ± 0.35	4.73 ± 1.20
Lipoprotein(a)	19 ± 14.64	69 ± 52.33	70 ± 55.95

The plasma concentrations of TC, triglycerides, LDL-cholesterol and non-HDL-cholesterol were higher in the hypertensive group with dyslipidemia than in the hypertensive group without dyslipidemia ($p < 0.001$) and than in the control group ($p < 0.001$).

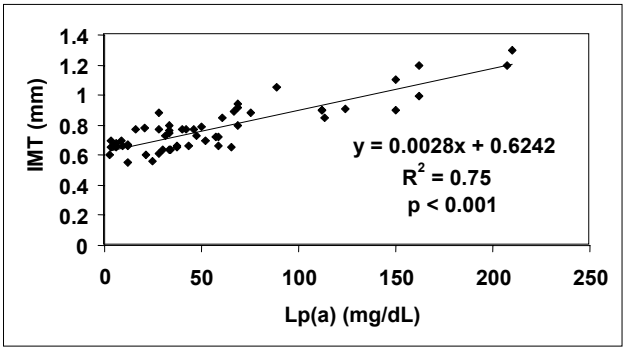

Fig. 1. Correlation between Lp(a) and carotid IMT.

The most elevated concentrations of Lp(a) were found in the hypertensive group with dyslipidemia (70 ± 55.95 mg/dL) comparative with the hypertensive group without dyslipidemia (69 ± 52.33 mg/dL, $p = 0.04$) and with the control group (19 ± 14.64 mg/dL, $p < 0.001$).

Lp(a) and fibrinogen levels were not statistically correlated with any traditional parameter of serum lipid and lipoprotein profiles.

We found a strong positive correlation between Lp(a) and carotid IMT ($R^2 = 0.75$, $p < 0.001$) (Figure 1) and a moderate positive correlation between Lp(a) and fibrinogen ($R^2 = 0.62$, $p < 0.001$) (Fig. 2), and between fibrinogen and carotid IMT ($R^2 = 0.47$, $p < 0.001$) (Fig. 3).

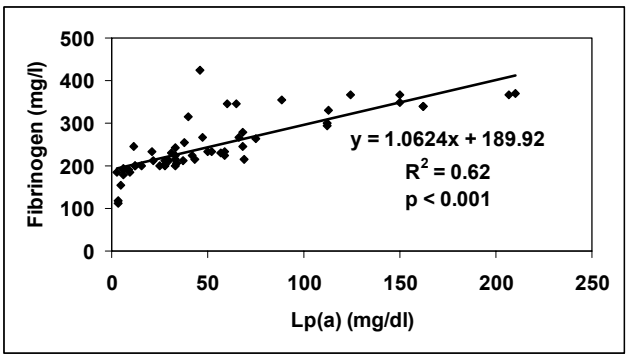

Fig. 2. Correlation between Lp(a) and fibrinogen.

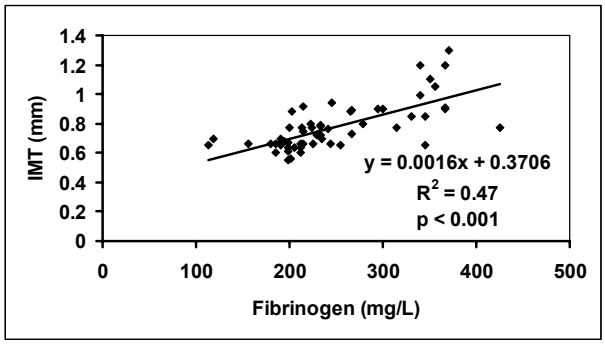

Fig. 3. Correlation between fibrinogen and carotid IMT.

In order to exclude a threshold effect, we dichotomized the study population according to plasma Lp(a) concentrations in a group with Lp(a) < 30 mg/dL (group A) and a group with Lp(a) ≥ 30 mg/dL (group B). Using Student t-test, no statistically significant differences between age, BMI values, creatinine values, and creatinine clearance values could be detected between the groups (Table 3).

Table 3

Clinical and biochemical characteristics in the study population dichotomized according to plasma Lp(a) concentrations: Lp(a) < 30 mg/dL, group A; or Lp(a) ≥ 30 mg/dL, group B

Parameters	Group A Lp(a) < 30 mg/dL (*n* = 18)	Group B Lp(a) ≥ 30 mg/dL (*n* = 38)	*p*
Sex M/F (%)	27/73	36/64	0.18
Age (years)	55 ± 4.24	55 ± 4.14	0.33
FH (+) (%)	11	55	**0.04**
Smokers (%)	27	36	0.36
BMI (kg/m^2)	23.32 ± 2.00	23.21 ± 1.66	0.41
Systolic BP (mmHg)	137 ± 21.78	159 ± 16.72	**<0.001**
Diastolic BP (mmHg)	87 ± 22	99 ± 61	**<0.001**
Creatinine (mg/dL)	0.85 ± 0.15	0.86 ± 0.18	0.46
Creatinine clearance (mL/min)	85 ± 17.26	82 ± 14.44	0.28
Fibrinogen (mg/L)	190 ± 33.51	276 ± 63.41	**<0.001**
Carotid IMT (mm)	0.67 ± 0.08	0.83 ± 0.17	**<0.001**

Legend: FH = family history of cardiovascular disease, IMT = intima media-thickness.

Table 4

Lipid profile status according to plasma Lp(a) concentrations: Lp(a) < 30 mg/L, group A; or Lp(a) ≥ 30 mg/L, group B

Parameters	Group A Lp(a)<30 mg/dL (*n* = 18)	Group B Lp(a)≥30 mg/dL (*n* = 38)	*p*
TC (mg/dL)	190 ± 25.80	202 ± 45.98	0.16
Triglycerides (mg/dL)	130 ± 31.38	143 ± 29.68	0.07
LDL-cholesterol (mg/dL)	118 ± 25.80	131 ± 45.32	0.12
HDL-cholesterol (mg/dL)	45 ± 6.62	41 ± 8.41	0.05
Non HDL-cholesterol (mg/dL)	145 ± 29.44	154 ± 46.26	0.22
TC/HDL-cholesterol ratio	4.31 ± 1.19	5.00 ± 1.73	0.06
LDL-cholesterol/HDL-cholesterol ratio	2.70 ±1.00	3.35 ± 1.53	0.05
Lipoprotein(a)	13.43 ± 9.76	75.57 ± 50.86	**<0.001**

The subjects with high Lp(a) levels were found to have significantly higher values of systolic blood pressure (159 ± 16.72 mmHg *vs*. 137 ± 21.78 mmHg, $p<0.001$) and diastolic blood pressure (99 ± 61 mmHg *vs*. 87 ± 22 mmHg, $p<0.001$) comparative with those with low Lp(a) levels.

We found a statistically significant difference in fibrinogen values between the groups (276 ± 63.41 mg/L in group B *vs*. 190 ± 33.51 mg/L in group A, $p < 0.001$) and in carotid IMT values between the groups (0.83 ± 0.17 mm in group B *vs*. 0.67 ± 0.08 mm in group A, $p < 0.001$).

There was a statistically significant difference in terms of FH (+) between the patients with higher Lp(a) levels comparative with those with low Lp(a) levels ($p = 0.04$).

DISCUSSION

Our results indicated that patients with arterial hypertension with or without dyslipidemia have increased levels of Lp(a). In a similar study, Catalano *et al*. reported significantly elevated levels of plasma Lp(a) in 123 Caucasian essential arterial hypertensive patients (47 men and 76 women) [5].

In our study, both Lp(a) and fibrinogen levels showed a statistically relevant correlation with carotid IMT. Previously, several studies have found Lp(a) to be related to early structural changes of the carotid arteries as shown by ultrasound measurements of IMT [17, 22]. The localization of Lp(a) within the arterial wall suggests a direct causative role for Lp(a) in the initiation or progression of atherosclerosis. In our simple tests, the presence of dyslipidemia was associated with a higher IMT value and Lp(a) was significantly correlated with IMT.

In the present study, majority of hypertensive patients had levels ≥ 30 mg/dL which, in general, is considered a factor of high-risk for atherogenesis. It needs to be confirmed using larger groups of hypertensive patients if this population has a bigger number of individuals with Lp(a) ≥ 30 mg/dL than the non-hypertensive population. In a similar study by Catalano *et al.* it was found that in Caucasians only 13% of hypertensive patients had Lp(a) > 30 mg/dL when compared to 8% in controls [5].

Fibrinogen, a plasma protein, contributes more than other proteins to plasma viscosity in healthy subjects. This contribution is greatly increased in disease states, particularly in hypertension [21]. Indeed, in our study, the levels of fibrinogen were increased in hypertensive patients as compared to control, and were even greater if hypertensive patients presented also dyslipidemia. Patients with higher levels of Lp(a) ≥ 30 mg/dL were also with higher levels of fibrinogen.

In vitro studies showed that over time Lp(a) binds with fibrinogen in a concentration dependent manner [21]. The deposition of Lp(a) within the fibrin clot is believed to be a contributing factor in atherogenesis, promoting plaque progression [14, 15, 21].

On the other hand, the association between Lp(a) and fibrinogen levels may indicate a multiple unstable plaque phenotype (advanced disease). Fibrinogen may be elevated as part of the acute phase response, and Lp(a) has also been shown to rise after plaque destabilization [25]. Two clinical studies showed that patients with elevated serum Lp(a) levels, when associated with high fibrinogen levels, had a significantly increased cardiovascular disease risk [4, 23].

CONCLUSION

In our study, essential hypertensive patients with or without dyslipidemia presented higher concentrations of Lp(a) and fibrinogen comparable to patients with normal blood pressure. There was a significant correlation between the level of Lp(a) and IMT, between Lp(a) and fibrinogen, and between fibrionogen and IMT.

The serum plasmatic level of Lp(a) can be considered an individual dyslipidemic marker of an elevated atherogenic risk present in essential hypertensive patients. The correlation between Lp(a) and serum plasmatic level of fibrinogen suggests an association of a proinflammatory status in essential hypertensive patients.

The measurement of IMT could represent a simple and noninvasive method to monitor hypertensive subjects with no clinical signs of associated pathologies or organ damage but with a positive family history of cardiovascular disease and higher levels of Lp(a) and fibrinogen, indifferently of the status of traditionally dyslipidemic risk factors.

New therapeutic methods may be identified to reduce Lp(a) and fibrinogen levels, which may prove to be useful in patients with essential hypertension.

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