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ABSTRACT

Background: Several novel criteria can improve detection of subclinical atherosclerosis. In particular, the clinical interest has focused on lipoprotein(a), a modified LDL particle which presents a structurally homologue protein to plasminogen.

Aim: The aim of our work was to evaluate the levels of lipoprotein(a), in hypertensive patients with or without atherogenic dyslipidemia comparative with a control group and to estimate the relationship of Lp(a) with other biological and functional parameters.

Methods: The study included 40 hypertensive patients with atherogenic dyslipidemia (HTN+DYS), 43 hypertensive patients without atherogenic dyslipidemia (HTN-DYS) and 35 control subjects, aged and sex matched. The hypertensive patients were not receiving pharmacological therapy and had no clinical signs of associated pathologies or organ damage. We determined in all groups the levels of Lp(a), apolipoprotein A-I and apolipoproteinB and fibrinogen. Lipoprotein(a) was measured by enzyme immuno assay (ELISA) test. Using B-mode ultrasonography we determined carotid intima-media thickness (IMT) and flow mediated vasodilatation (FMD) in all patients.

Results: Lp(a) was significantly higher in HTN+DYS group than in HTN-DYS group and than in control group (77.18 ± 48.51 mg/dL versus 58.14 ± 47.31 mg/dL versus 22.64 ± 11.86 mg/dL versus , $p<0.001$). A significant correlation was found between Lp(a) and IMT ($r = 0.64$, $p < 0.001$), between Lp(a) and fibrinogen ($r = 0.78$, $p < 0.001$), and between Lp(a) and brachial FMD ($r = -0.29$, $p < 0.001$). Lp(a) levels were not correlated with total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoproteins A-I or B or apoA-I/apoB.

Study Limitations: Potential limitations of our study are the relative small number of patients and controls and missing apo(a) phenotype.

Conclusion: Lp(a) levels are related to early structural changes of the carotid arteries as shown by ultrasound measurements of IMT and to early functional changes evaluated by brachial FMD and can be considered an emerging risk factor for premature atherosclerosis.

Background

Lipoprotein(a) [Lp(a)], first described by Berg in 1963, is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B-100 and a molecule of apolipoprotein A[1]. Lp(a) is involved in the pathogenesis and progression of atherosclerosis through different mechanisms. Apo(a) contains, in addition to the protease region and a copy of kringle 5 of plasminogen, a variable number of copies of plasminogen-like kringle 4, giving rise to a series of isoforms. This structural homology endows Lp(a) with the capacity to bind to fibrin and to membrane proteins of endothelial cells and monocytes, and thereby inhibits binding of plasminogen and plasmin formation. This mechanism favors fibrin and cholesterol deposition at sites of vascular injury and impairs activation of transforming growth factor-beta (TGF-β) that may result in migration and proliferation of smooth muscle cells into the vascular intima [2].

The role of Lp(a) as an independent biomarker of vascular risk has been investigated for more than 20 years, but recently the European Atherosclerosis Society (EAS) has issued a new consensus statement endorsing routine measurement of lipoprotein(a) [Lp(a)] among patients with moderate to high risk of cardiovascular disease [3].

Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with coronary heart disease (CHD) risk [4-6], but very limited case-control studies studied the association between elevated Lp(a) and essential hypertension that frequently occurs in conjunction with metabolic disturbances and in particular with atherogenic dyslipidemia [7].

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 [8].

Endothelium-dependent flow-mediated dilation (FMD) of the brachial artery has been demonstrated to be impaired in asymptomatic subjects with various established risk factors including those with hypercholesterolemia [9,10].

Because there are very limited case-control studies that studied the association between elevated Lp(a) and essential hypertension, the aim of our study was to evaluate the levels of lipoprotein(a), in hypertensive patients with or without atherogenic dyslipidemia comparative with a control group and to estimate the relationship of Lp(a) with other biological and functional parameters like carotid IMT and brachial FMD in hypertensive patients.

Material and method

The study enrolled 83 consecutive hospitalized patients with type 2 arterial hypertension. The patients receiving pharmacological therapy, the patients with signs of associated pathologies or organ damage (left ventricular hypertrophy diagnosed by electrocardiogram, the presence of hypertensive retinopathy or a history of a stroke), patients with secondary hypertension, diabetes mellitus, inflammatory diseases, malignancies, renal insufficiency or other diseases, which could affect the Lp(a) level, were excluded from the study.

After admission to hospital, detailed medical history was obtained, and careful physical exam was performed in all patients. Systolic and diastolic blood pressures were measured

three times in the right arm of the resting, seated participant using a random zero sphygmomanometer. The mean of the last two measurements was used in analyses. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Blood was drawn from the antecubital vein in seated patients who had fasted for 12 h. Lab tests included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-cholesterol (non HDL-C), fasting glycemia, serum creatinine, Lp(a), apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB) and fibrinogen.

The levels of TC, HDL-C, TG and serum creatinine levels were measured with an enzymatic method on an automated clinical chemistry analyzer (Dimension RxL Max, Siemens Healthcare Diagnostics) using original reagents from Siemens Healthcare Diagnostics. LDL-cholesterol was estimated by the Friedewald equation when triglycerides were < 400 mg/dl [11].

Lp(a) values were determined by a commercially available sandwich ELISA (Mercodia AB, Uppsala, Sweden). Serum Apo A-I and ApoB concentrations were determined by an immunoturbidometric method (Cobas Integra 400 automatic analyzer; Roche Diagnostics, Basel, Switzerland).

Atherogenic dyslipidemia was defined as the triad of elevated triglycerides, low HDL-C and small LDL-C according to the current European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice as the triad of elevated triglycerides, low HDL-C and small LDL-C [12].

Hypertensive patients were first divided in two groups considering the presence or absence of atherogenic dyslipidemia: 40 with atherogenic dyslipidemia (HTA+DYS) and 43

without atherogenic dyslipidemia (HTA-DYS) and then compared to a control group of 35 subjects, age and sex-matched.

The subjects from the control group had no history of heart or systemic disease; they had normal blood pressure levels, physical examination findings, electrocardiogram, echocardiogram, chest radiogram, and laboratory test results (including urinalysis; 24-hour microalbuminuria; and levels of serum cholesterol, triglycerides, electrolytes, creatinine, and creatinine clearance), fundus oculi, and echo Doppler study of major arteries.

Carotid ultrasonography

Carotid IMT was performed using high-resolution B-mode ultrasonography according to Mannheim Consensus [13]. Both carotid arteries were monitored in terms of carotid intima-media thickness (carotid IMT) in all patients using the high-resolution ultrasound system equipped with a mechanical sector probe with a 7.5 MHz annular imaging transducer. Patients were laid in supine position, with mild hyperextension of the neck to allow optimal visualization of the common carotid artery. The mid and distal portions of the common carotid artery, carotid bulb, and the proximal portions of the internal and external carotid arteries were systematically examined manually in short-axis and long-axis views. We measured the thickness of the intima-media on the far wall of the bilateral common carotid artery about 10-mm proximal to the bifurcation of the carotid arteries on the B-mode monitor and used the mean values for the study. Carotid plaque was defined as IMT ≥ 1.3 mm. Each measurement was calculated by considering the average of 3 readings. Carotid abnormalities were diagnosed if there was ≥ 1 carotid plaque or if there was diffuse

common carotid artery thickening defined as an average IMT ≥ 0.9 mm.

Brachial artery ultrasonography

High-resolution brachial artery ultrasonographic studies were performed according to guidelines[14] to assess endothelium-dependent responses [expressed as % flow-mediated dilatation (FMD)], using B – mode ultrasonography (ALOKA ProSound 4000, with linear transducer of 7.5 MHz). Before the FMD determination, the patients were relaxed in a stable room temperature between 20 – 25 ºC; smoking was prohibited.

The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia at a fixed distance, synchronized with the R-wave peaks of the electrocardiograph trace (D_i). Then, ischemia was induced by inflating the pneumatic cuff to a pressure 50 mmHg above the systolic one, in order to obliterate the brachial artery and induce ischemia. After 5 minutes, the cuff was deflated and the diameter was measured after 60 seconds post – deflation (D_f). FMD was calculated with the formula:

$$FMD = [(D_f - D_i)/D_i] \times 100$$

The study was reviewed and approved by the IVth Medical Clinic of University of Medicine and Pharmacy "Victor Babes" Timisoara and the informed consent was obtained from all subjects.

Statistical analysis

Continuous variables were expressed as means $\pm$ SD. Means were compared using analysis of variance or the Student t-test. Pearson's correlation was used to test bivariate correlations and results were verified using the non-parametric Spearmans's rank correlation test. Statistical significance was defined as two–sided $p < 0.05$. All statistical analyses were performed using Excel Microsoft Office 2007.

Results

The patients were similar in terms of age, sex, family history of cardiovascular disease, smoking habits, and body mass index (BMI), serum creatinine levels and creatinine clearance values. The baseline characteristics of the investigated patients were presented in Table 1.

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

Plasma concentrations of ApoB and the values of ApoB/ApoA-I ratio were significantly higher in the hypertensive group with atherogenic dyslipidemia than in the hypertensive group without atherogenic dyslipidemia ($p < 0.001$) and than in the control group ($p < 0.001$).

Plasma concentrations of Apo A-I and HDL-cholesterol were significantly lower in in hypertensive group with atherogenic dyslipidemia than in the hypertensive group without atherogenic dyslipidemia ($p < 0.001$) and than in the control group ($p < 0.001$).

The highest concentrations of Lp(a) were found in hypertensive patients with atherogenic dyslipidemia (70 ± 55.95 mg/dL) compared to those without atherogenic dyslipidemia (69 ± 52.33 mg/dL, p = 0.04) and to control subjects (19 ± 14.64 mg/dL, p < 0.001).

The mean IMT values were significantly higher in hypertensive group with atherogenic dyslipidemia (0.85 ± 0.19 mm) compared to the hypertensive group without atherogenic dyslipidemia (0.79 ± 0.16 mm, p = 0.01) and compared to the control group (p = 0.006).

Brachial FMD was significantly lower in control subjects (7.28±3.47%) (p < 0.001) compared to the hypertensive group without atherogenic dyslipidemia (7.41±3.33%), and the hypertensive group with atherogenic dyslipidemia (12.87±1.19%).

The Spearman correlation coefficient between Lp(a) and carotid IMT was 0.64, (p< 0.001) (Figure 1) between Lp(a) and fibrinogen 0.78, (p < 0.001) (Figure 2), and between Lp(a) and brachial FMD -0.29, (p < 0.001) (Figure 3).

Discussions

Although the clinical significance of the serum Lp(a) concentration is well recognized in the general population, information about its significance in hypertensive patients is still limited. A study showed that high serum Lp(a) concentrations and LMW apo(a) isoforms are associated with the presence and severity of TOD in patients with essential hypertension [15]. Another study reported an accumulation of Lp(a) in atherosclerotic lesions in the aorta and coronary arteries and suggested that Lp(a) can interact with macrophages to stimulate atherogenesis [16]. The present study showed that hypertensive patients with atherogenic

dyslipidemia had significantly higher serum Lp(a) concentrations than those without atherogenic dyslipidemia and then controls.

Carotid IMT provides information on atherosclerosis extent and, as such, can be very useful in individual patient's CV risk assessment [17]. Previously reported studies regarding the relationship between Lp(a) and early atherosclerotic changes of the extracranial carotid arteries yielded inconsistent data. Sramek et al. investigated carotid and femoral IMT in 142 patients with bone fractures or scheduled for orthopaedic surgery and did not find any correlation between Lp(a) levels and IMT [18]. Other studies by Raitakari et al. and Denti et al. (n = 71 and 100, respectively) also failed to detect a correlation between carotid IMT and Lp(a) [19, 20]. Contrary to these studies, but similar with data from the large population based Atherosclerosis Risk in Communities cohort (ARIC), our study found a significant correlation between Lp(a) concentration and IMT values [21].

Lp(a) lipoprotein activates monocytes, colocalizes with plaque macrophages, stimulates smooth-muscle cells, and can induce inflammation [22]. A correlation between Lp(a) and fibrinogen concentrations has been reported[23] but was not consistently found in the majority of previous studies [24]. Another 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 [25, 26]. The strength of the relationship between plasma fibrinogen and Lp(a) levels obtained in our study suggest that there is a possible link between Lp(a) and the inflammatory response, and this should be clarified in the future.

Few studies revealed an association between Lp(a) and hypertension. In vitro experiments have illustrated that oxidized Lp(a) is able to

impair the arterial endothelium-dependent dilation, and suggested a possible role of Lp(a) in the genesis of essential hypertension [27-29]. In our study, levels of Lp(a) were significantly negative correlated with flow-mediated vasodilatation and our results were similar with those reported by other two studies. Tsurumi et al. reported that elevated Lp(a) levels were associated with impaired endothelium-dependent vasodilation in the coronary arteries and Sorensen et al. found that flow-mediated dilation was inversely related to Lp(a) in the superficial femoral artery in hypercholesterolemic children [30, 31].

A new concept of cardiovascular risk mediated by high levels of lipoprotein(a) in a high-risk environment, such as high low-density lipoprotein cholesterol levels was proposed by Danik et al.[32]. In concordance with this concept, in the present study, hypertensive patients with atherogenic dyslipidemia had significant higher values of Lp(a) comparative with hypertensive without atherogenic dyslipidemia.

The data of the present study confirm the role of Lp(a) as predictor of the severity of coronary atherosclerosis, suggesting that Lp(a) levels should be determined in patients with arterial hypertension, especially in those with atherogenic dyslipidemia, since Lp(a) behaved as a predictive severity marker for coronary atherosclerosis. Thus, elevated serum Lp(a) is an emerging risk factor for cardiovascular disease in patients with arterial hypertension. In primary prevention of cardiovascular disease, Lp(a) seems to add predictive value to lipid screening and enhances risk prediction based on established risk variables. Larger studies that assess the atherothrombotic risk due to the Lp(a) particle in hypertensive patients are needed. Our study has some limitations, one of them being the relative small number of patients. Another potential major limitation of this study is lack of apo(a)

phenotyping. This is an important issue since previous studies have shown that small apo(a) phenotypes could be a stronger predictor than Lp(a) levels of familial clustering of atherosclerotic vascular disease [33, 34]. Another possible limitation of our study may be the fact that the patients were not divided considering the reported cut-off value of 30 mg/dl of Lp(a).

Conclusion

Our study proved that Lp(a) levels are correlated with structural changes of the carotid arteries as shown by ultrasound measurements of IMT and with functional changes evaluated by brachial FMD, thus can be considered an emerging cardiovascular risk factor for atherosclerosis in hypertensive patients.

Conflict of Interest: There is no conflict of interest.

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Table 1: Baseline characteristics of the patients (mean ± SD)

Parameters	CONTROL (n=40)	HTA-DYS (n=35)	HTA+DYS (n=40)	p
Age (years)	56 ± 5.07	55 ± 4.79	56 ± 3.72	0.44
Sex M/F (%)	40/60	44/56	37.5/62.5	0.38
Family history of cardiovascular disease + (%)	40	37	40	0.21
Smokers (%)	31	30	37	0.44
BMI (kg/m2)	22.96 ± 1.43	23.77 ± 0.83	23.82 ± 1.06	0.001
SBP (mmHg)	120 ± 7.17	165 ± 5.57	185 ± 4.98	< 0.001
DBP (mmHg)	78 ± 7.19	102 ± 4.06	104 ± 5.03	< 0.001
Serum creatinine (mg/dL)	0.76 ± 0.10	0.75 ± 0.10	0.73 ± 0.09	0.39
Fasting glycemia (mg/dL)	82.26 ±10.53	83.53 ±9.60	89.03 ±9.63	0.007

Legend: BMI =body mass index, SBP =systolic blood pressure; DBP=diastolic blood pressure

Table 2: Lipid profiles, brachial FMD and carotid IMT in the studied groups (mean± SD)

Parameters	CONTROL (n=40)	HTA-DYS (n=35)	HTA+DYS (n=40)	p
CT (mg/dL)	179.89 ± 8.19	179.67 ± 8.20	232.85 ± 36.93	< 0.001
TG (mg/dL)	120.46 ±27.34	126.81 ± 24.36	189.10 ± 34.22	< 0.001
LDL -C (mg/dL)	107.29 ± 6.67	104.35 ± 9.24	158.28 ± 35.79	< 0.001
HDL - C (mg/dL)	49.44 ± 5.02	48.63 ± 5.17	36.75 ± 5.79	< 0.001
non HDL – C (mg/dL)	131.26 ± 6.73	130.23 ± 8.88	196.10 ± 36.03	< 0.001
Lipoprotein(a) (mg/dL)	22.64 ± 11.86	58.14 ± 47.31	77.18 ± 48.51	< 0.001
ApolipoproteinB (g/L)	0.85 ± 0.13	0.86 ± 0.18	1.51 ± 0.21	< 0.001
Apolipoprotein A-I (g/L)	1.32 ± 0.13	1.29 ± 0.16	0.84 ± 0.10	< 0.001
ApoB/ApoA-I	0.66 ± 0.11	0.64 ± 0.11	1.82 ± 0.30	< 0.001
Fibrinogen (mg/L)	298.37 ± 12.66	317.44 ± 26.58	329.28 ± 36.12	< 0.001
Brachial FMD (%)	12.87±1.19	7.41±3.33	7.28±3.47	< 0.001
Carotid IMT (mm)	0.64±0.05	0.73±0.09	0.76±0.06	< 0.001

Legend: CT= Total cholesterol; TG = triglycerides; LDL-C=LDL-cholesterol; HDL-C=HDL-cholesterol; Non HDL-C = Non HDL-cholesterol; FMD = flow-mediated vasodilatation; IMT= intima-media thickness
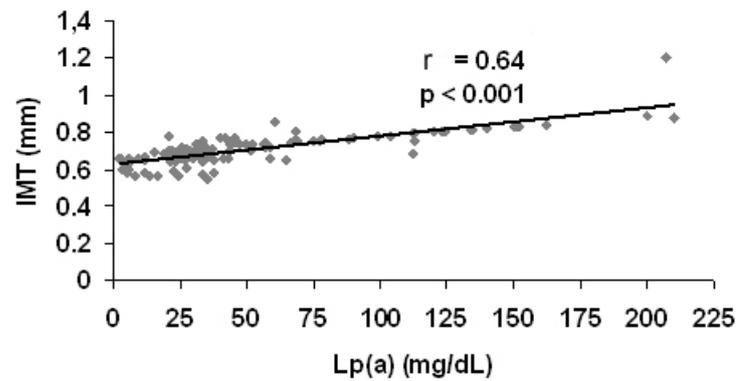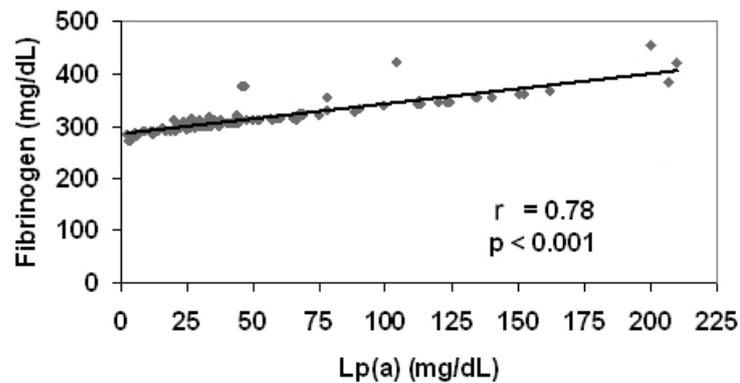
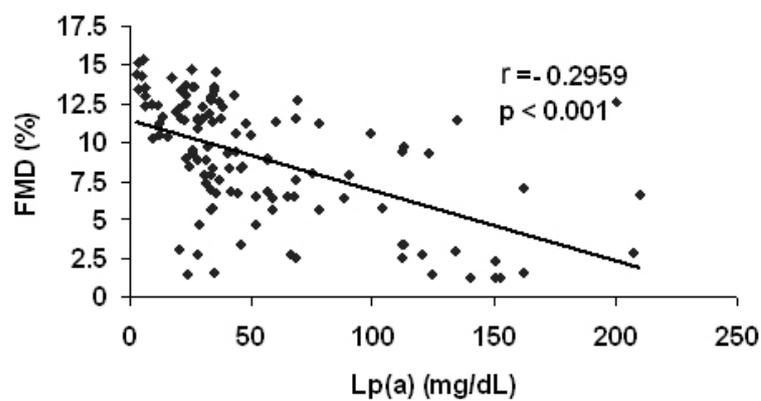**Figure 1: Correlation between Lp(a) and carotid IMT**

Figure 2: Correlation between Lp(a) and fibrinogen

Figure 3: Correlation between Lp(a) and FMD