Association of Serum Lipoprotein(a) with Intima-media Thickness as Target-Organ Damage in Essential Hypertensive Patients*

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Abstract

Background- Carotid intima – media thickness (IMT) is a marker of early atherosclerosis, its anatomic extent and progression. IMT is increased in subjects with several risk factors and is a predictor of cardiovascular events and target organ damage (TOD)**.** Some studies show an association between serum lipoprotein(a) [Lp(a)] and coronary artery disease and target organ damage in hypertensive patients, yet little is known about the association of serum LP(a) elevation with TOD in essential hypertensive patients. Some studies suggest a possible role of Lp(a) in the genesis of essential hypertension**.** We, therefore, aimed to investigate the association of serum Lp(a) elevation with carotid-IMT as target organ damage in a group of essential hypertensive patients.

Methods- Our total of 134 subjects consisted of 39 control subjects and 95 essential hypertensive patients, whose lipids (cholesterol, triglyceride, HDL-C and LDL-C), FBS, BUN, Creat, Ca, K and Na as well as lipoprotein (a) were measured. Carotid IMT was measured byB-mode ultrasonography, and carotid-femoral plaque occurrence (plaque score) was assesed.

Results- There were significant differences in the IMT and plaque scores between the two groups of hypertensive and normal subjects; however, there was no significant difference in LP(a) between the two groups**.** There were no significant correlations between serum LP(a) with IMT or plaque scores in the hypertensive group. There was no significant correlation of carotid IMT, serum LP(a) and plaque scores with stages of hypertension**.**

Conclusions- We could not show clearly the elevation of serum LP(a) in essential hypertensive patients, nor could we find any clear association between serum lipoprotein(a) with IMT as target-organ damage in essential hypertensive patients ***(Iranian Heart Journal 2004; 5(3): 55-63).***

Key words: Intima-media thickness (IMT)■ lipoprotein(a) ■ target organ damage■ essential hypertension

Essential hypertension is a genetic disease characterized by consistently elevated blood pressure values. Its clinical relevance arises from the associated increased predisposition to cardiovascular mortality and morbidity. The most important mechanism by which essential hypertension (EHTN) acts as a cardiovascular risk factor is the induction of arteriosclerosis.[1]

Hypertension is one of the most important risk factors in the development of atherosclerosis (AT), coronary artery disease (CAD) and cerebrovascular disease (CVD).[1]

Intima-media thickening complex has been proved to have significant association with CAD and CVD[2] due to the effect of arterial hypertension on structural changes in the cardiovascular system.[3]

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Carotid intima–media thickness (IMT) is a marker of early atherosclerosis, its anatomic extent and progression. Carotid intima–media thickness is increased in subjects with several risk factors and is a predictor of cardiovascular events and target organ damage (TOD).[4] In fact, considerable attention has been directed to the wall thickness of the carotid arteries as an early marker of atherosclerotic disease and as a mean of showing the effectiveness of medical therapies[4] and non-invasive techniques such as B-mode ultrasound that can directly assess the IMT, which corresponds to the thickness of the histological intima and media.[5,6] Some studies show an association between lipoprotein(a) [Lp(a)] and coronary artery disease and target organ damage in hypertensive patients.[7,8] Lp(a) is a cholesterol-rich particle existing in human plasma, first described by Berg in 1963.[9,10] Many epidemiological and case-control studies have shown that, when present in high levels in plasma, Lp(a) is recognized as an independent risk factor for premature atherosclerotic coronary heart disease.[10,11] The exact mechanism by which Lp(a) is a cardiovascular risk is unknown; however, both proatherogenic and prothrombogenic effects have been hypothesized. Nevertheless, the biological role and normal metabolism of this lipoprotein are not fully elucidated.[10,11] Atherosclerosis in hypertensive patients might therefore be accelerated by an interaction between hypertension and abnormal elevated Lp(a) values. High plasma levels of Lp(a) are considered a risk factor for the development of coronary artery diseases.[12,13] Lp(a) levels are largely genetically determined, but the detailed mechanism of Lp(a) elevation is uncertain.[12] Especially little is known about the association of serum LP(a) elevation with TOD in essential hypertensive patients, although *in vitro* experiments have shown that oxidized Lp(a) is able to impair the arterial endothelium–dependent dilation, thus suggesting a possible role of Lp(a) in the genesis of essential hypertension (EHTN).[12] Bodies of evidence have shown that IMT increases in EHTN; on the other hand, as mentioned above a few studies have shown that Lp(a) increases in EHTN. There are some other studies demonstrating that the intensification of target organ damage in EHTN is associated with higher Lp(a) values, and it has been shown that Lp(a) can be an aggravating factor in the intensification of TOD.[8] We, therefore, sought to investigate the association between serum Lp(a) elevation with carotid IMT as target organ damage in a group of essential hypertensive patients.

Methods

This is a cross-sectional study with subjects consisting of normal, healthy persons without any past history of hypertension or any other diseases (control group) and essential hypertensive patients (hypertensive group = HT group) who referred to the clinic of nephrology and hypertension or were admitted to the university hospital because of uncontrolled high blood pressure. Thus, our patients were comprised of admitted patients and out-patients. Exclusion criteria were cigarette smoking, body mass index (BMI) of more than 25, anti-lipid drug use or anti-hypertensive drugs which affect lipid profiles, as well as diabetes mellitus, recent MI, vascular diseases and acute or chronic infection. Selection criteria were patients who had not previously been treated and had their first referral for evaluation and treatment or who were uncontrolled hypertensive patients due to inadequate or inappropriate drug taking. All the patients received the primary routine evaluations of HTN for ruling-out the secondary forms of hypertension. Primary evaluation of

hypertensive patients were history taking, examination and lab exams consisting of Na, K, FBS, Ca, lipid profiles (triglycerides, cholesterol, LDL-C, HDL-C), CBC, BUN, creat, ECG, Echocardiography, kidney sonography and ophthalmology consultation for the evaluation of retinopathy. For the essential hypertensive patients, other factors serving as exclusion criteria in this group were any previous history of renal failure either acute or chronic, hypokalemia, hypercalcemia and renal size difference more than 15 mm, as well as any clinical suspicion of secondary forms of hypertension. The patients who had no clinical evidence or laboratory evidence of any secondary forms of hypertension were selected for the essential hypertension group. Group one, selected from hospital staff, had no history of hypertension or renal failure. In group two, apart from hypertension, some patients also had renal failure (RF). These patients had no previous history of RF or any other forms of kidney involvement and had a chief complaint of hypertention on admission; renal failure was diagnosed on evaluation. The patients were recruited in the study after renal paranchymal HTN or renovascular HTN as a primary cause of HTN was ruled out. After the subjects in the two groups were interviewed using a questionnaire, lab exams were performed after 14-hour fasting. All the subjects had their serum lipoprotein (a) measured by enzyme immunoassay (ELISA) with Immuno-Biological Laboratories (IBL) kit (Hamburg). Other lipids, FBS, urea, creatinine, Ca, K and Na were measured by standard kits, and serum LDL-C was calculated by Friedewald's formula.[14] Creatinine clearance (CLcr) was evaluated from serum creatinine, age and body weight.[15] According to the sixth and seventh reports of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the hypertensive patients were stratified from stages one to three.[16,17] Carotid ultasonography was performed by a single sonologist unaware of history or lab data of the patients, using a Honda-Hs-2000 Sonograph with a 7.5 MHZ linear probe. The procedure was done at the end of the diastolic phase. The sites of measurements were at the distal common carotid artery, area of bifurcation and at the proximal internal carotid artery. Carotid-IMT was measured at the plaque-free areas. The subjects were put in the supine position with neck hyperextension and rotation of the head in order to facilitate examination. Sonography revealed that the carotid artery had three different echoes. The intima-media thickness was defined as the distance from the leading edge of lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the far wall. IMT more than 0.8 mm was considered abnormal. The mean right and left carotid-IMT were cosidered for statistical analysis. Sonography for plaque occurrence, carried out in the right and left carotid and femoral arteries, was scored from 0 (no plaque) to 4 (plaque presence at all four sites). Regardless of the number and size of the plaques in each site, plaque occurrence in each site scored one point. Plaques were divided into 3 groups: soft, calcified and mixed. Plaques were considered as local intimal thickness of more than 1 mm. For statistical analysis, descriptive data are expressed as mean± SD and frequency distribution. Comparison between the groups was done with Chi-square, Mann Whitney U test and analysis of variance (ANOVA). For correlations, Spearman's rho test was used. All the statistical analyses were performed using SPSS (version 11.00), and statistical significance was inferred at a P value< 0.05.

Results

There was a total of 134 subjects (F=83, M=51), consisting of 39(F=22, M=17) normal, healthy subjects (control group) and 95(F =61, M =34) essential hypertensive patients (hypertensive group =HT group). The mean ± SD of ages in the control group and hypertensive group were 44±10 years and 57±12 years, respectively. Group one and two had CLcr of 103±5.5cc/min and 87±17.8min/cc, respectively.

Table I: Frequency distribution of age (years).

Variables		mean±SD	Minimum	Maximum
Group 1	Age	44 ±10.4	20	70
	D.D	---	---	---
	CLcr	103±5.5	100	120
Group 2	Age	57±12	25	82
	D.D	5.5±4.5	1	25
	CLcr	87±17.8	30	110

DD: duration of disease (known duration of hypertension, years) and creatinine clearance (cc/min).

Table I shows the patients' data. Table II shows that group 1 had an IMT of 0.83±0.2mm versus IMT of 1.25±0.36mm in the hypertensive group. Meanwhile, in groups one and two, serum LP(a) levels were 46.5±20mg/dl and 51±20mg/dl, respectively.

Table II: Frequency distribution of lipids (mg/dl) .

Variables		Mean±SD	Minimum	Maximum
Group 1	Lp (a)	46.5±20	10	94
	Chol	212±50	125	355
	LDL-C	132±39	75	265
	HDL-C	42±10	25	65
	Tg	154±56	50	325
Group2	Lp (a)	51±20.6	13	122
	Chol	224±50	100	385
	LDL-C	139±45	30	320
	HDL-C	43±16	20	135
	Tg	190±80	60	495

Table III. Frequency distribution of plaque scores.

	Plaque score	Frequency	Percent
Group 1	0	35	89.7
	1	3	7.7
	2	1	2.6
	3	0	0
	4	0	0
Group 2	0	55	57.9
	1	15	15.8
	2	11	11.6
	3	1	1.1
	4	13	13.7

Table III shows the frequency distribution of plaque scores in the two groups: the patients in group one had plaque scores of zero in 89.7% of the cases; one in 7.7%; and two in 2.6% of the cases, while there was no plaque occurrence in scores of 3 and 4. In group two, plaque scores were zero in 57.9%; one in 15.8%; two in 11.6%; score three in 1.1%; and score four was seen in 13.7% of the cases. In addition, all the plaques were calcified. Hypertensive patients were in stage one in 11.6%, two in 55.8% and three in 32.6%. Serum LP(a) more than 40 mg/dl was found in 56.4% of the control group and 70.5% of the HT group. For carotid-IMT, 36% of the control group had IMT more than 0.8 mm, while 85.3% of the HT group had IMT more than 0.8 mm. There were significant differences in IMT ($p<0.001$), cholesterol ($p<0.050$) and TG ($p<0.01$) between the two groups. There were no significant differences in HDL-C, LDL-C and serum LP(a) ($p>0.05$) between the two groups. Significant difference between the plaque scores of the control subjects with the HT group was observed ($p<0.01$). Statistical analysis on the normal subjects showed a significant positive correlation of plaque scores with age ($r =0.277$, $p<0.05$), as well as a significant positive correlation of carotid-IMT with age ($r =0.476$, $p<0.001$). In the hypertensive group, there were significant positive correlations of carotid-IMT with age ($r =0.416$, $p<0.001$) and also plaque scores with age ($r =0.448$, $p<0.001$). Moreover, the correlation of

plaque scores with carotid-IMT (r =0.201, p<0.05), a linear inverse correlation of carotid-IMT with creatinine clearance (r = -0.410, p<0.001) and a linear inverse correlation of plaque score with creatinine clearance (r = -0.408, p<0.001) were found, as well. There were no significant correlations of serum LP(a) with carotid-IMT or with plaque scores in this group (p>0.05). No significant association of carotid-IMT with stages of hypertention was found (p>0.05). There was no significant association of serum LP(a) with stages of hypertension, nor was there any significant association of plaque scores with stages of hypertension (p>0.05). In the normal group, there was also a positive correlation of serum LP(a) with LDL-C (r =0.362, p<0.05). In the HT patients, there was an inverse correlation of serum LP(a) with creatinine clearance (r=-0.175, p<0.05, Fig. 1).

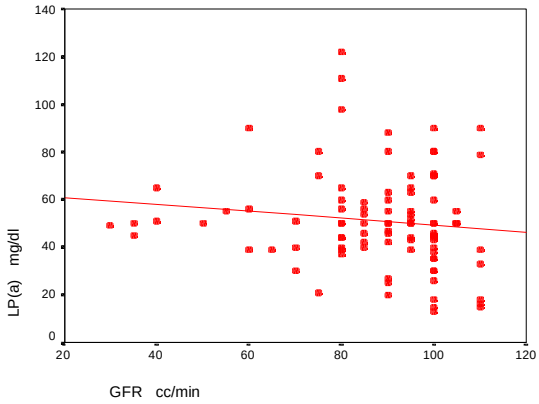

Fig. 1. Linear inverse correlation of LP(a) with CLcr in HT patients (r = - 0.175, p<0.05).

Significant positive correlation of serum LP(a) with age in hypertensive patients (r=0.191, p<0.05, Fig. 2) and positive correlation of serum LP(a) with the duration of HTN (known duration of hypertension period, Fig. 3) were found (r=0.362, p<0.05).

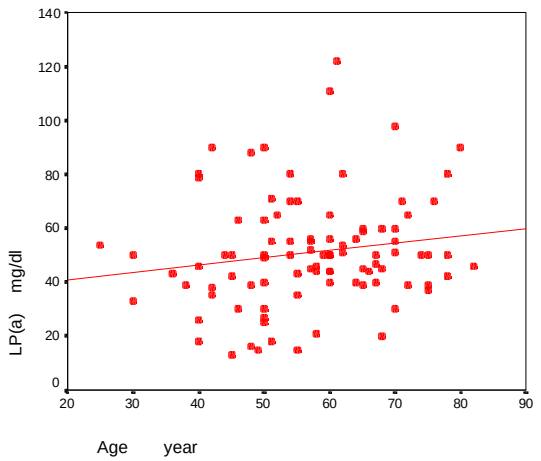

Fig. 2. Association of LP(a) with age in HT patients (r =0.191, p<0.05).

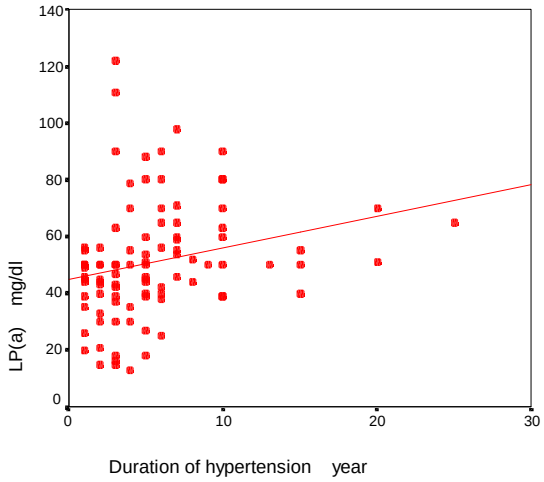

Fig. 3. Association of LP(a) with duration of hypertension in HT patients (r =0.362, p<0.05).

Discussion

This study demonstraed that hypertensive patients had more thickening of the intima-media complex, more plaque occurrence and higher serum values of cholesterol and triglyceride than normal subjects. Positive correlation of plaque scores with age in the hypertensive and control groups, positive correlation of carotid-IMT with age in the hypertensive and control groups and positive correlation of plaque scores with carotid-IMT in the hypertensive and control groups were noted. Also, inverse

correlation was found between carotid-IMT and plaque scores with creatinine clearance in the hypertensive patients. There were no significantly higher values of serum LP(a) in the HT patients compared to normal subjects. Furthermore, there was no significant positive correlation between serum LP(a) with carotid-IMT in the HT patients. Studies concerning the IMT as a marker of the onset of atherosclerosis and also as a marker of target-organ damage in essential hypertensive patients have shown some results. The study by Ghiadoni et al. on 44 patients with EHTN showed significant intima-media thickening compared with normotensive subjects.[1] Su et al., having demonstrated a significant dose-response relationship between the status of HTN and the severity of carotid sclerosis (by IMT measurement) in 263 hypertensive patients, showed that not only hypertension, male gender and age were factors which significantly increased the risk of thicker IMT but also normotensives, in comparison with hypertensives, were significantly less likely to have hypetriglyceridemia. They also observed more plaque occurrence with higher severity of HTN.[2] Hughes et al. showed a significant difference of thickening of IMT in their hypertensive group (n=34) compared with age and sex- matched normotensive individuals (n=37). Meanwhile, they observed a significant association between age and IMT in both groups.[3] Casiglia et al. in a study on 97 stage one hypertensive patients showed greater values of IMT than those in their control subjects (n=27).[18] In a study to evaluate the risk factors for subclinical carotid atherosclerosis in healthy men, Weber maintained that even in normotensive individuals, systolic blood pressure was a strong predictor of early carotid atherosclerosis.[19] In a study on 110 hypertensive patients compared with 100 normotensive subjects, Guarini et al. observed 75.4% IMT thickening versus 36% of the normotensive group; meanwhile atherosclerotic plaques were formed in 60.9% of the hypertensive group versus 25% of the normotensives.[20] Chironi et al. showed that IMT and diameter increased in the hypertensive groups treated or untreated, compared with the normotensive group.[21] Concerning plaque occurrence in essential hypertensive patients, Gariepsy evaluated carotid and femoral arterial structure in men with EHTN and showed that in 53 never treated hypertensive men and 133 matched normotensive men, there were more frequent carotid plaques in the EHTN group and that carotid and femoral-IMT was greater in this group than that in the normotensives, which is independently associated with age and systolic pressure in both arteries.[22] The studies of Guarini, Cuspidi, Gamero and their colleagues also clearly showed the increase in IMT values in hyperrtensive subjects.[24,25] Rossi et al. investigated the relationship between early carotid artery disease with Lp(a) in asymptomatic essential hypertensive patients and normotensive subjects and showed that both the prevalence and severity of sex and age-adjusted and unadjusted carotid artery lesions and IMT were significantly higher in hypertensive patients than those in controls. In this study, the predictors of IMT were age, mean blood pressure and duration of hypertension.[26] Netea et al. in a study on 168 patients with EHTN showed no difference between Lp(a) values in comparison to healthy volunteers.[27] In a study on 61 EHTN with CAD subjects, Gazzaruso et al. found higher Lp(a) levels compared to 188 EHTN patients without CAD and concluded that high Lp(a) levels were strong and independent genetic risk factors for CHD in hypertensive patients.[28] Gazzaruso in another study to evaluate the relationship between Lp(a) levels with a family history of coronary heart disease in

108 patients with EHTN showed that Lp(a) levels in hypertensives with a family history of CHD were significantly higher than those in individuals without a family history of CHD.[29] Sechi et al. investigated the association between Lp(a) and other plasma lipids and target-organ damage in patients with arterial hypertension (277 essential hypertensive patients with mild to moderate hypertension and 102 healthy controls) and demonstrated the association between Lp(a) concentrations and severity of TOD in EHTN. They concluded that Lp(a) was a sensitive indicator of the severity of TOD in EHTN, and its evaluation might permit the indentification of hypertensive subjects during the development of organ damage. They also showed that Lp(a) levels were related to TOD independent of the level of blood pressure.[8] In his study on 389 untreated essential hypertensive patients, Sechi also showed a significant correlation of Lp(a) concentration with age. Moreover, he showed that the relationship between Lp(a) and clotting variable was significantly stronger in hypertensive than in normotensive subjects.[30] In another study, Sechi evaluated Lp(a), hemostatic variables and cardiovascular damage in hypertensive patients and demonstrated elevated fibrinogen, D-dimer and Lp(a) levels, which were significantly and independently associated with clinical evidence of atherosclerotic disease (389 patients, 92control subjects). He concluded that there was a relationship between Lp(a) and clotting variables in hypertensive patients that might contribute to atherosclerotic damage in these patients. There is,however, no evidence of a genetic background for this relationship.[31] Antonicelli et al. in an interesting study concluded that Lp(a) and peroxidative stress might be involved as cofactors in EHTN with a mechanism which remains to be elucidated[12] The study of willeit et al. on a sample of 885 patients demonstrated a strong and independent association between elevated Lp(a) levels and carotid atherosclerosis and provides evidence of a potential role of Lp(a) in the evolution of carotid stenosis.[32] Catalano et al. in a study to pursue measurement of Lp(a) and the main parameters of lipid profiles in a group of essential hypertensive patients not receiving pharmacological treatment and with no clinical signs of associated pathologies or organ damage (on 123 essential hypertensive patients compared with 89 controls matched in terms of age, sex, BMI) found that hypertensive patients had higher plasma concentrations of Lp(a), total cholesterol, TG and VLDL-C than controls, with no differences in the plasma concentrations of Lp(a) between the two sexes.[33] Recently, Fytili et al., in response to the question of whether arterial hypertension is an underlying factor in the increased serum Lp(a) level in ESRD dialyzed patients, demonstrated statistically significant higher values of Lp(a) in hemodialyzed patients with HTN than in those hemodialyzed without HTN. In this study, they insisted that arterial hypertension might play an important role in Lp(a) serum titers in ESRD patients undergoing dialysis.[7] Taken together, many data point to accelerated atherosclerosis induced by HTN revealed by IMT (and plaques too). IMT is the sign of target-organ damage. We could not demonstrate the serum LP(a) elevation in our essential hypertensive patients, nor were we able to show that lipoprotein(a) had an association with carotid-IMT in our essential hypertensive patients. We, therefore, recommend more research on this aspect of essential hypertensive patients.

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