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RELATIONSHIP OF OXIDIZED LOW DENSITY LIPOPROTEINS TO CAROTID ARTERY INTIMA – MEDIA THICKNESS IN HYPERTENSIVE PATIENTS

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Abstract: Oxidation of LDL plays an important role in the pathogenesis of atherosclerosis. Increased wall thickness precedes plaque formation and noninvasive B-mode ultrasonographic measurement of IMT is considered a useful marker of the development of the carotid atherosclerosis. The present study was designed to assess the association of oxidized low-density lipoprotein (ox-LDL) with carotid intima-media thickness (IMT) in hypertensive patients. Oxidized LDL (enzyme-linked immunosorbent assay; Elisa) and carotid IMT (high-resolution B-mode ultrasonography) were assessed in 74 patients; aged between 45 and 65 years; diagnosticated with arterial hypertension. We observed significantly higher plasma levels of total cholesterol (236.32 mg %); LDL cholesterol (166.92 mg %); triglycerides (180.79 ± 72.05mg %) and low plasma levels of HDL-cholesterol (33.24 ± 7.99 mg %) in all patients. We noticed higher plasma levels of ox-LDL (77.34 mg %) and carotid IMT was increased (1.41 ± 0.31 mm). The statistically analysis done using Pearson's test and Student's t – test indicated that there were correlations of ox-LDL with: IMT ($p < 0.05$; $r=0.408$); total cholesterol ($p <0.05$; $r=0.498$); LDL-cholesterol ($p < 0.05$; $r= 0.527$); triglycerides ($p <0.05$; $r=$) and HDL-cholesterol ($p< 0.05$; $r = -0.442$). In conclusion; higher plasma levels of ox-LDL were associated with increased carotid IMT in hypertensive patients. Measurement of plasma Ox-LDL and carotid IMT may represent useful markers for atherosclerosis and may represent potential targets for therapeutic interventions. (231)

INTRODUCTION

After the initial studies by Goldstein (1979) on modification of low-density lipoprotein (LDL) and its role in atherosclerosis; several studies have investigated the role of modified LDL as a biochemical risk factor for atherosclerosis (8). Of the various modified forms of LDL; oxidized LDL (ox-LDL) has gained a lot of interest recently (2). The oxidative conversion of LDL to ox-LDL is considered to be an important event in the biologic process that initiates and accelerates the development of the early atherosclerotic lesion (10). Furthermore; circulating ox-LDL has also been proposed to give additive informations to that provided by Global Risk Assessment Scoring (6) for assessing the risk for cardiovascular diseases. Several studies have reported on increased circulating levels of ox-LDL in relation to late end points of atherosclerotic process (6) and few studies have looked at the relation of ox-LDL with subclinical atherosclerotic markers such as IMT (9). 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 (5). We investigated in our study if plasma circulating oxidized LDL was associated with the thickness of the common carotid intima-media in a group of 74 hypertensive patients.

MATERIAL AND METHODS

A number of 74 subjects (52 men and 22 women) have voluntarily completed a questionnaire for identification of cardiovascular risk factors; which comprised: personal data (age; gender); hypertension; obesity and cigarette smoking. An objective examination assessed systolic and diastolic arterial blood pressure. All patients underwent clinical and paraclinical investigations; considering hypertension evolutive stages; anatomical (bidimensional echography and Doppler ecography); morphological (carotid intima-media thickness) and functional changes (serum total cholesterol; HDL-cholesterol; LDL-cholesterol; triglycerides; oxidized LDL). Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg as mean of three measurements in at least three visits at 1-week intervals or receiving antihypertensive treatment in concordance with the guidelines for hypertension 2008. Exclusion criteria were systolic blood pressure of 220 mmHg or higher; ischemic heart disease; acute coronary syndrome; stroke; or presence of a major illness such as cancer; liver disease; renal insufficiency; insulin-treated diabetes and depression.

Measurement of intima-media thickness: Intima-media thickness (IMT) is a marker of subclinical atherosclerosis at the level of the carotid arteries. It was measured by high-frequency (≥ 8 MHz) ultrasound transducers 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 is determined as the average of 12 measurements (both sides 6 measurements each from the near and far wall of each of the three segments). A value > 1.3 mm was considered abnormal.

Biochemical analysis: The measurement of total cholesterol; HDL-cholesterol and triglyceride levels was made by current biochemical method; using Reflotom. LDL cholesterol was calculated with Friedewald formula (3). Ox-LDL was measured by enzyme-linked immunosorbent assay (Elisa). Statistic analysis: All the values were presented as mean ± standard deviation. The statistically analysis was done using Pearson's test (for correlation) and Student's t–test. $p < 0;05$ was considered statistically significant. All statistical analyses were performed using Excel Microsoft Office 2003. Pearson correlation analysis was carried out to determine the relation of ox-LDL with other risk variables (total cholesterol; HDL-cholesterol; LDL-cholesterol; triglycerides) and to determine the association of ox-LDL with IMT.

RESULTS AND DISCUSSIONS

Distribution of traditional cardiovascular risk factors and laboratory measurements of the study participants are shown in Table 1.The subjects were predominantly male and were commonly overweight. Many subjects reported current smoking and a history of hypertension.

Table 1

Characteristics of the study subjects (n = 74)

Characteristics	**Mean ± SD**
Age (years)	56.63 ± 11.62
Systolic blood pressure (mm Hg)	183.92 ± 19.06
Diastolic blood pressure (mm Hg)	98.42 ± 5.71
Total cholesterol (mg/dl)	236.32 ± 41.96
Triglycerides (mg/dl)	180.79 ± 72.05
LDL cholesterol (mg/dl)	166.92 ± 38.55
HDL cholesterol (mg/dl)	33.24 ± 7.99
Mean carotid IMT (mm)	1.41 ± 0.31
Ox-LDL (mg/dl)	77.34 ± 24.78

The correlation between ox-LDL and total cholesterol was direct; moderate and significant ($p < 0.05$; $r=0.498$). The correlation between ox-LDL and HDL-cholesterol was inverse; weak and significant ($p < 0.05$; $r = -0.442$). The correlation between ox-LDL and LDL was moderate; direct and significant ($p < 0.05$; $r= 0.527$). The correlation between ox-LDL and triglycerides was weak; direct and significant ($p=0.032$ and $r=0.285$).

The correlation between ox-LDL and IMT was direct; weak and significant (fig. 1)

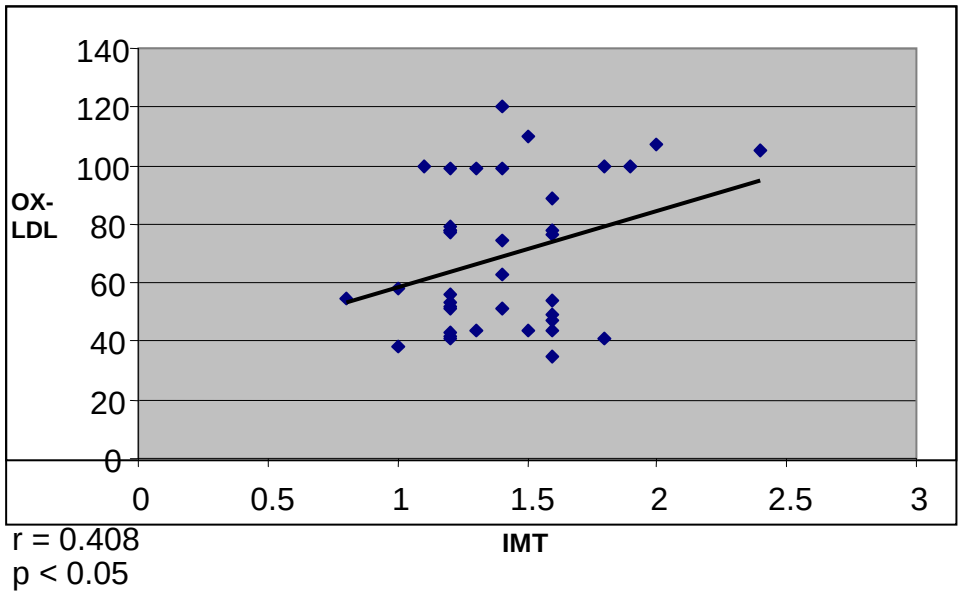

Fig. 1. Correlation between ox-LDL and IMT

Arterial thickening provides the earliest evidence of atherosclerosis; or hardening of the arteries; the beginning stage of a disease process that leads to heart disease and stroke (Figure 2). The correlations coefficient between ox-LDL; lipid parameters and IMT were presented in table II. The role of ox-LDL in atherosclerosis is well recognized (10).

The results of the present study showed that ox-LDL was related to carotid IMT and plaque occurrence in the carotid arteries. It has been hypothesized that LDL is oxidized in the intima of the arterial vessel wall. Oxidized LDL increases the adherence and penetration of monocytes; by stimulating monocyte chemoattractant protein-1 (MCP-1) and the inflammatory process; resulting in foam cell formation and thereby triggering the atherosclerotic lesion (11). Oxidized LDL is found in monocyte-derived macrophages in atherosclerotic lesion; but not in normal arteries (1). It has also been suggested that ox-LDL induces smooth muscle cell proliferation (7).

Table 2.

Correlations coefficient between ox-LDL; lipid parameters and IMT

Variant	**r**	**P**
CT	0.498	<0.05
LDL-Cholesterol	0.527	<0.05
HDLcholesterol	-0.442	<0.05
Triglycerides	0.385	0.032
IMT	0.408	<0.05

Our study also supports an earlier prospective study; which showed that baseline ox-LDL was associated with number of plaques in the carotid artery (12). Furthermore; ox-LDL has been shown to be directly related to the severity of the disease; assessed by angiography (9). In the study by Hulthe and Fagerberg 2002; ox-LDL showed a good correlation with cytokines; indicating its role in triggering the immune system. Furthermore; earlier studies provided evidence for the role of ox-LDL in triggering adhesion of monocytes favoring the progression of atherosclerotic process (10). Previous studies of patients with acute coronary syndromes have suggested that elevated serum levels of ox-LDL could be explained by ruptured atherosclerotic plaques; ischemic injury; or even remote inflammatory sources (13).

The results of the present study are also in accordance with the study of Hulthe; Fagerberg and Metso who showed that ox-LDL showed a strong association with IMT (12).

CONCLUSSIONS

To conclude; the finding that circulating oxidized LDL is associated with the severity of coronary atherosclerosis supports the hypothesis that oxidized LDL has a profound role in the development of atherosclerosis. Intima–media thickness of the internal carotid artery is strongly associated with the risk of myocardial infarction and stroke in hypertensive patients. Measurements of carotid-artery intima–media thickness retain predictive power with respect to new cardiovascular events even after traditional risk factors for cardiovascular events have been taken into consideration; moreover; such measurements seem more powerful predictors than these same risk factors.

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