OxLDL Is a Possible Marker for Increased Risk of Acute Coronary Syndromes in Syrian Patients

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□ ABSTRACT □

Objective: The aim of this study was to evaluate the usefulness of circulating oxidized low-density lipoprotein (OxLDL) as a risk marker of coronary artery disease (CAD) expressed in acute coronary syndromes (ACS) in comparison to low-density lipoprotein (LDL).

Methods: A total of 78 subjects were included: 60 patients with angiographically proven acute coronary syndromes divided into acute myocardial infarction group (AMI, n=30) and unstable angina group (UA, n=30) and 18 subjects without clinical evidence of coronary artery disease served as controls. OxLDL levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA). LDL levels were measured using enzymatic method.

Results: Plasma levels of OxLDL were significantly higher in each disease group than in control ($p<0.001$). The highest OxLDL levels were associated with the presence of hypertension and/or diabetes. OxLDL levels were correlated strongly with LDL levels in controls but weakly in ACS patients. The sensitivity and specificity for diagnosing ACS were 93% and 89% respectively for OxLDL versus 77% and 72% for LDL.

Conclusion: Circulating OxLDL is a better biomarker than LDL for discriminating between patients with ACS and healthy subjects. High levels of OxLDL could be a promising risk marker for coronary artery disease (CAD).

Key Words: oxidized low-density lipoprotein, low-density lipoprotein, acute coronary syndromes, risk marker.

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البروتين الشحمي منخفض الكثافة المؤكسد هو مؤشر محتمل لارتفاع خطورة الإصابة بالمتلازمات الإكليلية الحادة لدى المرضى السوريين

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□ ملخّص □

الأهداف: يعد البروتين الشحمي منخفض الكثافة المؤكسد عاملاً مفتاحياً في بدء وتطور التصلب العصيدي. الهدف من هذه الدراسة هو تقييم فائدة مستويات البروتين الشحمي منخفض الكثافة المؤكسد الجائل في الدم كمشعر خطورة للمتلازمات الإكليلية الحادة بالمقارنة مع البروتين الشحمي منخفض الكثافة.

الطرق: اشتملت الدراسة على 78 مشارك: 60 مريضاً تم تشخيص إصابتهم بالمتلازمات الإكليلية الحادة بواسطة القثطرة القلبية (30 مريضاً مصاباً باحتشاء العضلة القلبية الحاد و30 مريضاً مصاباً بخناق الصدر غير المستقر) و18 مشاركاً من الشواهد ممن ليس لديهم دليل سريري على الإصابة بداء قلبي إكليلي. تمت معايرة مستويات البروتين الشحمي منخفض الكثافة المؤكسد بتقنية الإليزا وتمت معايرة مستويات البروتين الشحمي منخفض الكثافة بطريقة أنزيمية.

النتائج: كانت مستويات البروتين الشحمي منخفض الكثافة المؤكسد أعلى بشكل هام إحصائياً في كل من مجموعتي المرضى منه لدى الشواهد ($p<0.001$) وكانت المستويات الأعلى لدى مرضى المتلازمات الإكليلية المصابين بارتفاع الضغط الشرياني و/أو الداء السكري. لوحظ وجود ارتباط قوي بين مستويات البروتين الشحمي منخفض الكثافة المؤكسد ومستويات البروتين الشحمي منخفض الكثافة لدى الشواهد، لكن الارتباط كان ضعيفاً لدى مرضى المتلازمات الإكليلية الحادة. بلغت الحساسية والنوعية في تشخيص المتلازمات الإكليلية الحادة بالنسبة للبروتين الشحمي منخفض الكثافة المؤكسد 93% و89% على التوالي مقابل 77% و72% بالنسبة للبروتين الشحمي منخفض الكثافة.

الاستنتاجات: مستويات البروتين الشحمي منخفض الكثافة المؤكسد هي مشعر حيوي أفضل من البروتين الشحمي منخفض الكثافة للتفريق بين مرضى المتلازمات الإكليلية الحادة والأصحاء. المستويات العالية من البروتين الشحمي منخفض الكثافة المؤكسد قد تكون مشعر خطورة واعد للداء القلبي الإكليلي.

الكلمات المفتاحية: البروتين الشحمي منخفض الكثافة المؤكسد، البروتين الشحمي منخفض الكثافة، المتلازمات الإكليلية الحادة، عامل خطورة.

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Introduction:

Coronary artery disease (CAD) is the leading cause of death worldwide (1). CAD is most often caused by atherosclerosis (2), Which is a multifactorial disorder, and involves many processes, such as lipoprotein retention, lipoprotein modification and aggregation, endothelial alteration, macrophage chemotaxis and foam cell formation, and smooth muscle cell migration and alteration (3), having as ultimate outcome the atheromatous plaque that gradually narrows the vessel lumen and impedes blood flow. This process may last for decades until rupture of plaque, resulting in acute coronary syndromes (4). Among the pathological mechanisms of atherosclerosis, lipid deposition has been most extensively studied (5). Accumulation of cholesterol in macrophages leads to foam cell formation which is an early critical step in the development of atherosclerotic plaque (6). Low-density lipoprotein (LDL) was suggested to be the main source of cholesterol accumulating in developing foam cells (7). Elevated level of LDL is a major risk factor for atherosclerotic disease (3). However, many cardiovascular events occur despite an optimal levels of LDL (8). Consequently, it was reported that oxidative modification of native LDL is a prerequisite for foam cells formation (7, 9). The modification of native LDL shifts the recognition and internalization of the lipoprotein from the LDL receptors (LDL-Rs) to novel receptors called scavenger receptors (SRs) (10). Contrary to LDL-Rs, SRs are not down regulated by elevated levels of intracellular cholesterol (11). The enhanced endocytosis of oxidized LDL (OxLDL) by macrophages leads to remarkable cholesterol accumulation (12). Therefore concentration of OxLDL that is needed to induce foam cell formation is 40-fold less than that of LDL (13). Several studies have confirmed that OxLDL is involved in the very early critical steps of atherogenesis, such as endothelial injury, expression of adhesion molecules, and leukocyte recruitment and retention, as well as thrombus formation (14). It has also been shown that OxLDL contributes to the endothelial dysfunction and plaque destabilization (15), Thus, it may represent a promising risk marker for clinical CAD complications. We therefore designed and performed the present study to examine the usefulness of circulating OxLDL levels as a biochemical risk marker of CAD in comparison to LDL.

Materials and methods

1. Study population

The study was performed at Tishreen University Hospital. Between October 2020 and August 2021, seventy eight individuals were included: 60 patients with angiographically proven acute coronary syndromes (ACS) [30 patients with acute myocardial infarction (AMI) and 30 patients with unstable angina (UA)] and 18 control subjects. The control group (n= 18) included healthy subjects with normal blood lipid, without evidence of CAD, stroke, hypertension or diabetes mellitus. Considering that statins can affect blood lipid levels and inhibit oxidative stress, anyone who treated with statins before sampling was excluded from the study. We also excluded patients who treated with antioxidants, patients under 18 years old and patients with renal, liver, or thyroid dysfunction.

2. Blood sampling

Venous blood samples were taken in the fasting state in patients with ACS and in control subjects. Blood was collected in both heparin and EDTA containing tubes and promptly centrifuged at 3000 g for 15 min within one hour after collection. After separation, Plasma LDL levels were determined immediately in heparinated samples using standard enzymatic method. Whereas, EDTA plasma aliquots were stored frozen at -20°C until the assay for determination of OxLDL levels was performed.

3. Laboratory analysis

Plasma OxLDL was measured by a sandwich ELISA method that is designed for the determination of oxLDL/MDA adducts. Briefly, plasma samples were diluted and added to the microtiter wells precoated with high affinity antibody, and incubated for 1 hour at room temperature on a horizontal shaker. OxLDL in the plasma would bind to the coated antibody. After sucking out the supernatant in the wells, the wells were washed with washing buffer for five times. After the final wash, the plate was inverted and tapped firmly against absorbent paper. After these procedures, the composition that had not binded to the coated antibody was washed off. Peroxidase-labeled goat anti-human oxLDL was added in each well and incubated for 1 hour at room temperature on a horizontal shaker. Supernatant was removed and wells were washed with washing buffer for five times. After the final wash, the plate was inverted and tapped firmly against absorbent paper. The unbinded composition was washed off. Tetramethylbenzidine (TMB) was added in each well and incubated for 10-20 min at room temperature without shaking. Then stop solution was added in each well and shaken gently to terminate the reaction. Optical density (OD) was determined immediately with an ELIZA reader at 450 nm.

4. Statistical analysis

SPSS version 22 was used for analyzing the present data. Continuous variables were presented as mean±SD and categorical variables as numbers (percentages). The distribution of the continuous data was analyzed with the Shappiro test. Chi-square test was applied to compare the difference of sex in each group. We used Mann-Whitney test and Kruskal-Wallis test for non-normally distributed variables, while independent sample t-test and ANOVA test were used for normally distributed variables. The correlation between circulating levels oxLDL and other variables was tested by pearson correlation coefficient. Receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of the candidate markers. A level of $p<0.05$ was considered statistically significant.

Results

1. Population characteristics:

Population characteristics are shown in (Table 1). There were no significant differences between groups with regard to gender and the prevalences of hypertension and diabetes mellitus. Whereas age mean was greater in UA group than AMI and control groups (p=0.004). The problem of age mismatching between groups was overcome by demonstrating the absence of relationship between age and OxLDL (fig 3) or LDL levels (data not presented).

TABLE 1. Population characteristics

Characteristics	AMI (n=30)	UA (n=30)	Control (n=18)	P-value
Age, y				
mean±SD	54.8±12.5	60.2±12.8	41.4±19	0.004
Range	38-48	37-87	18-71	
Sex (male %)	70	80	67	>0.05
Hypertension%	16.6	36.6	-	0.2
Diabetes mellitus%	16.6	6.6	-	0.26
Hypertension+diabetes mellitus%	20	16.6	-	0.73

Values are given as mean±SD or n%. AMI indicates acute myocardial infraction; UA, unstable angina.

2. OxLDL and LDL levels in study groups:

Plasma levels of OxLDL and LDL in each group are shown in (Table 2).

Plasma levels of OxLDL were significantly higher in ACS group than in controls. Mean value of OxLDL in control subjects were 108.3±36.3 ng/ml, whereas it was 4.2-fold higher in ACS group (p<0.001) [3-fold higher in patients with unstable angina (p<0.001) and 5.3-fold higher in patients with acute myocardial infarction (p<0.001)]. Standard deviations of OxLDL levels were high in each group.

Plasma levels of LDL were significantly higher in ACS patients than in controls (p<0.001), but there was no statistical difference between patient groups (p=0.182).

TABLE 2. Plasma levels of OxLDL and LDL in study groups

	AMI (n=30)	UA (n=30)	Control (n=18)	P-value
OxLDL (ng/ml)	581.8±170.2	329.2±144.8	108.3±36.3	<0.001
LDL (mg/dl)	119.2±20	112.3±19.3	92.2±19.2	<0.001

Values are given as mean±SD. OxLDL indicates oxidized low-density lipoprotein; and LDL, low-density lipoprotein

3. Correlation between OxLDL and LDL plasma levels

Plasma levels of OxLDL were positively correlated with LDL levels in both ACS patients and control groups. However, correlation was strong in controls, while it was weak in individuals with ACS, where OxLDL levels were increased more than LDL levels (Table 3).

TABLE. 3. Correlation between circulating levels of OxLDL and LDL in patients and controls

	OxLDL			
	Controls		ACS patients	
	R	P-value	R	p-value
LDL	0.647	0.004	0.026	0.045

4. Receiver-operating characteristic analyses

To understand the diagnostic role of OxLDL levels as an indicator of coronary artery disease, receiver-operating characteristic (ROC) curve analysis was done. ROC curve analysis of OxLDL levels compared to LDL revealed that OxLDL levels showed superior diagnostic performance in the overall patients.

The area under the curve (AUC) for both OxLDL and LDL were more than 0.5 (p<0.001). At a cutoff value of 155 ng/ml, the sensitivity for OxLDL was 93%, the specificity was 89%, false negative was 7% and false positive was 11%. At a cutoff value of 104.4 mg/dl, the sensitivity for LDL was 77%, the specificity was 72%, false negative was 23% and false positive was 28%. The cutoff value of OxLDL and LDL, the receiver-operating characteristic curve (ROC), and the AUC for diagnosing CAD are shown in (Table 4) and (Fig. 1).

TABLE 4. Area under the ROC curve, sensitivity and 1-specificty for OxLDL and LDL in ACS patients

	OxLDL	LDL
AUC	0.969	0.798
P-value	<0.001	<0.001
Cutoff value	155 ng/ml	104.4 mg/dl
Sensitivity (%)	93	77

Specificity (%)	89	72
1-sensitivity (%)	7	23
1-specificty (%)	11	28

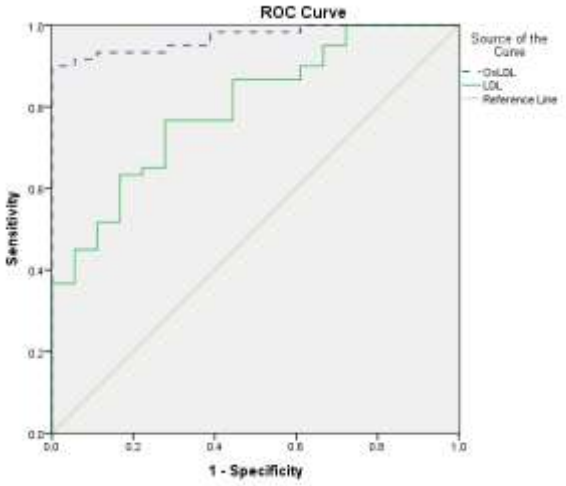
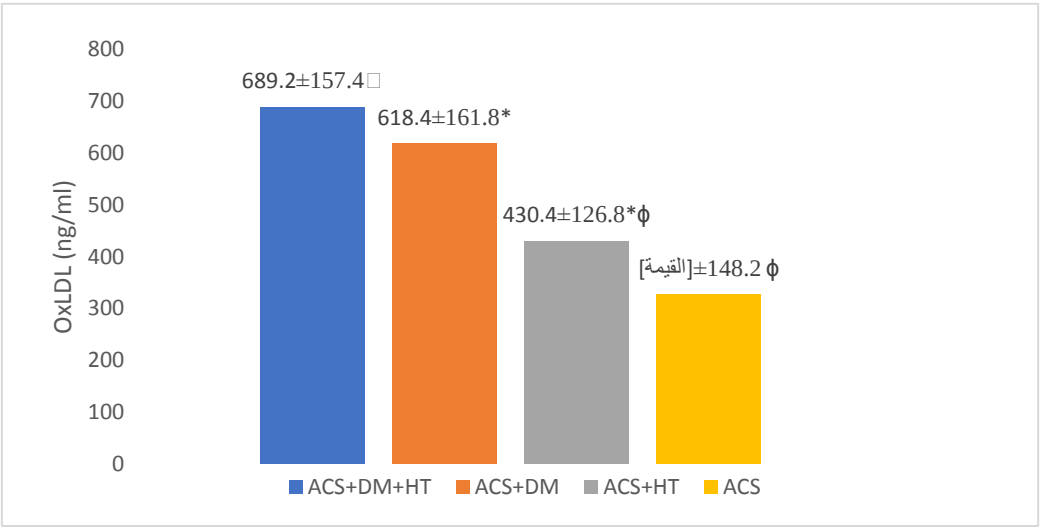


Fig. 1. Receiver-operating characteristic curves for OxLDL and LDL.

5. The relationship of OxLDL with some variables in study population

Firstly, we evaluated the impact of hypertension and diabetes mellitus as comorbidities on oxidation of LDL. Patients with ACS (defined as unstable angina or acute myocardial infarction) were further categorized into 4 groups: acute coronary syndrome alone (ACS) group, ACS with hypertension group (ACS+HT), ACS with diabetes mellitus group (ACS+DM), and ACS with hypertension and diabetes group (ACS+HT+DM). Data is shown in (Fig. 2).

Our findings demonstrate that OxLDL levels were higher in ACS+HT and ACS+DM groups than in ACS group, while the highest levels were found in ACS+HT+DM group.



***: p<0.05 vs ACS group ϕ: p<0.05 vs ACS+DM+HT group**

Fig. 2. Plasma OxLDL levels in ACS patients according to the presence of hypertension (HT) or diabetes mellitus (DM) as comorbidities.

Secondly, we analyzed the relationship of OxLDL with age and sex in study population. Concerning sex, mean levels of circulating OxLDL were similar among men and women in each group (Table 5).

To exclude the impact of age variation on levels of OxLDL, we studied correlation between plasma levels of OxLDL and age. No correlation was detected between the two variables (P=0.415, r=0.094) (Fig. 3).

TABLE 5. Plasma levels of oxLDL in men and women in study groups

		AMI (n=30)	UA (n=30)	Control (n=18)
OxLDL (ng/ml)	Male	578±129.6	345±145.9	105.4±29.3
	Female	590.7±250.8	266±133	114.2±50.3
P-value		0.57	0.3	0.6

Values are given as mean±SD.

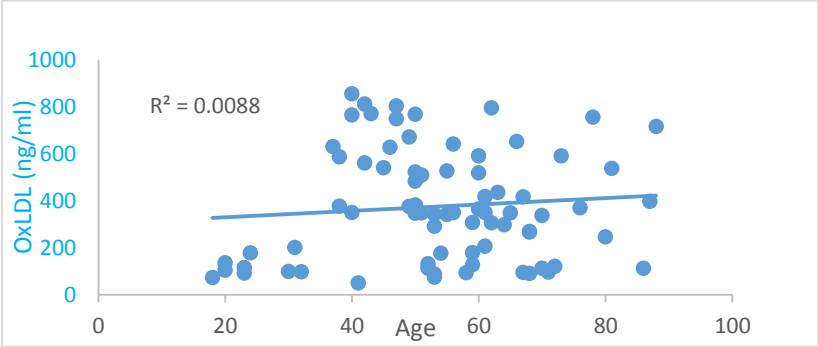


Fig. 3. Correlation between circulating levels of OxLDL and age in study population.

Discussion and conclusion

It is now widely accepted that oxidative modification of low-density lipoproteins (LDL) convert these native particles into atherogenic particles (16). In this study we investigated the usefulness of OxLDL plasma average as a risk marker for CAD compared to LDL plasma average. We found that plasma levels of OxLDL were 4.2 times higher in ACS patients than controls. This result strongly suggests that OxLDL plasma levels could serve as a marker for cardiovascular events. This finding is consistent with several studies. Imazu et al. reported that OxLDL plasma levels were higher in patients with ACS than in patients with normal coronary artery (7). Ehara et al. reported that OxLDL levels showed a significant positive correlation with the severity of acute coronary syndromes (17). Consistent with this finding, we found that OxLDL levels were higher in AMI group (5.3-fold higher than control) than UA group (3-fold higher than controls). This indicates that the severity of ACS increases with the increasing of OxLDL levels.

Several studies have suggested that elevated plasma levels of OxLDL may reflect its release from atheromatous plaque (18, 19). In our study, the correlation between plasma levels of OxLDL and LDL was strong in controls. However, correlation was weak in patients group. The release of OxLDL from ruptured plaque into the circulation may be the source of its elevated levels, and thereby the lack of its correlation with LDL levels in ACS group, which suggests a diagnostic potential of OxLDL levels in ACS. Imazu et al. concluded a similar result. In their study, there was no correlation between levels of OxLDL and LDL in ACS group (p=0.27) despite the presence of a moderate correlation in healthy subjects (r=0.42, p=0.05) (7). In contrast, Meisinger et al. reported a strong

correlation in both patients and control groups (r=0.69, r=0.66, respectively; p<0.001) (14). However, their study included ACS patients in addition to patients with stable angina, a condition that does not involve ruptured plaque, which may influence the correlation significantly in patients group.

In this study, we compared the diagnostic accuracy of OxLDL with LDL, which is a biomarker that has been suggested to identify patients with an increased risk of CAD. Receiver-operating characteristic curve analysis confirmed superior performance of OxLDL levels. The present observations suggest that OxLDL is a better biomarker than LDL for discriminating between patients with ACS and healthy subjects. Patients who have plasma levels of OxLDL over 155 ng/ml may have a higher risk for ACS. Our result is consistent with several studies showing the diagnostic potential of OxLDL levels in the management of atherosclerotic disease (4, 6).

It is well established that hypertension and diabetes mellitus are risk factors of CAD. In this study we investigated the possible role of hypertension and diabetes in increasing circulating OxLDL. Our results demonstrated that OxLDL levels were higher in ACS+HT and ACS+DM groups than in ACS group. Moreover, the highest level of OxLDL was in ACS+HT+DM group. This finding suggests that hypertension and diabetes mellitus may accelerate the oxidation of LDL.

Atherosclerosis tends to occur earlier and to be more aggressive in patients with diabetes (20). One of the mechanisms that could accelerate atherosclerosis in diabetes is the non-enzymatic glycosylation of lipoproteins in arterial walls (13). The glycosylation process occurs both on the apoprotein B (apoB) and phospholipid components of LDL (21). Therefore, glycation increases LDL susceptibility to oxidative modification and leads to functional alterations in LDL affinity to LDL receptors, which affects LDL clearance (22). Moreover, the formation of advanced glycation end-products (AGEs) is associated with enhanced production of free radicals in arterial wall (23). Thus LDL in these patients could be more easily oxidized, simply because of its presence in an oxidative milieu (24).

Furthermore, our findings confirmed those of previous studies suggesting that LDL obtained from patients with hypertension is more susceptible to oxidation (25-27). It was shown that LDL from hypertensive patients has increased content of lipid peroxides and unsaturated fatty acids, compared to control LDL, and this could be related to the enhanced LDL oxidizability in these patients (28). Keidar et al. reported that angiotensin II (Ang-II) stimulates macrophage lipid peroxidation, thus it can lead to cell-mediated oxidation of LDL. Moreover, Ang-II enhances scavenger receptor affinity to OxLDL and increases the number of these receptors on macrophages. Therefore, it was suggested that angiotensin II might play an important role in the development of atherosclerosis in patients with hypertension via LDL oxidation (29).

Plasma levels of OxLDL were independent of sex and not correlated with age in the study population. Thus OxLDL levels were not affected by these factors in our study.

In this study we observed that OxLDL has high standard deviatons in all tested groups, and this may be due to the wide range of its levels in each group. .

Our study have several limitations. First, control group was determined based on the absence of clinical symptoms and family history of CAD not on the basis of catheterization. Second, the study population was small. Our findings need to be proven in a larger patient population.

In conclusion, our study suggested that OxLDL could be a better indicator of CAD clinically expressed in acute coronary syndromes than LDL. Patients who have higher

levels of OxLDL may have a higher risk for CAD. In other words, OxLDL could be a possible promising marker of increased risk for CAD. However, further investigations should be directed toward establishing the diagnostic implications of this biomarker.

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