

Assessment of immunoglobulin G antibodies against oxidized low-density lipoproteins in patients with acute coronary syndrome

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Background

Oxidative modification of low-density lipoproteins (LDLs) induces formation of immunogenic epitopes in the LDL molecule, which leads to the formation of antibodies against oxidized low-density lipoprotein (OxLDL) that can be detected in serum.

Aim of the study

The objective of this study was to evaluate the association between autoantibodies against OxLDL and acute coronary syndrome (ACS).

Patients and methods

A total of 50 patients diagnosed as having ACS (37 male patients and 13 female patients), age ranging between 19 and 82 years and admitted to the critical care department, Cairo University, and 19 matched healthy controls were enrolled in our study. All patients were subjected to detailed medical history-taking and physical examination, serial 12-lead ECGs, serial cardiac biomarkers on admission and 24 h later, echocardiography, coronary angiography and assessment of severity using the Gensini score, and IgG anti-OxLDL antibodies measurement.

Results

We found significant difference in the level of antibody between patients with ACS and matched healthy controls ($P < 0.001$). With respect to the correlation of anti-OxLDL antibodies and the severity of ACS, we found significant correlation between the level of antibodies in patients with ACS as assessed by the Gensini score ($r = 0.709$) as well as between the echocardiographic findings as assessed by the wall motion score index ($r = 0.589$). During hospitalization, there was significant correlation of the antibody level with mechanical complications ($P = 0.047$) and needed immediate intervention ($P < 0.001$). However, the antibody level was correlated with malignant arrhythmias but P value (0.219) was insignificant because of high SD, and there was no correlation with ischemic complications ($P = 0.798$).

Conclusion

With respect to the correlation of anti-OxLDL antibodies and ACS, the patients with ACS had higher anti-OxLDL antibodies level. In addition, anti-OxLDL antibodies level was correlated with the Gensini score, wall motion score index, and major adverse cardiovascular events during hospitalization.

Keywords:

acute coronary syndrome, low-density lipoprotein antibodies, Immunoglobulin G

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Introduction

Atherosclerosis is a syndrome affecting arterial blood vessels.

Oxidative modification of low-density lipoproteins (LDLs) induces formation of immunogenic epitopes in the LDL molecule, which leads to the formation of antibodies against oxidized low-density lipoproteins (OxLDL) that can be detected in serum [1].

The clinical importance of these autoantibodies is still under discussion.

Some studies have questioned the actual contribution of anti-OxLDL in atherogenesis and had no significant differences between the titers of these antibodies in normal controls and in patients with chronic or acute coronary artery disease (CAD) [2]. Within this context, the objective of this study was to evaluate the

association between autoantibodies against OxLDL and acute coronary syndrome (ACS).

Patients and methods

Between October 2011 and December 2012, 50 patients diagnosed as having ACS (37 male patients and 13 female patients), age ranging between 19 and 82 years and admitted to the Critical Care Department, Cairo University, and 19 matched healthy controls were enrolled in our study. Patients with ACS who had major adverse cardiovascular events (MACE) were stratified as the high-risk group and those without as the low-risk group.

Patients with connective tissue diseases, malignancies, liver failure, renal failure, and patients maintained on corticosteroids were excluded from the study.

All patients were subjected to the following: detailed medical history-taking and physical examination, serial 12-lead ECGs, serial cardiac biomarkers on admission and 24 h later, echocardiography for assesment of the severity using the wall motion score index (WMSI), global systolic function, ejection fraction (EF) and assessment of the WMSI, coronary angiography and assesment of the severity using the Gensini score, and immunoglobulin G (IgG) anti-OxLDL antibodies measurement.

The WMSI is a numerical score assigned to each wall segment on the basis of its contractile function as assessed visually: 1 = normal (>40% thickening with systole); 2 = hypokinesis (10–40% thickening); 3 = severe hypokinesis to akinesis (<10% thickening); 4 = dyskinesis; and 5 = aneurysm. On the basis of this wall motion analysis scheme, a WMSI is calculated to semiquantitate the extent of regional wall motion abnormalities.

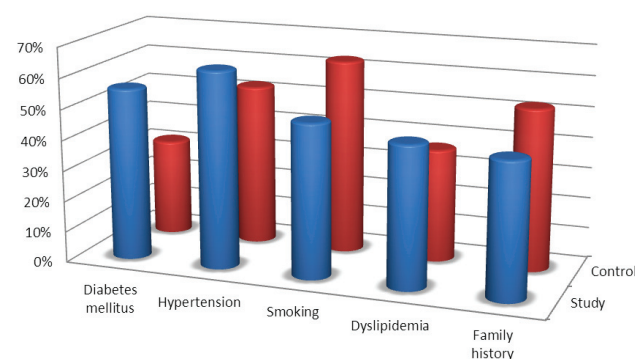
$$\text{WMSI} = \frac{\text{Sum of wall motion scores}}{\text{Number of segments visualized}}$$

Peripheral blood was obtained by routine venipuncture at the time of admission, and serum samples were processed and IgG anti-OxLDL antibody levels were determined using ELISA.

Statistical analysis

Data were statistically described in terms of mean±SD, frequencies (number of cases), and % when appropriate. Comparison of numerical variables between the study groups was carried out using the Student *t*-test for independent samples. For comparing categorical data, the χ^2 -test was performed. Correlation between various variables was determined using the Spearman rank correlation equation for non-normal variables. *P* values less than 0.05 was considered statistically significant.

Figure 1



Risk factors in study and control groups

All statistical calculations were carried out using computer programs, Microsoft Excel 2007 (Microsoft Corporation, New York, USA) and statistical package for the social sciences (SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

Descriptive data

Demographic analysis

The age of our patients ranged between 19 and 82 years. Gender distribution in the study patients (37 male patients and 13 female patients) (Fig. 1).

Risk factors for CAD

The risk factors for CAD.

Complications of ACS

In our study group, malignant arrhythmias were present in nine patients (18%), mechanical complications were present in 16 (32%), and 10 patients (20%) in the study group had recurrent ischemia as shown in Figure 2.

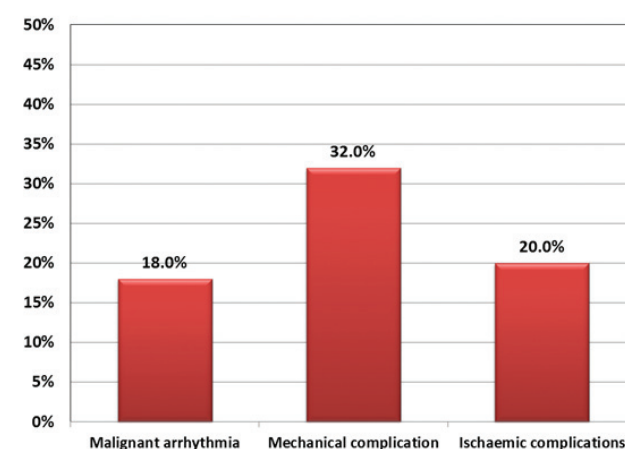
ECG and cardiac biomarkers

In our study group, 11 patients (22%) had unstable angina, 12 (24%) had NSTEMI (Non st segment elevation myocardial infarction), and 27 (54%) had STEMI (st segment elevation myocardial infarction) against 19 healthy controls.

Echocardiographic data

Left ventricular ejection fraction (LVEF): In our study, the systolic function of LV was assessed by echocardiography and mean LVEF is shown in Figure 3.

Figure 2



Complications of acute coronary syndrome in the study group.

WMSI: In our study, we found that WMSI averaged 1.46 ± 0.36 in the high-risk group (24 patients) as against 1.29 ± 0.25 in the low-risk group (26 patients), whereas it was 1.0 in the control group as shown in Table 1.

Gensini score: Our results showed that the median number of the Gensini score varied according to the study group. It was 66.5 in the high-risk group and 39 in the low-risk group, whereas in the control group it was 0 as shown in Figure 4.

OxLDL antibodies: Our study population showed variable levels of antibodies. The median number was 7250 in the high-risk group and 7255 in the low-risk group, whereas in the control group it was 198 as shown in Tables 2 and 3.

Immediate coronary intervention: In our study, 21 (42%) patients had primary percutaneous coronary intervention (PCI) as against none of the participants in the control group (Figs. 5–13 and Tables 4–8).

Correlations

OxLDL antibodies and correlations with other variables

- (1) *OxLDL antibodies and age and sex:* There was no statistically significant correlation between age or sex of the patients in the whole study groups and the antibodies level.
- (2) *OxLDL antibodies and diabetes:* There was no statistically significant difference between diabetes and the antibody level ($P = 0.421$).
- (3) *OxLDL antibodies and hypertension:* There was no statistically significant difference between hypertension and the antibody level ($P = 0.985$).
- (4) *OxLDL antibodies and smoking:* There was no statistically significant correlation between smoking and the antibody level ($P = 0.459$).

- (5) *OxLDL antibodies and dyslipidemia:* There was no statistically significant difference between dyslipidemia and the antibody level ($P = 0.813$).
- (6) *OxLDL antibodies and family history of ischemic heart disease:* There was no statistically significant difference between patients with family history

Table 1 WMSI in the study population

Groups	Number of patients	Mean	±SD
Study			
Low-risk group	26	1.29	0.25
High-risk group	24	1.46	0.36
Control	19	1	0

WMSI, wall motion score index.

Table 2 OxLDL antibodies in the study population

Groups	Frequency	Median	Minimum	Maximum
Study				
Low-risk group	26	7255	146	36 500
High-risk group	24	7250	48	17 500
Control	19	198	33	7000

OxLDL, oxidized low-density lipoprotein.

Table 3 Correlation between OxLDL antibodies and mechanical complications

Mechanical complication	OxLDL antibodies level (μ/ml)			P value
	Median	Minimum	Maximum	
No	5620	33	36 500	0.047
Yes	7500	3250	17 500	

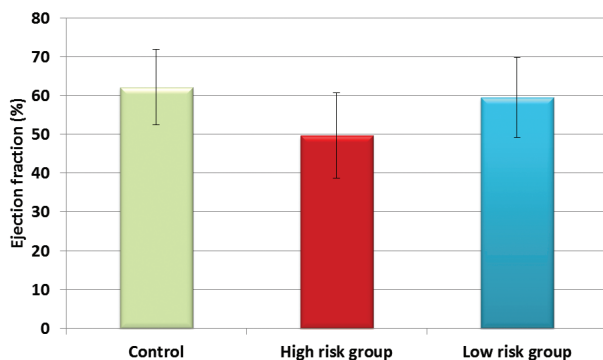
OxLDL, oxidized low-density lipoprotein.

Table 4 Correlation between OxLDL antibodies and patients who had primary PCI

Primary PCI	OxLDL antibodies level (μ/ml)			P value
	Median	Minimum	Maximum	
No	4175	33	36 500	<0.001
Yes	8100	3250	25 000	

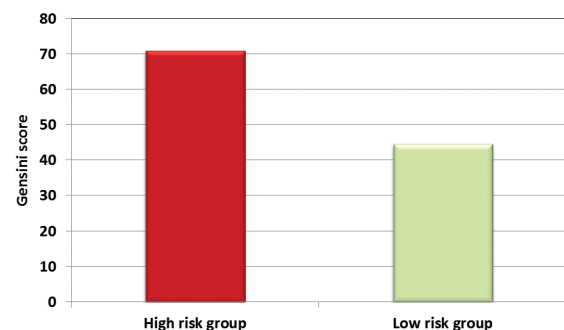
OxLDL, oxidized low-density lipoprotein; PCI, percutaneous coronary intervention.

Figure 3



Left ventricular systolic function (ejection fraction) in the three studied groups.

Figure 4



Median Gensini score in the high-risk and low-risk groups.

of ischemic heart disease and the antibodies level ($P = 0.393$).

- (7) *OxLDL antibodies and malignant arrhythmias*: There was no statistically significant difference between patients with malignant arrhythmias and the antibody level ($P = 0.219$).
- (8) *OxLDL antibodies and mechanical complications*: There was statistically significant relationship between patients with mechanical complications and the antibodies level ($P = 0.047$) and demonstrated in Figure 5.
- (9) *OxLDL antibodies and ischemic complications*: There was no statistically significant difference between patients with ischemic complications and the antibody level ($P = 0.798$).
- (10) *OxLDL antibodies and primary PCI*: There was statistically significant positive difference between patients who had primary PCI and the antibody level ($P < 0.001$) as shown in Table 4 and demonstrated in Figure 6.
- (11) *OxLDL antibodies and MACE*: Patients with ACS who had MACE and those without MACE when compared together and with the control healthy

Table 5 Correlation between OxLDL antibodies and MACE

	OxLDL antibodies level (μml)		
	Median	Minimum	Maximum
High risk	7450	48	25 000
Low risk	7140	146	36 500
Control	198	33	7000

MACE, major adverse cardiovascular events; OxLDL, oxidized low-density lipoprotein.

Table 6 Comparison of the groups of study with respect to MACE

Groups	P value
Control vs. high risk	0.000
Control vs. low risk	0.002
High vs. low risk	1.000

MACE, major adverse cardiovascular events.

Table 7 Correlation between OxLDL antibodies and RWMI

Groups	OxLDL antibodies level	
	r (correlation coefficient)	P value
All	0.589	<0.001
High risk	0.407	0.048
Low risk	0.034	0.867

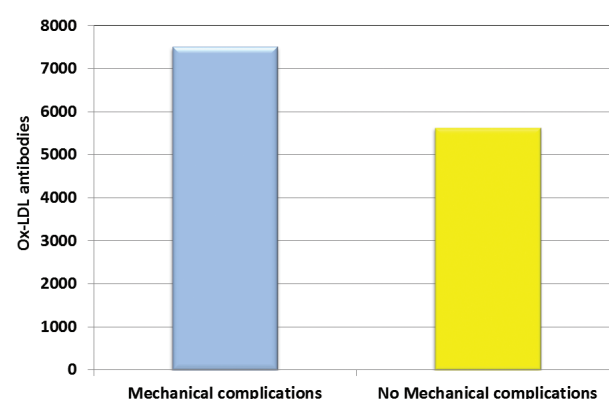
OxLDL, oxidized low-density lipoprotein.

Table 8 Correlation between WSMI and ischemic complications

	Segmental score index		P value
	Mean	$\pm\text{SD}$	
Ischemic complications			
No	1.27	0.33	0.301
Yes	1.29	0.24	

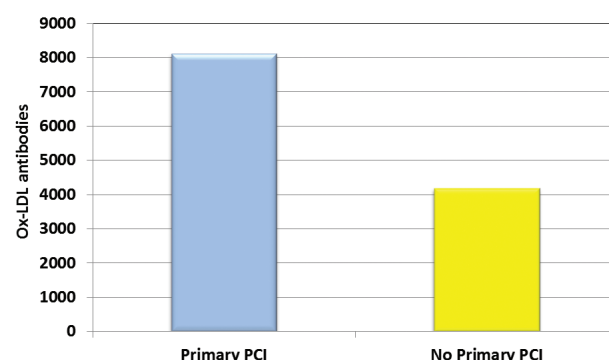
WSMI, wall motion score index.

Figure 5



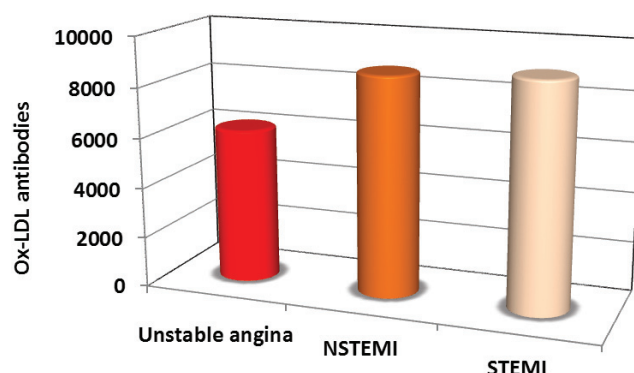
Relationship between OxLDL antibodies level and mechanical complications. OxLDL, oxidized low-density lipoprotein.

Figure 6



Relationship between OxLDL antibodies level and primary PCI. OxLDL, oxidized low-density lipoprotein; PCI, percutaneous coronary intervention.

Figure 7



Relationship between OxLDL antibodies level and ECG findings. OxLDL, oxidized low-density lipoprotein.

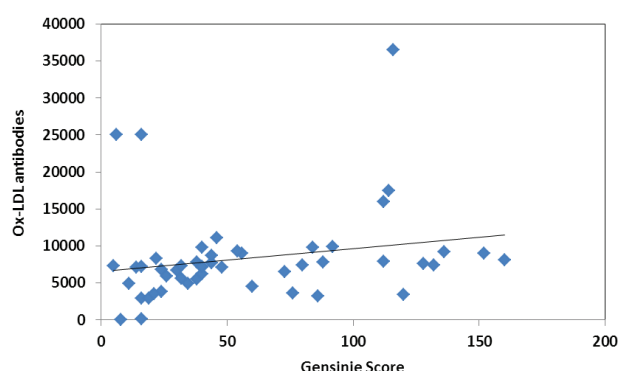
group with respect to the level of antibodies, we found statistically significant difference in the level of OxLDL antibodies between matched healthy controls and patients with ACS in both the high-risk and low-risk groups ($P > 0.001$ in both groups). There was no statistically significant difference in the level between the high-risk and low-risk groups as shown in Tables 5 and 6.

- (12) *OxLDL antibodies and ECG findings and cardiac biomarkers:* There was statistically significant difference in the level of OxLDL antibodies between matched healthy controls and patients with ACS, either unstable angina, NSTEMI, or STEMI ($P > 0.001$), whereas there was no statistically significant difference in the level of antibodies between patients with unstable angina and NSTEMI ($P = 1.00$), between patients with unstable angina and STEMI ($P = 0.626$), and also

between patients with NSTEMI and STEMI ($P = 0.601$) as demonstrated in Figure 7.

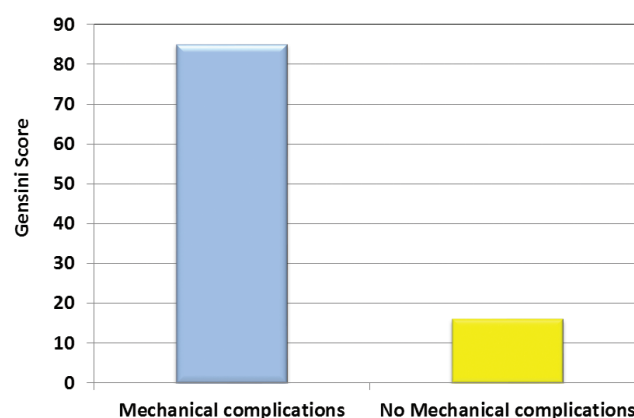
- (13) *OxLDL antibodies and global systolic functions:* There was no statistically significant correlation in the level of OxLDL antibodies and LVEF between matched healthy controls and patients with ACS in both the high-risk and low-risk group ($r = 0.142, 0.223$, and 0.195 , respectively).
- (14) *OxLDL antibodies and RWMI:* There was statistically significant correlation in the level of OxLDL antibodies and RWMI (regional wall motion abnormality) in the whole study groups ($r = 0.589$), but the correlations became less significant in subgroup analysis ($r = 0.407$ and 0.034 in the high-risk and low-risk groups, respectively) as shown in Table 7.
- (15) *OxLDL antibodies and the Gensini score:* There was statistically significant correlation in the level of

Figure 8



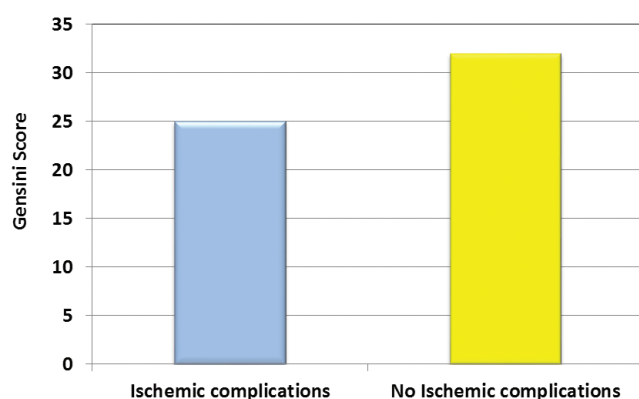
Correlation between OxLDL antibodies and the Gensini score. OxLDL, oxidized low-density lipoprotein.

Figure 9



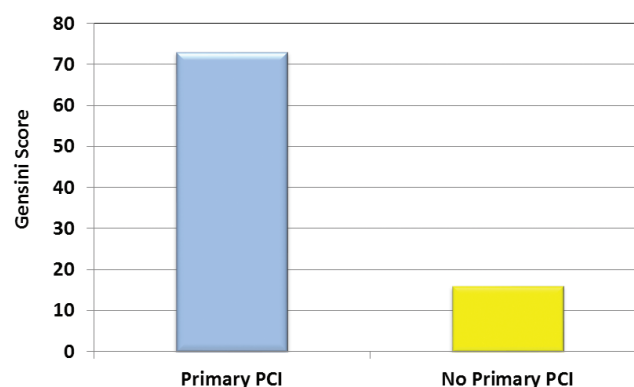
Relationship between the Gensini score and mechanical complications.

Figure 10



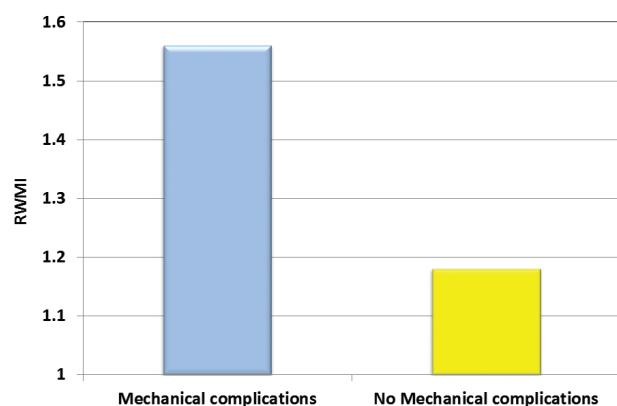
Relationship between the Gensini score and ischemic complications.

Figure 11



Relationship between the Gensini score and immediate coronary intervention. PCI, percutaneous coronary intervention.

Figure 12



Relationship between RWMI and mechanical complications.

OxLDL antibodies and the Gensini score in the whole study groups ($r = 0.709$), but the correlations became less significant in subgroup analysis ($r = 0.444$ and 0.429 in the high-risk and low-risk groups, respectively) as demonstrated in Figure 8.

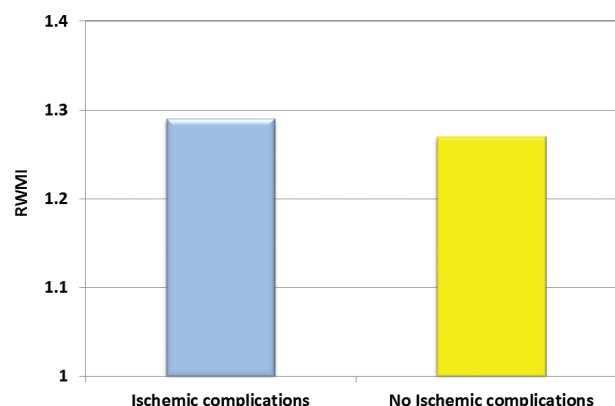
Correlations of the Gensini score with MACE

- (1) *Gensini score and mechanical complications:* There was statistically significant correlation between the Gensini score and patients with mechanical complications ($P < 0.001$) as demonstrated in Figure 9.
- (2) *Gensini score and ischemic complications:* There was no statistically significant correlation between the Gensini score and patients with ischemic complications ($P < 0.575$) as demonstrated in Figure 10.
- (3) *Gensini score and patients who had immediate coronary intervention:* There was statistically significant correlation between the Gensini score and patients who had immediate coronary intervention ($P < 0.001$) as demonstrated in Figure 11.

Correlations of WMSI with MACE

- (1) *WMSI and mechanical complications:* There was statistically significant difference between WMSI and patients with mechanical complications ($P < 0.001$) as demonstrated in Figure 12.
- (2) *WMSI and ischemic complications:* There was no statistically significant difference between WMSI and patients with ischemic complications ($P = 0.301$) as shown in Table 8.
- (3) *WMSI and patients who had immediate coronary intervention:* There was statistically significant correlation between WMSI and patients who had immediate coronary intervention ($P = 0.001$) as demonstrated in Figure 13.

Figure 13



Relationship between WMSI and immediate coronary intervention. WMSI, wall motion score index.

Discussion

OxLDL is a prominent autoantigen, which has been implicated in the development and progression of plaque. LDL molecules become immunogenic during oxidative modification, a process considered as a critical step during early atherogenesis [3].

Accordingly, a clear correlation between anti-OxLDL antibodies and atherosclerosis as well as cardiovascular disease has been described by a number of investigators [4,5].

As there is limited information on the possible role of IgG type anti-OxLDL antibodies in inflammatory responses underlying ACS, our aim in this study was to evaluate the prognostic value of IgG anti-OxLDL antibodies.

We have studied the relationship between the inflammatory process in atherosclerosis (using anti-OxLDL antibodies level) and the severity of acute CAD (as assessed by coronary angiogram using the Gensini score) and echocardiography (using the WMSI) and finally correlated the levels of antibodies of anti-OxLDL with incidence of complications of ACS.

With respect to the correlation of anti-OxLDL antibodies with ACS, we found that there was significant difference in the level of antibody between patients with ACS and matched healthy controls ($P < 0.001$).

Our data agreed with the study by Laczik *et al.* [4–6], who studied the prognostic value of IgG anti-OxLDL antibodies in 54 patients with ACS and 41 matched healthy controls prospectively and found significantly higher IgG anti-OxLDL levels in patients with ACS compared with controls ($P < 0.0001$), concluding that anti-OxLDL antibodies were involved in ACS.

Medeiros *et al.* [7] studied the relationship between antibodies against OxLDL and ACS in 90 patients in the first 12 h of ACS (cases) and in 90 patients with chronic CAD (controls) and found that the titers of anti-OxLDL were significantly higher ($P = 0.017$) in cases compared with controls.

In the study by Puurunen *et al.* [8] on 135 patients and controls, the mean antibody level against OxLDL was found to be significantly higher in patients than in controls ($P = 0.002$). Elevated levels of antibodies against OxLDL were predictive of myocardial infarction.

Dotevall *et al.* [9] studied the association between the immune response, as measured by antibody titers to anti-OxLDL, and levels of C-reactive protein, diabetes mellitus, and MI (myocardial infarction) in women. Diabetic women ($n = 18$) and 46 nondiabetic women who had been treated in a hospital for MI were compared with 35 diabetic women without MI and 70 healthy controls and found that, compared with healthy women, the women with diabetes and/or MI had higher IgG ($P < 0.05$) titers against OxLDL and higher CRP levels ($P < 0.001$) independently of other cardiovascular risk factors.

Ma *et al.* [10] measured CRP and anti-OxLDL level in 96 participants with ACS including 26 with AMI, 29 with unstable angina pectoris, 20 with stable angina pectoris, and 20 controls, and they found that both CRP and anti-OxLDL levels in patients with ACS, including AMI and unstable angina pectoris, were significantly higher compared with those in stable angina pectoris patients and controls ($P < 0.05$).

In the study by Sherer *et al.* [11] on 126 coronary heart disease (CHD) patients and 20 healthy controls, they found that the level of anti-OxLDL was significantly higher in CHD patients compared with controls ($P < 0.001$) and concluded that anti-OxLDL antibodies are elevated in CHD patients irrespective of coronary calcification.

Similarly, Soltesz *et al.* [6] studied 33 patients with ACS, 62 stable CAD patients, and 50 healthy controls and found that the level of antibodies to OxLDL was significantly higher in both groups of patients with ACS and stable CAD compared with controls. The comparison between the acute and stable groups showed that anti-OxLDL levels were higher in the acute group, but, because of high SD, the difference was not significant.

The study by Greco *et al.* [12] showed that antiphospholipid antibodies (aPLs) including anti-OxLDL have been implicated in atherogenesis in 344 patients with ACS. They found that aPLs including anti-OxLDL were positive in 43.7% of patients

with angiographically documented CAD and 34.9% of patients without CAD and concluded that anti-OxLDL antibodies were associated with CAD.

Our results matched with the previously mentioned studies (Table 9), despite the difference in sample size and methods in assessment of CAD.

With respect to the correlation between anti-OxLDL antibodies and the severity of ACS, our data showed that there was significant correlation between the level of antibodies in patients with ACS as assessed by the Gensini score ($r = 0.709$) as well as between the echocardiographic findings as assessed by the WMSI ($r = 0.589$). During hospitalization, there was significant correlation of the antibody level with mechanical complications ($P = 0.047$) and needed immediate intervention ($P < 0.001$). However, antibody level was correlated with malignant arrhythmias but P value (0.219) was insignificant because of high SD, and there was no correlation with ischemic complications ($P = 0.798$).

Our data were in agreement with the study by Greco *et al.* [12], who measured aPLs including anti-OxLDL in 344 patients with ACS who angiographically documented CAD and found that aPLs including anti-OxLDL were correlated with the severity of CAD ($P = 0.012$). Adverse events occurred in 16.7% patients with CAD. Patients who were aPL-positive with severe CAD had more adverse events compared with those who were aPL-negative with severe CAD ($P = 0.005$). They concluded that anti-OxLDL was correlated with CAD severity and adverse outcomes.

Laczik *et al.* [4] studied the association between antibodies against OxLDL and ACS in 54 patients with ACS and 41 matched healthy controls and found that IgG anti-OxLDL concentrations were significantly higher in ACS patients with unstable clinical complications (circulatory insufficiency, malignant arrhythmias, recurring ischemic pain, positive stress-test, need for urgent coronary intervention, or sudden cardiac death) compared with those without such

Table 9 Studies on anti-OxLDL antibodies and ACS

References	Number of patients	P value
Laczik <i>et al.</i> [4]	54 ACS 41 controls	<0.001
Medeiros <i>et al.</i> [7]	90 ACS patients 90 chronic CAD	0.017
Puurunen <i>et al.</i> [8]	135 ACS	0.002
Dotevall <i>et al.</i> [9]	99 AMI \pm diabetic 70 controls	<0.05
Ma <i>et al.</i> [10]	96 ACS 20 controls	<0.05
Sherer <i>et al.</i> [11]	126 CAD 20 controls	<0.001
Soltesz <i>et al.</i> [6]	33 ACS 62 chronic CAD 50 controls	0.09
Greco <i>et al.</i> [12]	344 ACS	0.012
This study	50 ACS 19 controls	<0.001

ACS, acute coronary syndrome; CAD, coronary artery disease; Ox LDL, oxidized low-density lipoprotein.

complications ($P < 0.001$); this may suggest a role for this antibody in plaque destabilization.

In the study by Soltesz *et al.* [6] on 33 patients with ACS, 62 stable CAD patients, and 50 healthy individuals as controls, the level of antibody to OxLDL was significantly higher in both groups of patients with ACS and stable CAD compared with controls. Anti-OxLDL levels were found to be significantly higher in ACS patients with unstable clinical state ($P < 0.001$) (circulatory insufficiency, malignant arrhythmias, recurring ischemic pain, need for urgent coronary intervention, and death). Their findings support the notion that the presence of antibodies to OxLDL, a plaque-specific antigen, may play a major role as a predictor of ACS complications.

In the study by Inoue *et al.* [5], they found that the anti-OxLDL titer was higher ($P < 0.01$) in 68 patients with multivessel CAD compared with 32 controls. However, no significant difference was shown between the single-vessel CAD group and controls or between the multivessel CAD group and the single-vessel CAD group. They concluded that anti-OxLDL may be a marker of plaque instability depending on the angiographic findings in correlation with anti-OxLDL.

Tsai *et al.* [13] investigated the relationship between anti-OxLDL titers and the extent of coronary atherosclerosis in a total of 70 patients with significant coronary atherosclerosis demonstrated by coronary angiography. These patients were divided into the AMI ($n = 33$) and chronic stable CAD ($n = 37$) groups. They found that the anti-OxLDL was significantly higher in patients with AMI than in those with chronic CAD ($P = 0.018$) and concluded that higher anti-OxLDL levels in patients with AMI were correlated with myocardial damage to a greater degree compared with the severity of coronary atherosclerosis and lipid profiles.

In disagreement with our data is the study by Rossi *et al.* [2] on 529 patients undergoing coronary angiography for suspected CAD. They found no significant differences in anti-OxLDL titer between the groups of patients with and without different CAD severity. Similarly, no differences in anti-OxLDL titer between patients with and without ACS were found. They concluded no evidence for the association of IgG anti-OxLDL titer with angiographically assessed CAD in whites.

In addition, Che *et al.* [14] disagreed with our data, as they found that the anti-OxLDL titers were significantly lower in 117 of the 154 patients with CHD compared with those in 37 controls ($P < 0.01$).

Titers of anti-OxLDL are inversely associated with the severity of coronary stenotic lesions calculated by the Gensini scores, supporting a protective role for anti-OxLDL against the progression of atherosclerosis.

Hence, we can conclude that the correlation between anti-OxLDL and the severity of CAD is present independent of the number of patients, sex, or the different methods of assessment of severity of CAD. However, Rossi *et al.* [2] results were different and did not show significant correlation. This may be because of the larger sample of patients. Finally, Che *et al.* [14] results were in contrast to our findings in the correlation between anti-OxLDL and the Gensini score. They studied CHD patients, not ACS patients as we did.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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