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Elevated Levels of Anti-oxLDL Antibody in Relation with Acute Myocardial Infarction

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Objectives: We aimed to determine the serum level of anti-oxLDL antibody at the involving of acute myocardial infarction. **Methods:** In the case-control study, patients with acute myocardial infarction (coronary stenosis > 85%) as determined by quantities coronary angiography in the case group (n = 26) and healthy people with carotid artery stenosis (< 0.7 mm) have been involved in the control group (n = 50). We determined Anti-oxLDL antibody and oxLDL titers by ELISA. **Results:** Anti-oxLDL antibody levels for the case group were greater than the control group ($p < 0.01$). Using binary logistic regression, the anti-oxLDL antibody was significantly associated with acute myocardial infarction (OR = 1.082, $p < 0.01$). **Conclusions:** Elevated serum anti-oxLDL antibodies may be a risk factor for developing acute myocardial infarction and concerning the correlation of anti-oxLDL antibodies and acute myocardial infarction.

Keywords: Anti-oxLDL Antibody, Low-density Lipoprotein, Coronary Atherosclerosis, Acute Myocardial Infarction, Coronary Angiography

Introduction

Acute myocardial infarction is the leading cause of death in most countries (43.1% of all deaths) [1]. In Mongolia, the incidence of cardiovascular disease increased by an average of 7.05% per year from 1988 to 2012, and one in three deaths was due to cardiovascular disease. Among cardiovascular diseases, coronary artery disease causes approximately 43% of deaths and has been the leading cause of death for the last 15 years [2, 3].

Oxidized low-density lipoprotein (oxLDL) has an established role in the pathogenesis of atherosclerosis. It acts as a proinflammatory and proatherogenic compound by inducing auto-antibodies and endothelial dysfunction [4]. Subendothelial retention of LDL on account of accumulation of oxLDL in macrophages and formation of foam cells are critical early events in atherogenesis [5]. Researchers have recently linked coronary

atherosclerotic plaque rupture to anti-oxLDL autoimmunity [6, 7]. As total antioxidant levels decrease and peroxidation intensifies, coronary atherosclerotic plaques become more oxLDL-producing and autoantigenic, resulting in increased synthesis of anti-oxLDL antibodies [8].

Other studies have questioned the actual contribution of anti-oxLDL in atherogenesis and found no significant differences between the titers of these antibodies in normal controls and patients with chronic or acute coronary artery disease [9]. However, the oxidative modification of LDL leads to immunogenic epitopes that can induce specific antibodies against oxLDL [10]. Circulating antibodies against oxLDL represent a durable measure of lipid peroxidation [11]. Next to involvement in atherosclerosis, anti-oxLDL antibodies could also play a role in acute myocardial infarction (AMI). Recent studies showed that patients with AMI and unstable angina had higher levels of anti-oxLDL antibodies than patients with stable angina and controls ($p < 0.05$) [5, 12]. Some studies have determined a positive correlation between the levels of circulating anti-oxLDL antibodies and atherosclerotic diseases, whereas others have shown an opposite result [13, 14].

Some researchers in Mongolia have found that atherosclerosis is more intense, resulting from Mongolia's geographical features, continental climate change, and saturated animal fats leading to metabolic syndrome. The metabolic syndrome increases oxidative stress and decreases antioxidants from a young age [15-17]. This is due to increased LDL levels and instant oxidative stress, which intensifies the oxidation of LDL in atherosclerotic plaques, resulting in the immediate formation of anti-oxLDL antibodies. In turn, increased serum anti-oxLDL antibodies may increase the risk of AMI and coronary heart disease [18].

Within this context, the objective of this study was to determine the serum level of anti-oxLDL antibodies at the involving of AMI.

Materials and Methods

Patients and control subjects

The study conducted using a case-control study model. The case group included 26 patients with coronary angiography diagnosed and treated with percutaneous coronary intervention for an AMI with severe coronary stenosis (proximal and middle site > 85%). The control groups ($n = 50$) were matched to each case by sex, age (within 5 years) and atherosclerotic evaluation of carotid and peripheral artery. The control group's carotid artery wall thickness was < 0.7 mm, and the cardio-ankle vascular index, as an indicator of arterial stiffness, was < 0.9.

Non-invasive assessments

The coronary artery wall thickness was measured ultrasonically (Diasus 9.0, Nikon Ultrasound 1999, Japan). The cardio-ankle vascular index was measured using a vascular screening system (VaSera VS-1000, Fukuda Denshi, Japan)

Quantitative coronary angiography

PCI was performed according to the guidelines for the percutaneous coronary intervention of the American Heart Association [19].

Serum lipid measurements

The serum cholesterol, triglycerides, LDL, and HDL, were measured using a fully automated analyzer (Abbott Architect c8000 analyzer, Third State Central Hospital, 2008).

Specific biomarkers

Anti-oxLDL antibody titers and oxLDL content were determined using Anti-oxLDL ELISA Kit (Eucardia Lab, USA) and oxLDL ELISA kit (Mercodia, USA) reagents, respectively. The determination was performed by an ELISA according to the manufacturer's recommended protocol.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± SD. The case and control groups were compared with an unpaired t-test or a Mann–Whitney U test when the distribution was not normal. Binary logistic regression was used to analyze the difference in antibody levels between the patient group and the control group, the sensitivity of these serum markers using the ROC curve. A value of $p < 0.05$ was considered indicative of statistical significance for all tests. The statistical analyses were performed using the SPSS 22.0 (IBM software, Inc. USA).

Ethical statement

All procedures performed in studies involving human participants were by the ethical standards of the institutional research committee (the Research Ethics Committee of Mongolian National

University of Medical Sciences No.6/3/201506, approved on Jan 21, 2015) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

The average age of the participants was 54.5 ± 9.74 years, with 26 (33%) in the case group and 50 (67%) in the control group. Table 1 shows the general characteristics of the survey participants. The titer of anti-oxLDL antibodies was higher in the case group with AMI than the control group (694 ± 30.91 vs. 627 ± 14.11 mU / mL, $p < 0.01$).

Table 1. Average values and standard deviations for each group.

Parameters	Case (n=26)	Control (n=50)	p-value
Age, years	60 ± 12	51 ± 6	0.131
Systolic pressure, mmHg	141 ± 25	135 ± 22	0.212
Diastolic pressure, mmHg	86 ± 13	85 ± 14	0.321
Brinkmann index†	584 ± 439	258 ± 247	0.001
Pulse	83 ± 11	78 ± 12	0.081
OxLDL, mU/l	73.3 ± 2.47	45.1 ± 2.59	0.001
Anti-oxLDL antibody, mU/ml	694 ± 30.91	627 ± 14.11	0.011

†Number of cigarettes smoked per day x number of years

Binary logistic regression analysis showed that the level of anti-oxLDL antibodies was a significant risk factor for AMI (OR = 1.082, $p < 0.01$). This means that every 1 mU/ml increase in the titer of anti-oxLDL antibodies increased the risk of AMI by 1.082-fold, or 8% (Table 2).

Table 2. Serum lipids (case and control group).

Parameters	Case group n=26	Control group n=50	p-value
Cholesterol (mg/dl)	201 ± 33	159 ± 56	0.001
Triglycerides (mg/dl)	160 ± 88	127 ± 41	0.050
LDL (mg/dl)	166 ± 36	120 ± 51	0.000
HDL (mg/dl)	45 ± 8	62 ± 7	0.050

The ROC curve analysis evaluates the specificity and sensitivity of the anti-oxLDL antibody, result in area = 0.62 (area > 0.5), $p < 0.05$ (Figure 1). A statistically significant difference between the groups was observed when determining the amount of serum fat in the case and control groups, which is one of the risk factors for AMI (Table 3).

Table 3. The logistic regression of some serum markers on the presence or absence of AMI.

Variable	OR	95% CI	p-value
OxLDL	1.01	1.00-1.01	0.008
Anti-oxLDL antibody	1.08	1.02-1.15	0.009
Constant			0.000

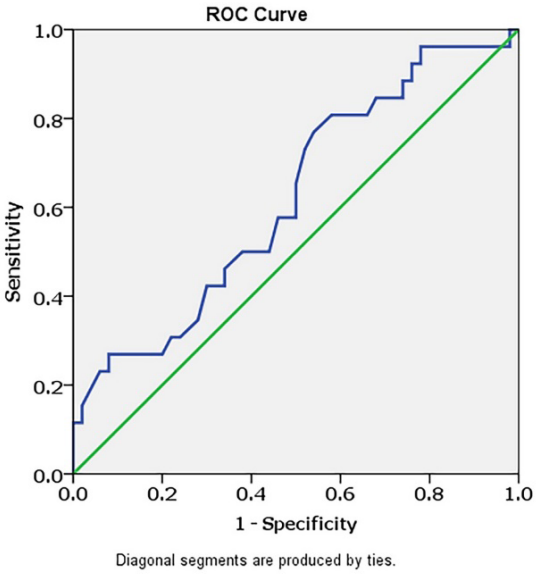

Figure 1. The ROC curve analysis of serum anti-oxLDL antibody.

Discussion

OxLDL is a prominent autoantigen that has been implicated in the development and progression of plaque. LDL molecules become immunogenic during oxidative modification, a process considered a critical step during early atherogenesis. Circulating antibodies to oxLDL and anti-oxLDL antibody have been studied for many years in coronary heart disease and other atherosclerotic diseases [20 - 23]. The increased levels of circulating anti-oxLDL antibodies promote immune complexes with oxLDL, which could adhere to the artery intima and cause damages to the endothelium [4]. It has been shown that increased levels of circulating antibodies to oxLDL may be regarded as predictors of atherosclerosis and AMI [22]. The highest anti-oxLDL antibody levels were observed in patients with multi-vessel cardiovascular disease. In fact, increased anti-oxLDL antibody levels appear to be pathological and may damage the walls of blood vessels, leading

to atherosclerotic changes [7] and instability of atherosclerotic plaques [13].

These antibodies are elevated in patients with early-onset peripheral vascular disease [23], severe carotid atherosclerosis [24], and angiographically verified coronary artery disease [25, 26]. Moreover, the proinflammatory effects of anti-OxLDL antibodies are believed to be partly responsible for thinning of the plaque fibrin cap and its ultimate rupture leading to AMI or stroke [27]. Our binary logistic regression results of the association of increased anti-oxLDL antibody titers in the AMI ($OR = 1.05$ $p < 0.05$) were smaller but similar to that of Tsimikas ($OR = 1.54$, $p < 0.05$) [28]. In our study, the serum levels of anti-oxLDL antibodies were also significantly associated with AMI ($OR = 1.08$, $p < 0.01$). Increased titers of anti-oxLDL antibodies may bind to oxLDL in coronary atherosclerotic plaques to form an immune complex, which may lead to sudden rupture of the plaque and thrombus formation due to increased attachment, cell toxicity, immune and inflammatory responses. Furthermore, increased levels of anti-oxLDL antibodies were predictive of carotid atherosclerosis progression [27], AMI occurrence and mortality, and higher risk for restenosis in patients undergoing percutaneous transluminal coronary angioplasty [28].

The increased anti-oxLDL antibody levels appear to be pathological and may damage the walls of blood vessels, leading to atherosclerotic changes [13] and instability of atherosclerotic plaques [14]. We also found that the level of anti-oxLDL antibodies was significantly associated with AMI ($OR = 1.08$, $p < 0.01$). This means that a 1 mU/ml increase in the level of anti-oxLDL antibodies may increase the risk of AMI by 8% (1.08-fold). Moreover, Berg et al. found that elevated levels of anti-oxLDL antibodies were associated with a greater risk of developing future events (HR 1.18, 95% CI 1.03–1.37), and HR for the forth quartile versus the first quartile: 1.97, 95% CI 1.30–2.99, respectively) [28]. One of the causes of the accumulation of oxLDL and its antibodies in the blood is thought to be impaired pro-oxidant and antioxidant systems. Our study showed an increase in the levels of serum anti-oxLDL antibody, reflecting the oxidative status, and representing the pro-oxidant and antioxidant systems, respectively. However, an increase in these markers does depend on the AMI.

Limitations

Anti-oxLDL antibodies were assessed only in the short-term follow-up of an AMI. Stable cardiovascular disease with risk factor control and pharmacological therapy may impact anti-oxLDL antibody generation and consumption over time. We did not perform intravascular ultrasound, which could have been valuable for the evaluation of non-obstructive atheroma.

In future studies, we need to use assays to determine the role of epitope binding specificity of antibodies in determining their involvement in leading to AMI. The immunohistochemical studies of atherectomy specimens clearly demonstrate that the number of anti-oxLDL antibodies related immunocomplex in the culprit lesions of AMI patients is significantly higher than in those of the patient with stable angina. Testing of circulating anti-oxLDL antibodies to linear antigens derived from specific oxLDL may have a potential benefit for the diagnosis and prognosis of AMI.

Conclusions

Elevated serum anti-oxLDL antibodies may be a risk factor for the development of AMI. With respect to the association of anti-oxLDL antibodies and AMI, the patients with AMI had higher anti-oxLDL antibody levels.

Conflict of Interest

The authors declare no conflict of interests.

Acknowledgments

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