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Serum autoantibodies against human oxidized low-density lipoproteins are inversely associated with severity of coronary stenotic lesions calculated by Gensini score

Jingjin Che, Guangping Li, Weiding Wang, Qiang Li, Hongtao Liu, Kangyin Chen, Tong Liu

Department of Cardiology, Tianjin Institute of Cardiology, 2nd Hospital of Tianjin Medical University, Tianjin, People's Republic of China

Abstract

Background: *The relationship between autoantibodies against human oxidized low-density lipoprotein (anti-oxLDL) and the progression of atherosclerotic diseases is unclear. This study aimed to investigate the association between serum anti-oxLDL titers and the severity and extent of coronary stenotic lesions.*

Methods: *We measured the titers of IgG anti-oxLDL by enzyme-linked immunosorbent assay (ELISA) in 154 consecutive patients undergoing coronary angiography for suspected coronary heart disease (CHD). The severity and extent of coronary stenotic lesions were evaluated on coronary angiography findings by Gensini score.*

Results: *The anti-oxLDL titers were significantly lower in 117 patients with CHD than those in 37 controls ($p < 0.01$). The serum anti-oxLDL titers were significantly correlated to serum levels of globulin ($r = 0.405$), conjugated bilirubin ($r = 0.280$), high-density lipoprotein (HDL) cholesterol ($r = 0.238$), homeostatic model assessment for insulin resistance (HOMA-IR) ($r = –0.267$), high sensitivity C-reactive protein (hs-CRP) ($r = –0.230$), triglyceride ($r = –0.207$), advanced glycation end products (AGEs) ($r = –0.200$), and malondialdehyde ($r = –0.165$). However, only HDL cholesterol and AGEs remained independent predictors of the anti-oxLDL titers after adjusting for confounders. Multivariate regression analysis showed that the anti-oxLDL titers, as well as serum levels of hs-CRP, fasting glucose, and albumin, were significantly associated with Gensini scores.*

Conclusions: *Titers of anti-oxLDL are inversely associated with complicated proatherogenic metabolic risk factors, and the severity of coronary stenotic lesions calculated by Gensini scores, supporting a protective role for anti-oxLDL against the progression of atherosclerosis.* (Cardiol J 2011; 18, 4: 364–370)

Key words: autoantibodies against human oxidized low-density lipoprotein, Gensini score, coronary heart disease

Address for correspondence: Prof. Guangping Li, Cardiology Department, 2nd Hospital of Tianjin Medical University. Pingjiang Road 23, Hexi District, Tianjin, 300211, People's Republic of China, tel: +86 22 88328368, fax: +86 22 28261158, e-mail: guangpingli001@eyou.com

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Introduction

Atherosclerotic cardiovascular disease is the commonest cause of death worldwide. A large amount of evidence supports a pivotal role of inflammation and immune responses in all phases of atherosclerosis, from initiation of the fatty streak to final breakout of acute coronary syndromes (ACS) [1–3]. Multiple antigenic stimuli have been demonstrated to be associated with atherogenesis [4]. Most of these stimuli come from modified self-molecules such as modified low-density lipoproteins (LDL) [5, 6], heat shock proteins [7], and protein components of the extracellular matrix including collagen and fibrinogen in the form of advanced glycation-end products (AGEs) [8], of which oxidized LDL (oxLDL) is the most important one [5]. Autoantibodies against human oxLDL (anti-oxLDL) occur in the plasma of humans in small amounts [9]. Both IgM and IgG anti-oxLDLs are produced during atherosclerosis. The potential roles of these autoantibodies, especially IgG autoantibodies, in atherogenesis remain unclear. Results from Salonen et al. [10] and Inoue et al. [11] indicate that anti-oxLDL is an independent predictor of the progression of carotid or coronary atherosclerotic lesions. But immunization of atherosclerosis-susceptible animals with LDL, modified LDL, or apoB100 induced high levels of the autoantibodies with decreased atherosclerosis, suggesting that the humoral immune response to oxLDL may be antiatherogenic [12–16].

The aim of the present study was to determine whether anti-oxLDL titers are associated with serum metabolic parameters, and whether the titers are associated with the severity and extent of coronary stenotic lesions angiographically evaluated by Gensini score.

Methods

Subjects

Between September 2008 and August 2009, 154 consecutive subjects were selected from patients referred to the Second Hospital of Tianjin Medical University and undergoing coronary angiography because of chest pain and/or clinically suspected coronary heart disease (CHD). Exclusion criteria were refusal to participate, exposure to hypolipidemic drugs in the month prior to admission, previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), complication of active infection, hepatic and/or renal dysfunction, or connective tissue disease. The study was approved by an institutional review committee. One hundred and seventeen subjects who had at least one significant lesion (e.g. stenosis ≥ 50% in luminal diameter) in a major coronary artery were diagnosed with CHD; 37 patients who had no significant lesion in any epicardial branch of coronary arteries proven by coronary angiography served as control subjects.

Patient age, gender, smoking habits, past history of hypertension and diabetes, and current medications were carefully ascertained. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Laboratory measurements

Peripheral venous blood samples were drawn from each patient after overnight fasting. Serum levels of fasting glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, malondialdehyde (MDA), blood urea nitrogen (BUN), creatinine, uric acid (UA), bilirubin, albumin, globulin, and high-sensitivity C-reactive protein (hs-CRP) were measured using conventional methods. Insulin resistance was quantified using the homeostasis model assessment (HOMA-IR): fasting glucose × fasting insulin level/ /22.5 [17]. Serum AGEs were measured by competitive enzyme-linked immunosorbent assay (ELISA) as previously described [18]. IgG anti-oxLDL was assayed with a commercially available ELISA kit (Anti-oxLDL Antibody ELISA KIT, IMTEC Diagnostic Inc) as previously described [19]. Sera were diluted 1:101, and low- and high-titer samples were included in each assay. Furthermore, a standard curve with samples at known anti-oxLDL titers was determined for each assay. All measurements were blinded and done on coded serum samples.

Assessment of coronary stenosis by coronary angiography

Gensini score [20] was calculated for each patient according to coronary angiography results. The score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion, were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery × 5; the proximal segment of left ante-

Table 1. Demographic and clinical characteristics of control subjects and patients with coronary heart disease.

Variables	Controls (n = 37)	CHD group (n = 117)	P
Age (years)	62.0 ± 11.5	63.7 ± 10.6	0.475*
Male	24 (64.9%)	73 (63.4%)	0.681#
Hypertension	26 (70.3%)	75 (64.1%)	0.279#
Diabetes	6 (16.2%)	29 (24.8%)	0.247#
Smoker	9 (24.3%)	51 (43.6%)	0.027#
Body mass index [kg/m^2]	24.6 ± 3.0	25.0 ± 3.2	0.683*
hs-CRP [mg/L]	3.03 (1.70–5.34)	8.9 (6.30–10.30)	< 0.001#
Triglyceride [mmol/L]	1.43 (1.05–1.84)	1.34 (1.00–1.930)	0.800*
HDL cholesterol [mmol/L]	1.30 ± 0.20	1.21 ± 0.30	0.447*
LDL cholesterol [mmol/L]	3.00 ± 0.90	2.86 ± 0.80	0.424*
Malondialdehyde [μmmol/L]	5.21 (4.36–6.99)	6.61 (5.00–9.35)	0.005#
Anti-oxLDL titers [U/mL]	27.2 (21.9–31.3)	21.2 (16.7–27.0)	0.001#
Fasting glucose [mmol/L]	5.79 (5.06–6.17)	6.47 (5.77–8.29)	< 0.001#
HOMA-IR	3.4 (2.5–5.1)	4.3 (2.92–5.3)	0.350#
AGEs [pg/mL]	41.4 (28.7–56.0)	47.9 (37.5–59.4)	0.115#
Serum albumin [g/L]	39.2 ± 2.7	37.7 ± 3.0	0.004#
Serum globulin [g/L]	29.2 ± 7.5	26.4 ± 4.1	0.005#
Conjugated bilirubin [μmmol/L]	2.9 (2.0–3.5)	2.9 (2.0–3.7)	0.563#
Blood urea nitrogen [mmol/L]	5.0 ± 1.2	5.6 ± 1.3	0.008#
Creatinine [μmmol/L]	78.1 (61.8–87.5)	79.1 (65.3–94.8)	0.479#
Uric acid [mmol/L]	315.6 (251.0–357.0)	313.0 (246.0–363.0)	0.956#
Gensini score	3.5 (2.5–5.4)	53.5 (26.0–80.5)	< 0.001#

*Independent-samples *t* test; #nonparametric Mann-Whitney test; CHD — coronary heart disease; hs-CRP — high-sensitivity C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; anti-oxLDL — autoantibodies against human oxidized LDL; HOMA-IR — homeostatic model assessment of insulin resistance; AGEs — advanced glycation-end products

rior descending coronary artery (LAD) × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5.

Statistical analysis

Clinical data and anti-oxLDL values of controls without CHD were compared to those of patients with CHD using independent-sample *t* test or non-parametric Mann-Whitney test as appropriate. Kruskal-Wallis test was used to compare anti-oxLDL titers among controls, patients with angina pectoris (AP), and patients with acute myocardial infarction (AMI). To analyze the correlations of anti-oxLDL titers to other variables, we used Pearson correlation test (for serum globulin, conjugated bilirubin, HDL cholesterol, hs-CRP) and nonparametric Spearman correlation test (for triglyceride, AGEs, HOMA-IR, and MDA) as appropriate. A multiple linear stepwise regression model was used to analyze the predictors of anti-oxLDL titers. To analyze the value of Gensini score, log transformation [Ln(Gensini score +1)] was firstly performed. The association between Gensini score and other variables was demonstrated by a linear stepwise regression analysis. A $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population are presented in Table 1. The serum levels of anti-oxLDL and globulin were significantly lower in patients with CHD than those in controls ($p < 0.001$). In contrast, serum levels of hs-CRP, MDA, fasting glucose, and smoker ratio were significantly higher in patients with CHD. Anti-oxLDL titers tended to be lower in patients with AMI than those with AP [23.96 (18.04–28.00) *vs* 19.34 (16.41–26.78) U/mL, Mann-Whitney test, $p = 0.084$], but the difference was of no statistical significance, as shown by Figure 1.

Using Pearson and nonparametric Spearman correlation tests for all collected variables, it was found that in all subjects anti-oxLDL titers were

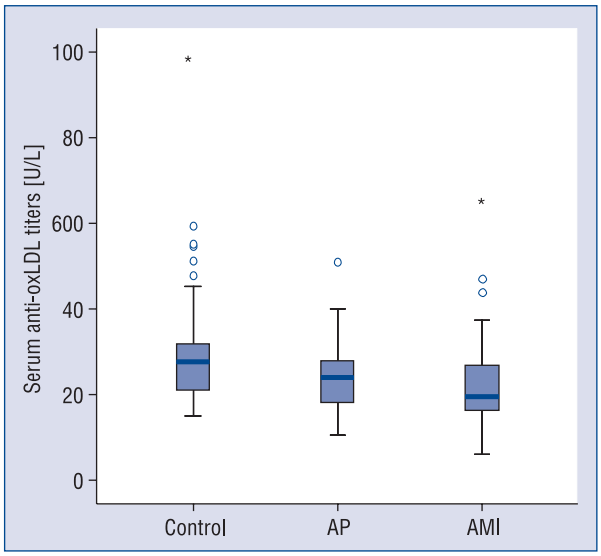

Figure 1. Box-plots representing the distribution of serum autoantibodies against human oxidized low-density lipoprotein (anti-oxLDL) titers in control, angina pectoris (AP), and acute myocardial infarction (AMI) subjects; Kruskal-Wallis test, p = 0.002; Mann-Whitney tests established significant differences of anti-oxLDL titers between controls and patients with AP (p = = 0.018), and between controls and patients with AMI (p = 0.001), but no significant differences between patients with AP and those with AMI (p = 0.084).

Table 2. Variables significantly correlated to anti--oxLDL titers in all subjects (n = 154).

Variables	Correlation coefficient	P
Serum globulin [g/L]	0.405	< 0.001*
Conjugated bilirubin [μmmol/L]	0.280	0.001*
HDL cholesterol [mmol/L]	0.238	0.004*
HOMA-IR	–0.267	0.018#
hs-CRP [mg/L]	–0.230	0.005*
Triglyceride [mmol/L]	–0.207	0.011#
AGEs [pg/mL]	–0.200	0.029#
Malondialdehyde [μmmol/L]	–0.165	0.042#

*Pearson correlation test; #nonparametric Spearman correlation test; anti-oxLDL — autoantibodies against human oxidized low-density lipoprotein; hs-CRP — high-sensitivity C-reactive protein; HDL — high-density lipoprotein; HOMA-IR — homeostatic model assessment of insulin resistance; AGEs — advanced glycation end products

significantly correlated to levels of globulin, conjugated bilirubin, HDL cholesterol, hs-CRP, triglycerides, HOMA-IR, AGEs, and MDA (Table 2), but not to age, smoking status, BMI, fasting glucose, LDL cholesterol, BUN, creatinine, UA, unconjugated bilirubin or albumin. Importantly, after adjusting for these confounders, only AGEs (B = –0.16, p = 0.03) and HDL cholesterol (B = 11.62, p = 0.03) were demonstrated to be independently associated with anti-oxLDL titers in a multiple linear stepwise regression analysis.

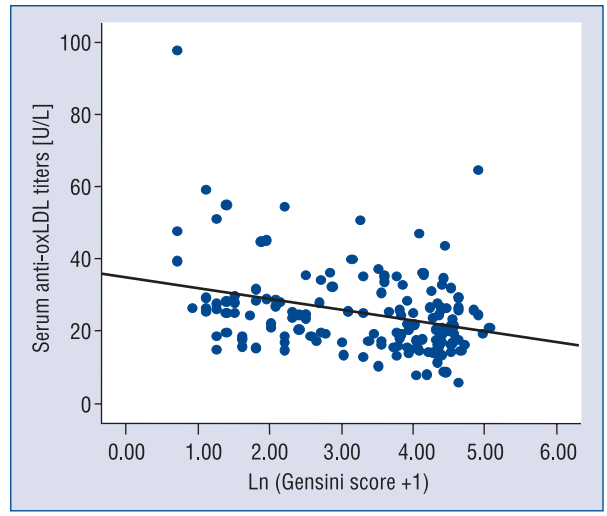

Figure 2. Correlation of serum autoantibodies against human oxidized low-density lipoprotein (anti-oxLDL) titers to Gensini scores in all subjects (n = 154); Spearman correlation analysis showed a negative correlation between serum anti-oxLDL titers and Gensini score [Ln(Gensini score +1)] in all subjects; R = –0.306, p < 0.001.

Then the Gensini scoring system was introduced to evaluate the severity and extent of coronary stenotic lesions. Using univariate stepwise linear regression analysis for all collected variables, we demonstrated that Gensini scores were significantly associated with hs-CRP, fasting glucose, anti-oxLDL (Fig. 2), BUN, albumin, MDA, and globulin, as shown by Table 3. Of these variables, anti-oxLDL titers, serum albumin and globulin were negatively associated with Gensini scores, whereas the others were positively associated with the scores in all subjects. After adjusting for these confounders by a multiple linear stepwise regression analysis, hs-CRP, fasting glucose, anti-oxLDL titers, and serum albumin remained independently associated with Gensini scores (Table 3).

Discussion

Innate and adaptive immune responses against oxLDL are believed to play important roles in atherosclerosis [21, 22], although reports on the clinical significance of anti-oxLDL are still inconsistent. In the conventional view, the antigen-antibody re-

Table 3. Linear regression analysis of factors associated with Gensini score (n = 154)*.

	B	95% CI for B	P
Univariate stepwise:			
hs-CRP [mg/L]	0.182	0.131–0.234	< 0.001
Fasting glucose [mmol/L]	0.168	0.092–0.244	< 0.001
Anti-oxLDL titers [U/mL]	–0.031	–0.047–0.016	< 0.001
Blood urea nitrogen [mmol/L]	0.250	0.108–0.392	0.001
Malondialdehyde [μmmol/L]	0.054	0.019–0.089	0.003
Serum albumin [g/L]	–0.096	–0.159–0.032	0.003
Serum globulin [g/L]	–0.055	–0.091–0.018	0.003
Multivariate stepwise#:			
hs-CRP [mg/L]	0.144	0.093–0.195	< 0.001
Fasting glucose [mmol/L]	0.125	0.058–0.193	< 0.001
Anti-oxLDL titers [U/mL]	–0.020	–0.033–0.006	0.006
Serum albumin [g/L]	–0.060	–0.114–0.005	0.033

*Dependent variable is Gensini score [Ln(Gensini score +1)]; #in multiple linear stepwise regression, induced variables are age, hs-CRP, fasting glucose, anti-oxLDL titers, serum albumin, serum globulin, blood urea nitrogen, malondialdehyde; CI — confidence interval; hs-CRP — high-sensitivity C-reactive protein; anti-oxLDL — autoantibodies against human oxidized low-density lipoprotein

action is prone to enhance inflammation and results in exacerbation of atherosclerosis. Reports on elevated anti-oxLDL titers in humans with increased carotid atherosclerosis [10] and CHD [11] suggest a proatherogenic role for the autoantibodies. However, Rossi et al. [23] found that there was no difference of anti-oxLDL titers between patients with and without ACS. The method they used to evaluate the severity of coronary lesions was to count the diseased vessels, which is prone to neglect the difference between severe lesions such as total occlusion and moderate stenosis, or the difference between multiple plaques and just one plaque in one coronary artery. Their study found a tendency for patients with multiple vessels disease to have lower anti-oxLDL titers, but the differences were not statistically significant. Similarly to our data, Santos et al. [24] recently reported that anti-oxLDL titers were higher, whereas levels of hs-CRP were lower in hypertensive patients than in individuals who experienced a recent ACS. However, coronary angiography was not used in their study, meaning the conditions of diseased coronary arteries were unknown. In the present study, we introduced the Gensini scoring system to evaluate the extent and severity of coronary stenotic lesions, because the coronary trees in this system are divided into 15 segments and even mild lesions (e.g. less than 25% stenosis in diameter) are also calculated in the final score. Therefore our data enriched the previous findings: the titers of anti-oxLDL are negatively associated with the severity and extent of coronary stenotic lesions.

Recently, increasing evidence has supported the protective role of the autoantibodies and humoral immunity against modified LDL. Evidence from innate natural antibodies, represented by the prototypic antibody E06, has shown the ability of the antibodies to bind to oxidized phospholipids (PL) of oxLDL, and inhibit the uptake of oxLDL by macrophage scavenger receptors, thus inhibiting the development of foam cells [25]. Furthermore, immunization of atherosclerosis-prone mice directly with modified or native LDL [12, 14, 15], or with the protein part of modified LDL [13, 16], exerts a protective effect on lesion formation, supporting the involvement of adaptive immune response in atherogenesis and its protective roles. More interestingly, it has been demonstrated that passive immunization with polyclonal immunoglobulin preparations [26], monoclonal anti-phosphorylcholine IgM antibody [27] or recombinant human antibodies against aldehyde-modified apolipoprotein B-100 peptide sequences [28, 29] significantly inhibited atherosclerosis and dose-dependently reduced the extent of atherosclerosis, as well as the plaque content of oxLDL epitopes and macrophages. Recent results from an oxLDL-pulsed mature dendric cells--transferred study demonstrated that a reduced T helper cell-1 profile and an increment in oxLDL--specific IgG levels contributed to a reduction in foam cell formation [30]. The relationship between Gensini scores and the titers of anti-oxLDL in our study also suggested that anti-oxLDL may confer a protective role against the progression of atherosclerosis, although the role is weak.

In the present study, anti-oxLDL titers were correlated to multiple metabolic and inflammatory risk factors, including HDL cholesterol, hs-CRP, triglycerides, HOMA-IR, AGEs, and MDA. But only AGEs and HDL were independent predictors of the anti-oxLDL titers after adjusting for these confounders: AGEs levels were negatively associated with anti-oxLDL titers; whereas HDL levels were positively associated with anti-oxLDL titers. It has been shown that anti-oxLDL titers are selectively higher in a good metabolic homeostasis. Kara et al. [31] demonstrated that anti-oxLDL levels were inversely correlated to hemoglobin A1c (HbA1c) levels in children with diabetes, and when metabolic control worsened, the free anti-oxLDL levels decreased concurrently. Garrido-Sánchez et al. [32] also reported that the levels of IgG and IgM anti-oxLDL in morbidly obese patients rose after bariatric surgery, but this increase was only significant in the diabetic patient who experienced an improvement in their metabolic profile. AGEs are modifications of proteins or lipids that become nonenzymatically glycated and oxidized after contact with aldose sugars [33]. The AGEs accumulation is not just a measure of hyperglycemia, but represents cumulative metabolic burden, oxidative stress and inflammation [34]. Low HDL-C level is an important cardiovascular risk factor. HDL not only has a central role in the reverse transport of cholesterol, but also has anti-oxidative and anti-inflammatory properties [35]. Therefore our data suggests that low anti-oxLDL titer might reflect a complicated proatherogenic metabolic profile, including both glucose and lipid metabolic disorders.

It is well-known that serum CRP level is an independent predictor of CHD, especially the unstable coronary plaques, and its prognostic value exceeds that of LDL cholesterol [36–38]. CRP *in vitro* has been shown to be able to bind both oxLDL [39], and native LDL [40] to opsonize their intake by macrophages, thus resulting in the formation of foam cells. In our study, anti-oxLDL titers were negatively associated with Gensini scores, whereas CRP remained positively associated with the scores, suggesting a possible opposite role of anti-oxLDL on atherogenesis against CRP.

Interestingly, we found that serum albumin was also an independent predictor of Gensini scores. This agrees with a previous study of patients with chronic kidney disease, in which serum albumin level was shown to be independently associated with multivessel CHD and Gensini scores by stepwise regression analysis [41]. An early study in patients without chronic kidney disease also showed that serum albumin had an independent negative association with the angiographic severity of CHD [42]. We presumed that coexistent renal lesions, including endothelial dysfunction and progression of atherosclerosis, may be possible underlying mechanisms, as seen in the review of Schiffrin et al. [43].

Conclusions

In conclusion, our data showed that titers of anti-oxLDL were inversely associated with complicated proatherogenic metabolic risk factors, and the severity of coronary stenotic lesions calculated by Gensini scores. The results suggest that anti-oxLDL may play a protective role against the progression of atherosclerosis. However, this assumption should be treated with caution, because it was based on a relatively small number of subjects and represented a phenomenon occurring at a single time of atherogenesis.

Limitations of the study

Our data was only based on coronary angiography findings, by which less stenotic plaques may not be detected. Therefore, this result did not include all atherosclerotic lesions in coronary arteries.

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The authors do not report any conflict of interest regarding this work.

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