Oxidized low-density lipoprotein cholesterol and the ratio in the diagnosis and evaluation of therapeutic effect in patients with coronary artery disease

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Abstract. Objective: The purpose of the present study was to investigate the value of ox-LDL and oxidation ratio of LDL (ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C) in diagnosis and prognosis evaluation in CAD patients. Also, we aimed to observe the effect of statins on reducing level of ox-LDL and oxidation ratio of LDL, and explore whether statins still have similar effect on ox-LDL in a short period of therapy (within 2 weeks).

Methods: Blood ox-LDL, TC, HDL-C, LDL-C, and TG were measured in cases with acute myocardial infarction (AMI, n = 177), unstable angina pectoris (UAP, n = 195), stable angina pectoris (SAP, n = 228), normal control (n = 120), and high risk control (n = 140).

Results: Mean value of ox-LDL and oxidation ratio of LDL was significantly higher in the CAD group than in the two control groups. The AUC of ROC curve of ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/LDL-C and apoA1/apoB were more than 0.50 (P < 0.001). Multivariate logistic regression analysis showed that age and ox-LDL/LDL-C related with short-term, while ox-LDL/LDL-C and ox-LDL/TC related with long-term prognosis (P < 0.05). Furthermore, after treatment with statins for 2 weeks, TC, LDL-C, ox-LDL, ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C decreased by 22%, 28%, 38%, 29%, 23% and 25% respectively. And the reduction of ox-LDL by statins is independent of lowering of LDL-C and TC.

Conclusions: Ox-LDL and oxidation ratio of LDL are closely related with AS, and they are better biomarkers for discriminating between patients with coronary artery disease and healthy subjects. In addition, statins can decrease level of ox-LDL significantly, which is independent of lowering of LDL-C and TC.

Keywords: Coronary artery disease, oxidized low density lipoprotein, diagnosis, prognosis

Abbreviations list

| Abbreviation | Description |
|--------------|-------------|
| CAD          | Coronary artery disease |
| AS           | Atherosclerosis |
| AMI          | Acute myocardial infarction |
| DM           | Diabetes |
| HT           | Hypertension |
| LDL-C        | Low-density lipoprotein cholesterol |
| Ox-LDL       | Oxidized low-density lipoprotein cholesterol |
| Statin       | HMG-CoA reductase inhibitor |
| SAP          | Stable angina pectoris |
| UAP          | Unstable angina pectoris |

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1. Introduction

There have been numerous hypotheses trying to explain the correlation of hypercholesterolemia with the development of atherosclerosis (AS) in the past decades. Now it is believed that “oxidative modification hypothesis” is the main mechanism of AS [1]. Although low-density lipoprotein cholesterol (LDL-C) has been confirmed to play an important role in the development of AS, including endothelial cell injury, inflammation, foam cell formation, and unstable plaque rupture [2,3], and the NCEP ATP III guidelines have emphasized that lowering LDL-C is an important target in the prevention and treatment of coronary heart disease, some evidence indicates that oxidized low-density lipoprotein cholesterol (ox-LDL) plays a more crucial role in the process of AS these years. Holvoet et al. demonstrated that ox-LDL was increased in patients with coronary heart disease [4]. Ehara et al. found that unstable plaques were filled with ox-LDL [5], and they discovered that elevated level of ox-LDL was positively correlated with acute coronary syndrome, and level of ox-LDL is regarded as an index of severity of acute coronary syndrome. All of these suggest that ox-LDL plays an important role in the pathogenesis of coronary heart disease. Recently a new point of view is raised by Huang et al. [6], they revealed that oxidation ratio of LDL has a stronger correlation with coronary heart disease in comparison with plasma oxidized LDL. They also found the level of ox-LDL and oxidation ratio of LDL (ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C) were significantly higher in CAD group than controls (P < 0.001).

HMG-CoA reductase inhibitors (statins) are considered as the frontline medication which can reduce cardiovascular morbidity and mortality in both primary and secondary prevention [7,8] by lowering LDL. Studies have also shown that statins can slow down progression or even regress coronary AS [9,10]. Recently, some studies have found that statins also have pleiotropic effects such as antioxidant, anti-inflammatory, and stabilization of plaques which are independent of LDL lowering [11–13]. A case-limited research run by Trvridou et al. [14] showed that simvastatin can significantly reduce circulating ox-LDL levels in subjects with coronary artery disease (CAD). And thus far it is still lack of larger scale research on CAD patients. As the variation of ox-LDL in the circulation is big, it is difficult to figure out a specific cut off point for evaluating the risk for CAD so far. So the study aims to observe the effect of statins on reducing level of ox-LDL and oxidation ratio of LDL (ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C) in long, as well as short-period (within 2 weeks) therapy.

2. Methods

Ethics Statement: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (NO: 2012012). We did formally obtain permission from each patient for using their blood samples for the study and have their signature on the informed consent.

This was a prospective study. The enrollment was during December 2004 to August 2008 in the First Affiliated Hospital of Sun Yat-sen University. 600 CAD cases (177 AMI, 195 UAP, 228 SAP) and 260 controls were recruited. The controls were categorized into normal (n = 120) and high risk controls (n = 140). AMI and UAP patient were hospitalized, SAP and high risk control patient were partly recruited from out-patient department; while normal controls were from Health Examination Center, who were healthy subjects with normal blood lipid, the high risk controls were individuals without evidence of CAD or diabetes mellitus, but with hypertension and dislipidemia (LDL-C > 3.62 mmol/l or TC > 5.70 mmol/l). Individual whose creatinin > 115 µmol/l,or glutamate-pyruvate transaminase (GPT) > 2 times of upper normal limit, or had an evidence of stroke was excluded from this study. Considering that statins have an effect of anti-oxidative stress, anyone who treated with statins three months within sampling was excluded also. All CAD cases received statin treatment based on indication. The number of patients who took atrovastatin (20–40 mg/day), simvastatin (40–80 mg/day), pravastatin (40 mg/day), and fluvastatin (40–80 mg/day) was 360, 80, 100, and 60 respectively. Population characters were showed on Tables 1–2.

At baseline and two weeks after statin therapy, overnight fasting blood samples were drawn for measurement of ox-LDL, total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and fasting plasma glucose. TC and TG were measured by enzymic method, and HDL-C and LDL-C by homogeneous method. Ox-LDL was measured by competitive ELISA with mAb4E6 antibody [4]. Samples were saved in a refrigerator at −80°C and measured within 6 months.

SPSS 13.0 was used for statistical analyses. ANOVA and rank test were applied for significance tests. Spear-
man rank correlation and Pearson correlation analysis were used to recover correlation ship. Receiver operating characteristic curves were used to evaluate the diagnostic accuracy of candidate markers. Impact of ox-LDL and its oxidation rate on patients’ short- and long-term prognosis was evaluated by multiple logistic regression analysis. \( P < 0.05 \) was considered statistically significant.

### 3. Results

Ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/HDL-C and ApoA1/ApoB in each group were mildly negative correlated with HDL-C, while not significantly correlated with TC nor LDL-C.

The predictive value of ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/LDL-C and apoA1/apoB for diagnosing CAD, the receiver-operating characteristic curve (ROC curve), and the area under the curve (AUC) were shown in Fig. 1. The AUC of ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/LDL-C and apoA1/apoB were more than 0.50 (\( P < 0.001 \)), while the AUC of TC, LDL-C, HDL-C were less than 0.50 (\( P < 0.001 \)).

Sixteen of 600 cases died from cardiac events within two weeks. Multiple logistic regression analysis revealed that age, ox-LDL/LDL-C had relevance with short-term prognosis, and the OR was 1.069, 1.009 (\( P < 0.05 \)) respectively.

Twenty two of 584 CAD patients lost of follow up. So that 562 cases were followed up for 44 months. Sixteen of 600 cases died from cardiac events within two weeks. Multiple logistic regression analysis revealed that age, ox-LDL/LDL-C had relevance with short-term prognosis, and the OR was 1.069, 1.009 (\( P < 0.05 \)) respectively.

Twelve of 600 cases died from cardiac events within two weeks. Multiple logistic regression analysis revealed that age, ox-LDL/LDL-C had relevance with short-term prognosis, and the OR was 1.069, 1.009 (\( P < 0.05 \)) respectively.

### Table 1

Baseline character of each group. Data are expressed as mean ± SD or as percent.

| Sex (male %) | Age (years) | BMI (Kg/m²) | Never smokers (%) | Former smokers (%) | Current smokers (%) | Cr (µmol/l) |
|-------------|-------------|-------------|-------------------|-------------------|---------------------|-------------|
| SAP (n = 228) | 59.6 ± 10.2 | 23.88 ± 3.60 | 32.0 ± 0.29 | 35.5 ± 0.29 | 32.5 ± 0.29 | 85.74 ± 3.15 |
| UAP (n = 195) | 61.0 ± 10.6 | 23.46 ± 3.06 | 31.8 ± 0.29 | 34.9 ± 0.29 | 33.3 ± 0.29 | 94.11 ± 7.27 |
| AMI (n = 177) | 78.5 ± 11.5 | 23.72 ± 2.69 | 28.6 ± 0.29 | 35.0 ± 0.29 | 36.2 ± 0.29 | 107.52 ± 8.16 |
| Normal control (n = 120) | 84.5 ± 11.3 | 23.16 ± 2.28 | 37.5 ± 0.29 | 34.2 ± 0.29 | 28.3 ± 0.29 | 88.43 ± 3.60 |
| High risk control (n = 140) | 57.1 ± 11.3 | 23.78 ± 3.00 | 35.0 ± 0.29 | 35.0 ± 0.29 | 30.0 ± 0.29 | 82.40 ± 4.60 |
| P value | 0.05 | NS | NS | NS | NS | NS |

**Table 2**

Baseline lipid profile in each group. Data are expressed as mean ± SD

| TC (mmol/l) | TG (mmol/l) | HDL-C (mmol/l) | LDL-C (mmol/l) | ApoA1 (mmol/l) | ApoB (mmol/l) |
|-------------|-------------|----------------|----------------|----------------|---------------|
| SAP (n = 228) | 4.93 ± 1.07;‡ | 1.83 ± 2.37 | 1.16 ± 0.29;* | 3.05 ± 0.86;‡ | 1.05 ± 0.28;‡ | 0.90 ± 0.28;‡ |
| UAP (n = 195) | 5.28 ± 1.04;† | 1.68 ± 1.22 | 1.42 ± 0.29;* | 3.11 ± 0.84;‡ | 1.00 ± 0.23;† | 0.91 ± 0.25;† |
| AMI (n = 177) | 5.57 ± 1.02;‡ | 1.74 ± 0.80 | 0.97 ± 0.31;* | 3.43 ± 0.82;‡ | 0.80 ± 0.23;† | 0.85 ± 0.22;† |
| Normal control (n = 120) | 4.83 ± 0.59 | 1.54 ± 0.87 | 1.56 ± 0.41 | 2.67 ± 0.54 | 0.89 ± 0.21 | 0.83 ± 0.17 |
| High risk control (n = 140) | 6.01 ± 0.98;* | 1.72 ± 0.97 | 1.59 ± 0.37;* | 4.00 ± 0.92;* | 0.99 ± 0.30;* | 1.08 ± 0.22;* |
| P value | 0.001 | NS | NS | NS | NS | NS |

*P < 0.001 vs. group normal control; †P < 0.001 vs. group AMI; ‡P < 0.001 vs. group high risk control.

**Table 3**

Baseline serum oxidized LDL and oxidation ratio of LDL in each group

| Ox-LDL (mmol/l) | Ox-LDL/TC | Ox-LDL/HDL-C | Ox-LDL/LDL-C | ApoA1/apoB |
|----------------|-----------|--------------|--------------|------------|
| SAP (n = 228) | 1.19 ± 0.44;†;‡ | 0.28 ± 0.14;†;‡ | 1.37 ± 0.50;†;‡ | 1.30 ± 0.78;†;‡ |
| UAP (n = 195) | 1.93 ± 0.56;‡;† | 0.49 ± 0.16;‡;† | 1.99 ± 0.18;‡;† | 1.19 ± 0.48;‡;† |
| AMI (n = 177) | 2.75 ± 0.76;‡;† | 0.67 ± 0.11;‡;† | 3.26 ± 1.52;‡;† | 1.02 ± 0.45;‡;† |
| Normal control (n = 120) | 0.37 ± 0.21 | 0.10 ± 0.06 | 0.37 ± 0.12 | 0.13 ± 0.11 | 1.12 ± 0.35;† |
| High risk control (n = 140) | 0.66 ± 0.22 | 0.16 ± 0.04 | 0.56 ± 0.26 | 0.23 ± 0.06 | 0.96 ± 0.31;‡ |
| P value | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |

*P < 0.001 vs. group normal control; ‡P < 0.001 vs. group UAP; †P < 0.001 vs. group high risk control; §P < 0.001 vs. group AMI.
no obvious discomfort during the period. As shown on Table 5. Multivariate logistic regression analysis (age, TC, HDL-C, LDL-C, ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/HDLC and apoA1/apoB in CAD patients. The AUC of ox-LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/HDLC and apoA1/apoB were more than 0.50 (P < 0.001), while the AUC of TC, LDL-C, HDL-C were less than 0.50 (P < 0.001). (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-2012-00941)

and 25% respectively (P < 0.05), which was recovered by paired t test as detailed on Table 7 and Fig. 2. Pearson correlation analysis showed that the change of ox-LDL had no significant correlation with the changes of LDL-C, nor TC, suggested that the effect of decreasing ox-LDL by statins is independent of lowering LDL-C and TC.

4. Discussion

There is increasing evidences suggest that oxidative modification of LDL plays a pivotal role in the development of atherosclerosis [3,6,15,16]. In this study, ox-LDL was measured by competitive ELISA, developed by Holvoet et al. The study found that the levels of ox-LDL and oxidation ratio of LDL were significantly higher in CAD cases than in controls, which was similar to our previous findings. These findings indicate that plasma ox-LDL level and oxidation ratio of LDL are closely related with CAD. More interesting, data from the study revealed that the correlationship between CAD and relative degree of LDL oxidation is stronger than with the level of oxidized LDL in vivo.
It is known that AS is a systemic disease and there are peculiarities in patients with CAD and peripheral arterial disease (PAD). While there is no evidence shows PAD have the same ox-LDL and oxidation ratio of LDL profile by now. Rosoky et al. have investigated 85 PAD patients with an ankle-brachial pressure index (ABPI) \(< 0.9\) [17], and found that there was no significant difference between the quartiles (divided according to ABPI for this population \(p = 0.33\)). No correlation was found between ABPI and ox-LDL in subjects with clinically evident PAD, which suggested that ox-LDL is not a good predictor of PAD severity. So further studies are necessary for elucidating the relationship between ox-LDL and PAD.

The study found that the level of ox-LDL was significantly higher in CAD patients than controls. Since Ox-LDL can elicit localized inflammatory response [18, 19], therefore, level of Ox-LDL may reflect the degree of inflammatory reaction and even severity of CAD. This may be the explanation that some patients without CAD, while their TC and (or) LDL-C are high; on contrary, some patients who have severe CAD while their TC and (or) LDL-C are not elevated.

Hypertension and diabetes are risk factors of CAD. As to evaluate the contribution to these factors to oxidation of LDL, in our previous study, we categorized the patients into CAD only, CAD+HT, CAD+DM and CAD+HT+DM. The study found that ox-LDL, ox-LDL/TC, ox-LDL/LDL-C, ox-LDL/HDL-C and ox-LDL/ALB ratio were higher in group CAD+HT and CAD+DM than in CAD only, while highest in CAD+HT+DM. It suggested high risk factors as hypertension and diabetes may accelerate the oxidation of LDL, and then compromise inflammation in arteries [18,19] consequently.

High risk controls of the present study were individuals without evidence of CAD or diabetes mellitus, but with hypertension and dyslipidemia. Mean value of ox-LDL and oxidation ratio of LDL were significantly higher than in normal controls, indicating that inflammatory reaction is also strong in high risk population without CAD.

In this study, we compared the diagnostic accuracy of 8 different lipid or lipoprotein biomarkers that have been suggested to identify patients with an increased risk of CAD. Diagnostic accuracy was determined by AUC of receiver operating characteristic curve, which is the most common method for quantifying and comparing the accuracies of different diagnostic tests. The present observations suggest that oxidized LDL, ox-LDL/TC, ox-LDL/HDL-C, ox-LDL/LDL-C and apoA1/apoB are better biomarkers than popular lipid profile (TC, LDL-C, HDL-C) for discriminating between patients with CAD and healthy subjects. Some researches found that apoB/apoA1 showed a significant positive correlation with myocardial infarction, stroke, and other cardiovascular diseases, which was a better biomarker for CAD than popular lipid pro-
Fig. 2. Comparison of changes of lipid profile by the treatment of statins in two weeks (n = 584). After 2 week-statins therapy, HDL-C and apoA1/apoB improved by 10% and 14%, while TC, LDL-C, ox-LDL, ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C decreased by 22%, 28%, 38%, 29%, 23% and 25% respectively. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/DMA-2012-00941)

file (TC, LDL-C, HDL-C) and lipoprotein (apoA1, apoB) [20]. Differently, we found that apoA1/apoB was a better biomarker for CAD than popular lipid profile (TC, LDL-C, and HDL-C) in this study, while the AUC of ox-LDL, ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C were even better than apoA1/apoB. Multivariate logistic regression analysis demonstrated that age, ox-LDL/TC and ox-LDL/LDL-C relate with both short-term and long-term prognosis (p < 0.05). A perspective study [21] with 178 CAD patients, who were followed up for 52 months, revealed that the level of ox-LDL may be a good biomarker for predicting cardiovascular events, including angina, nonfatal myocardial infarction and cardiovascular mortality. Our prior study [6] found that the level of ox-LDL and the oxidation ratio of ox-LDL were better biomarkers than TC, HDL-C and LDL-C for discriminating between patients with coronary artery disease and healthy subjects. Now this further study showed that the value of them for evaluating short-and long-term prognosis was better than popular lipid profile, especially ox-LDL/TC and ox-LDL/LDL.

In the past years, several large-scale clinical trials [15,16,20,21] proved that statins lower plasma LDL-C, decrease incidence of cardiovascular events and mortality, which is crucial in primary and secondary prevention for CAD. Clinical trials such as HPS, PROVE-IT and so on further showed that the lower the LDL-C, the more benefit achieves. Current evidence suggests that the clinical benefit is not dependent on the kind of statins, but the extent of LDL-C been lowered [22]. Besides lowering cholesterol, statins have pleiotropic effects, such as antioxidation, anti-inflammation, stabilization of plaques, which are independent of LDL lowering, although some experts hold different opinions, who believe that the clinical benefit is only from the reducing of cholesterol [23,24]. So further studies are necessary for elucidating pleiotropic effects of statins.

There have been some studies about effects of lowering ox-LDL in long-term statin’s therapy, but few researched on short period therapy. As far as we know, it is the first study concerning on whether statins still have similar effect on reduction of ox-LDL in earlier period (within 2 weeks). This study observed 584 CAD patients (16 of 600 died in two weeks) who accepted statins’ treatment for 2 weeks, and found that TC, LDL-C, ox-LDL and the ratio of ox-LDL were all decreased to some extent, while HDL-C was increased, which is consistent with the clinic benefits achieved from statins.
In this study, we found that TC, LDL-C, ox-LDL, ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C were decreased by 22%, 28%, 38%, 29%, 23% and 25% respectively. Pearson correlation analysis showed that the decrease in ox-LDL has no significant correlation with the change of LDL-C, nor TC, suggesting that statins have effect of anti-oxidant beyond reducing of cholesterol.

In conclusion, this study found that ox-LDL and oxidation ratio of LDL (ox-LDL/TC, ox-LDL/HDL-C and ox-LDL/LDL-C) are closely related with AS, and they are better biomarkers for discriminating between patients with coronary artery disease and healthy subjects than the usual tests. Furthermore, they are valuable for prognostic evaluation in CAD patients. Statins can reduce level of ox-LDL significantly, which is independent of lowering of LDL-C and TC.

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