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Clinical Investigations

Effect of Preexisting Statin Use on Expression of C-Reactive Protein, Adhesion Molecules, Interleukin-6, and Antioxidized Low-Density Lipoprotein Antibody in Patients with Unstable Angina Undergoing Coronary Stenting

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Summary

Background: Statins are believed to reduce coronary heart disease by mechanisms in addition to their well-known cholesterol lowering effect.

Hypothesis: We studied the effect of statins on expression of C-reactive protein (CRP), interleukin-6 (IL-6), adhesion molecules, and antioxidized low-density lipoprotein antibody (anti-oxLDL Ab) in patients with unstable angina (Braunwald class IIb or IIIb) undergoing coronary stenting.

Methods: Consecutive 50 patients with unstable angina were included in the study. We classified the study subjects as patients using statins (Group A, n = 20, men 10, mean age 62 years) and patients not using statins (Group B, n = 30, men 15, mean age 60 years).

Results: Baseline levels of inflammatory markers were similar in the two groups. However, 24 h after coronary stenting, serum levels of CRP (2.00 vs. 4.63 mg/l, $p < 0.05$), intercellular adhesion molecule-1 (ICAM-1) (217 vs. 261 ng/ml, $p < 0.01$), and anti-oxLDL Ab (8.97 vs. 12.96 U/ml, $p < 0.05$) were significantly higher in Group B than in Group A. Furthermore, 72 h after coronary stenting, serum levels of CRP (3.00 vs. 5.50 mg/l, $p < 0.01$) and ICAM-1 (222 vs. 277 ng/ml, $p < 0.05$) were significantly higher in Group B than in Group A.

Conclusions: Preexisting statin therapy plays a role in reducing the serum levels of CRP, ICAM-1, and anti-oxLDL Ab after coronary stenting in patients with unstable angina. These data support an anti-inflammatory or plaque-stabilizing effect of statin therapy.

Key words: unstable angina, statin, inflammation, coronary stenting

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Introduction

Recent studies have provided evidence that inflammation is an independent risk factor for and plays a role in the pathogenesis of cardiovascular disease.[1–4] There is strong evidence that serum C-reactive protein (CRP) levels are an independent risk factor for ischemic heart disease.[3, 4] Oxidized low-density lipoprotein (oxLDL) is also believed to play a key role in the development of atherosclerosis,[5, 6] and antibodies against oxLDL have been demonstrated both in human sera and in atherosclerotic lesions.[7, 8] Several studies have found that higher antioxidized low-density lipoprotein antibody (anti-oxLDL Ab) titers are associated with the presence of atherosclerotic disease.[9, 10] Leukocyte binding to cellular adhesion molecules (CAMs) on the surface of vascular endothelial cells appears to be one of the earliest events in atherosclerosis.[11–13] Pathologic studies have demonstrated CAMs within atherosclerotic plaque,[14, 15] and clinical studies have suggested a role for CAMs in plaque disruption and subsequent acute coronary events.[16–18]

Statin therapy has been shown in many randomized, controlled, primary and secondary prevention trials to reduce the risk of coronary events and stroke.[19–23] These benefits appear to derive largely from a stabilizing effect on high-risk atherosclerotic plaques through modification of lipid profiles as well as other properties not directly related to lipid lowering.[24–27] The purpose of this study was to assess the effect of statins on expression of CRP, interleukin-6 (IL-6), adhesion molecules,

and anti-oxLDL Ab in patients with unstable angina undergoing coronary stenting.

Materials and Methods

Patient Population

In all, 52 consecutive patients were admitted to our hospital during the period August 2002–January 2003 with a diagnosis of unstable angina (Braunwald class IIb or IIIb). Of these, we excluded 2 patients with concomitant current infection (n = 1, chronic otitis media) and 1 patient who developed non-Q-wave myocardial infarction (n = 1, creatine kinase ≥ three times the upper normal limit, with a concomitant rise in MB isoenzyme) after intervention, leaving 50 patients (25 men and 25 women; mean age 61 years) included in the study. We classified the 50 study subjects as patients using statins (Group A, n = 20, 10 men, mean age 62 years) and patients not using statins (Group B, n = 30, 15 men, mean age 60 years). The study was revised and approved by our institution's ethics committee, and all eligible patients gave written informed consent.

Study Design

Blood samples were obtained before and at 24 and 72 h after intervention. All samples were measured as a single batch at the end of the study. Patients received aspirin 200 mg once per day and ticlopidine 250 mg twice per day before intervention. Also before intervention, heparin was given as an intravenous bolus of 8,000 to 10,000 units and then additional heparin, as required, to maintain an activated clotting time of ≥ 250 s. Coronary angiography as well as percutaneous coronary intervention via the radial artery, except in five cases, were performed using standard technique in all patients.

Laboratory Assays

Anti-oxLDL Ab titers were determined using a solid-phase, enzyme-linked immunosorbent assay (ELISA) (oxLDL immunoglobulin ELISA test, Biomedica Inc., Vienna, Austria). Concentrations are expressed as units/ml (U/ml). Intra- and interassay variabilities were < 5%. The levels of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and IL-6 were determined using a commercially available ELISA kit (R & D Systems, Minneapolis, Minn., USA) with intra- and interassay coefficients for each moiety of < 5 and < 10%, respectively. C-reactive protein was measured by rate nephelometry (Immage® Immunochemistry System, Beckerman Coulter, Inc., Fullerton, Calif., USA). The CRP detection range corresponded to concentrations of 0.1 to 96 mg/l (normal values < 8.0 mg/l).

Statistical Analysis

The Statistical Package for Social Sciences version 10.0 (SPSS, Inc., Chicago, Ill., USA) was used for statistical analysis. Data are presented as means ± standard deviation (SD). Serum CRP levels are presented as medians. Continuous variables were compared using the Mann-Whitney U-test or the Wilcoxon signed-rank test (CRP) and using the unpaired Student's *t*-test or paired Student's *t*-test (anti-oxLDL Ab, adhesion molecules, and IL-6). The chi-square test was used to compare discrete variables. A p value of < 0.05 was taken to indicate statistical significance.

Results

Baseline Characteristics

Baseline clinical and angiographic characteristics are shown in Table I. The levels of LDL cholesterol in Groups A and B were 129 and 125 mg/dl, respectively. Body mass index (the weight in kg divided by the square of the height in meters), risk factors for coronary artery disease (CAD), and medications such as antiplatelets and angiotensin-converting enzyme (ACE) inhibitors were similar in the two groups (Table I).

TABLE I Baseline characteristics of subjects

	Group A (n = 20 patients)	Group B (n = 30 patients)
Age (years)	62 ± 9	60 ± 9
Men / women	10 / 10	15 / 15
Body mass index (kg/m^2)	23.7 ± 4.5	23.0 ± 3.7
History of		
Systemic hypertension (%)	11 (55)	15 (50)
Diabetes mellitus (%)	9 (45)	10 (33)
Hypercholesterolemia (%) [a]	20 (100)	5 (17)
Smoking (%)	7 (35)	15 (50)
Lipid status		
LDL cholesterol (mg/dl)	129 ± 37	125 ± 31
Triglyceride (mg/dl)	103 ± 55	127 ± 60
HDL cholesterol (mg/dl)	49 ± 10	45 ± 9
Ejection fraction (%)	60 ± 10	60 ± 11
Medication at enrollment		
Aspirin (%)	11 (55)	9 (30)
Beta blockers (%)	7 (35)	7 (23)
ACE inhibitor (%)	7 (35)	10 (33)
Multivessel disease (%)	10 (50)	14 (47)
Lesion length (mm)	17.4 ± 4.9	16.4 ± 4.5
Reference diameter (mm)	3.4 ± 0.4	3.4 ± 0.6
Minimal luminal diameter		
Pre intervention (mm)	0.7 ± 0.4	0.6 ± 0.4
Post intervention(mm)	3.2 ± 0.6	3.3 ± 0.7

[a] $p < 0.001$ versus Group A.

Age, lipid profile, ejection fraction, lesion length, and minimal luminal diameter are presented as mean ± standard deviation.

Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein, ACE = angiotensin-converting enzyme.

Inflammatory Markers

Before intervention, serum concentrations of CRP, anti-oxLDL Ab, VCAM-1, ICAM-1, E-selectin, and IL-6 were similar in the two groups. However, 24 h after coronary stenting, serum levels of CRP (2.00 vs. 4.63 mg/l, $p < 0.05$), ICAM-1 (217 ± 70 vs. 261 ± 62 ng/ml, $p < 0.05$), and anti-oxLDL Ab (8.9 ± 3.9 vs. 12.9 ± 6.9 U/ml, $p < 0.05$) were significantly higher in Group B than in Group A. Furthermore, 72 h after coronary stenting, serum levels of CRP (3.0 vs. 5.50 mg/l, $p < 0.01$) and ICAM-1 (222 ± 50 vs. 277 ± 71 ng/ml, $p < 0.05$) were significantly higher in Group B than in Group A. At 24 and 72 h after coronary stenting, serum levels of VCAM-1, E-selectin, and IL-6 were similar in the two groups (Table II, Figs. 1, 2). In Group B (no-statin group), serum levels of CRP and anti-oxLDL Ab increased significantly 24 h after coronary stenting, from a baseline value of 2.1 mg/l and 7.9 U/ml to 4.63 mg/l and 12.9 U/ml ($p < 0.05$, respectively). However, in response to coronary stenting, serum levels of CRP and anti-oxLDL Ab did not significantly change in Group A (Table II). The levels of VCAM-1, ICAM-1, E-selectin, and IL-6 were not significantly changed in response to coronary stenting in both Groups A and B. At 24 h after intervention, CRP levels were elevated (> 4.1 mg/l, median level of all patients at 24 h after intervention) in 4 (20%) of 20 patients in Group A but in 17 (57%) of 30 patients in Group B ($p < 0.05$), and anti-oxLDL Ab levels were also elevated (> 11.2 U/ml, mean value of all patients at 24 h after intervention) in 3 (15%) of 20 patients in Group A but in 14 (47%) of 30 patients in Group B ($p < 0.05$) (Table II).

Discussion

Our findings show that preexisting statin therapy plays a role in reducing serum levels of CRP, ICAM-1, and anti-oxLDL Ab after coronary stenting in patients with unstable angina. Therefore, these results provide evidence of an anti-inflamma-

TABLE II Serum levels of inflammatory markers before and after intervention

	Group A (n = 20 patients)	Group B (n = 30 patients)
Anti-oxLDL Ab (mean, U/ml)		
Before stenting	8.2 ± 3.2	7.9 ± 3.3
24 h after stenting	8.9 ± 3.9	12.9 ± 6.9 [a,c]
72 h after stenting	8.4 ± 4.0	10.1 ± 4.1 [c]
CRP (median, range, mg/l)		
Before stenting	1.10 (0.06~5.41)	2.19 (0.06~11.7)
24 h after stenting	2.00 (0.06~10.3)	4.63 (0.06~11.3) [a,c]
72 h after stenting	3.00 (0.06~7.10)	5.50 (0.06~21.0) [b,c]
VCAM-1 (mean, ng/ml)		
Before stenting	645 ± 150	625 ± 140
24 h after stenting	663 ± 165	669 ± 186
72 h after stenting	588 ± 180	671 ± 201
ICAM-1 (mean, ng/ml)		
Before stenting	227 ± 55	230 ± 93
24 h after stenting	217 ± 70	261 ± 62 [a]
72 h after stenting	222 ± 50	277 ± 71 [a]
E-selectin (mean, ng/ml)		
Before stenting	50 ± 25	49 ± 22
24 h after stenting	51 ± 29	48 ± 28
72 h after stenting	35 ± 15	45 ± 27
IL-6 (mean, pg/ml)		
Before stenting	8.1 ± 5.1	8.5 ± 5.3
24 h after stenting	8.9 ± 4.9	9.5 ± 6.7
72 h after stenting	8.5 ± 3.1	8.8 ± 5.2
At 24 h after stenting		
CRP ≥ 4.1 mg/l (%)	4 (20)	17 (57) [a]
Anti-oxLDL Ab ≥ 11.2 U/ml (%)	3 (15)	14 (47) [a]

[a] $p < 0.05$.

[b] $p < 0.01$ versus Group A.

[c] $p < 0.05$ versus before stenting.

Abbreviations: Anti-oxLDL Ab = antioxidized low-density lipoprotein autoantibody, CRP = C-reactive protein, VCAM-1 = vascular cell adhesion molecule-1, ICAM-1 = intercellular adhesion molecule-1, IL-6 = interleukin-6.

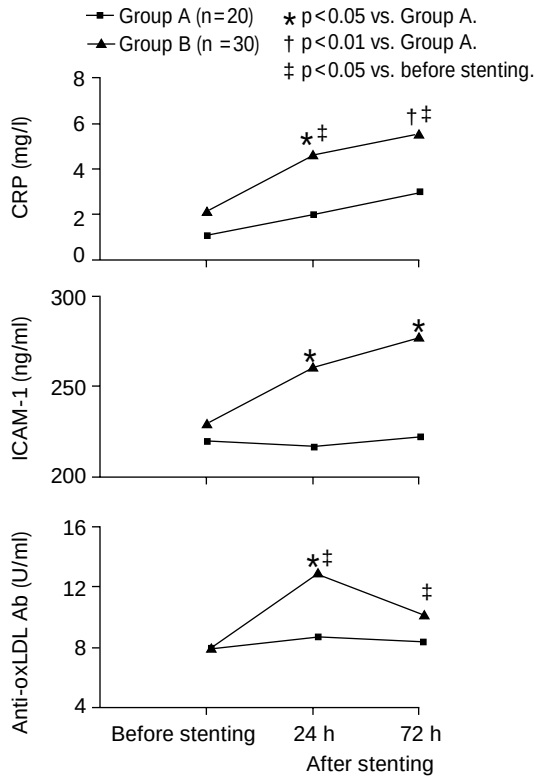

FIG. 1 Trends of CRP (median), ICAM-1 (mean), and anti-oxLDL Ab (mean) levels. Serum levels of CRP, ICAM-1, and anti-oxLDL Ab significantly increased in Group B, but not in Group A; CRP, ICAM-1, and anti-oxLDL Ab levels 24 h after coronary stenting in Group A were significantly lower than in Group B. CRP = C-reactive protein, ICAM-1 = intercellular adhesion molecule-1, anti-oxLDL Ab = antioxidized low-density lipoprotein antibody.

tory effect of statin therapy and may help explain the greater than expected benefits of statin therapy in such patients.

Statin therapy has been shown in many randomized, controlled, primary and secondary prevention trials to reduce the risk of coronary events and stroke.[19–23] These benefits have been observed in diverse patient populations with a wide range of risk according to standard risk factors. It has been long observed by angiography that the slight degree of atherosclerosis regression seen with statin therapy is unlikely to account for the extensive clinical benefits. These benefits appear to derive largely from a stabilizing effect on vulnerable plaques through modification of lipid profiles even in patients with normal cholesterol levels, as well as anti-inflammatory actions and other properties not directly related to lipid lowering.[24–27] These mechanisms by which statins make plaques less vulnerable are not well understood. Intravascular ultrasound can now delineate statin-induced changes in plaque constituents. The observation of reduced plaque lipid content and increased fibrous cap thickness in association with statin therapy, in the virtual absence of changes in overall plaque size, is consistent with the long-observed clinical and angiographic effects of this treatment.[28] In investigations using an intravascular thermography catheter, the elevated temperatures long associated with unstable plaques were observed in plaques that had ruptured previously. It was observed, however, that statin therapy attenuated these temperature elevations in the previously ruptured lesions.[29] In another study that helps clarify the mechanisms of statin's clinical benefits, statin therapy was seen to improve the resistance of LDL cholesterol to oxidation. The study also found that statin therapy is associated with reduced production of a cytokine that promotes atherogenesis by contributing to the development of foam cells within plaques.[30]

Our data are in line with these findings. Serum levels of CRP, anti-oxLDL Ab, and ICAM-1, which were inflammatory markers of interest in atherosclerotic development and plaque instability, were not significantly increased by coronary stenting in patients with compared with those without preexisting statin therapy. Therefore, the findings indicate that statin therapy has an anti-inflammatory effect that literally reduces the response of inflammatory system to injury, leading to an improvement in the plaque stabilizing effect. However, in the present study, the baseline levels of inflammatory markers were similar in the two groups. Many recognized risk factors for CAD, such as dyslipidemia, hypertension, diabetes, and obesity, have close pathophysiologic associations with inflam-

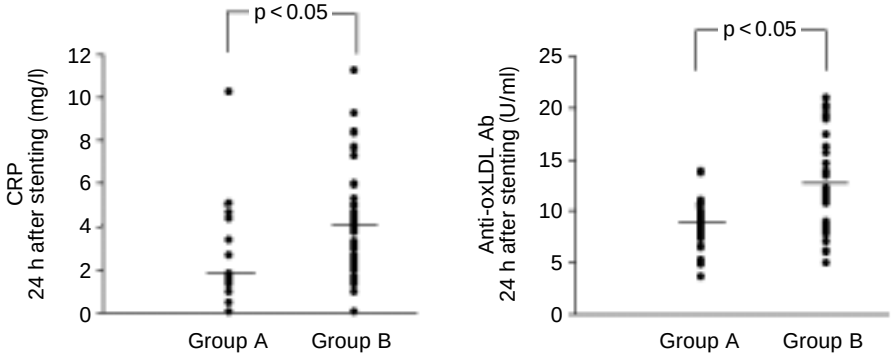

FIG. 2 Distribution of CRP (median) and anti-oxLDL Ab (mean) levels 24 h after coronary stenting in Groups A and B; CRP and anti-oxLDL Ab levels 24 h after coronary stenting in Group A were significantly lower than in Group B. Abbreviations as in Figure 1.

matory processes.[30] Thus, the baseline levels of inflammatory markers may be similar in the two groups even though patients in Group A had undergone statin therapy previously. In the present study, serum levels of CRP, ICAM-1, and anti-oxLDL Ab did not increase significantly by coronary stenting in patients with preexisting statin therapy, but serum levels of VCAM-1, E-selectin, and IL-6 did not respond to statin therapy. The mechanisms underlying these distinctly different results for the inflammatory markers are unknown. However, these differences may be explained by differences in half-life, the shedding process, and the different expression sites of inflammatory markers. C-reactive protein (half-life of 19 h) and anti-oxLDL Ab represent more practical markers of inflammation than IL-6 because of its much shorter half-life (4 h). In addition, in contrast to ICAM-1, levels of soluble VCAM-1 do not reflect the expression of membrane-bound VCAM-1.

The major limitation of our study is the small number of patients; however, we adopted strict enrollment criteria to achieve a homogeneous population. The duration of clinical follow-up was not long enough to evaluate the effect of statins. These limitations should be considered when assessing the study results.

Conclusions

Our findings show that preexisting statin therapy plays a role in reducing the serum levels of CRP, ICAM-1, and anti-oxLDL Ab after coronary stenting in patients with unstable angina. Therefore, these results provide evidence of an anti-inflammatory effect of statin therapy and may help explain the greater than expected benefits of statin therapy in patients with unstable angina.

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