SCIENTIFIC LETTER

Neurohumoral and inflammatory activation in patients with coronary artery disease treated with statins

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Inflammation plays an important part in the pathophysiology of coronary artery disease (CAD).[1] High sensitive C reactive protein (hsCRP) reflects activation of the inflammatory system and independently predicts risk of first coronary events at all levels of low density lipoprotein (LDL)-cholesterol and a full spectrum of Framingham risk categories.[2] Recent trials indicate that statins reduce inflammation.[3 4] This leads to a better clinical outcome and reduces the rate of atherosclerosis progression independently of the reduction in cholesterol levels. The reasons why patients with raised levels of C reactive protein (CRP) have a worse outcome are, however, not clear.

The inflammatory biomarkers interleukin 6 (IL6), soluble tumour necrosis factor receptors (sTNFr) 1 and 2 have proinflammatory and procoagulant properties. Our first aim was to evaluate whether high levels of hsCRP in patients with stable CAD receiving standard statin treatment are associated with activation of these biomarkers. Our second aim was to evaluate whether hsCRP and cytokine levels are determined by LDL-cholesterol or by neurohumoral activation measured by levels of N-terminal pro-B type natriuretic peptide (NT-proBNP).

METHODS

We analysed a subgroup of an ongoing prospective study comprising 153 statin treated patients with stable CAD. They were evaluated >6 months from myocardial infarction or cardiac revascularisation, and were free from infection, inflammatory diseases, malignancy and anti-inflammatory treatment. Left ventricular ejection fraction (LVEF) and volumes were determined scintigraphically. Fasting blood samples were centrifuged within 1 h and plasma was frozen at −80℃ until assaying. NT-proBNP was measured with an electrochemiluminescence sandwich immunoassay (Roche Diagnostics, Mannheim, Germany). CRP concentrations were measured by a high-sensitivity, particle-enhanced immunoturbidimetric method (Integra 400 analyser, Roche Diagnostics). sTNFr 1 and 2 were measured with ELISA kits from BioSource (Camarillo, California, USA). IL6 was measured with a high-sensitivity ELISA kit from Roche Diagnostics. White cell count, glucose, lipids and creatinine were determined with standard laboratory tests; glomerular filtration rate (GFR) was calculated. All patients gave informed consent and the protocol was approved by the ethical committee.

Statistical analysis

Independent samples t tests were used to compare patients with hsCRP levels <2 mg/l (group 1, n = 77) and those with levels ⩾2 mg/l (group 2, n = 76). NT-proBNP, IL6 and sTNFr 1 and 2 were not normally distributed and underwent logarithmic transformation before statistical analysis. Linear regression analysis was used to fit different models to predict inflammatory biomarkers hsCRP, IL6, and sTNFr 1 and 2. The following predictors were included in the models: age, body mass index, GFR, ejection fraction, New York Heart Association (NYHA) class, and log(NT-proBNP). Median values of hsCRP, IL6, and sTNFr 1 and 2 were used to divide patients in low and high level categories and construct a ''multimarker'' with the following extremes: 0 if patients belong to the low level categories and 4 if patients belong to the high level categories of these inflammatory markers.

RESULTS

Demographics: age 69 (6) years, 119 (78%) men, LVEF 55% (14%); 91 (60%) patients were in NYHA class I, 62 (40%) in class II–III. Age, sex and body mass index did not differ between the 2 groups (table 1). Systolic and diastolic blood pressure was comparable: 147(23)/77(14) mm Hg versus 144(21)/77(12) mm Hg, p = non-significant (NS). Cardiac history, risk factors (table 1) and medical treatment were also comparable (aspirin: 82% and 75%, angiotensin converting enzyme inhibitors: 55% and 51%, angiotensin II receptor blockers: 13% and 20%, p = NS). Information on alcohol use and dietary micronutrients was not available. The most frequently prescribed statins were (no significant differences between groups 1 and 2): simvastatin 20 mg (41%) and 40 mg (22%); atorvastatin 10 mg (5%), 20 mg (11%) and 40 mg (3%); pravastatin 40 mg (9%). Patients in group 2 had a lower ejection fraction and higher NYHA class (table 1). Left ventricular volumes were comparable. Renal function, fasting glucose and lipid values did not differ between the hsCRP groups (table 1). Percentage of patients achieving LDL-cholesterol <2.6 mmol/l was 57% in group 1 and 42% in group 2 (p = NS); for LDL-cholesterol <1.8 mmol/l this was 19% and 18% respectively (p = NS). Neutrophile count was higher in group 2. Proinflammatory cytokine and NT-proBNP levels were considerably higher in group 2 (table 1). The only factor that consistently remained significant in all linear regression models to predict the inflammatory markers hsCRP, IL6, sTNFr 1 and 2 was NT-proBNP. LDL-cholesterol levels were not significantly associated with the inflammatory biomarkers. Log(NT-proBNP) increased gradually from 2.2 (0.5) for multimarker = 0 to 2.6 (0.5) for multimarker = 4, p<0.01.

DISCUSSION

Statin treated patients with acute coronary syndromes have worse clinical outcomes if hsCRP levels ⩾2 mg/l regardless of the LDL-cholesterol levels achieved.[3] How do patients with high CRP levels differ from patients with hsCRP <2 mg/l?

Abbreviations: CAD, coronary artery disease; CRP, C reactive protein; GFR, glomerular filtration rate; hsCRP, high sensitive C reactive protein; IL6, interleukin 6; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; sTNFr, soluble tumour necrosis factor receptors

Table 1 Results according to high sensitive C reactive protein levels

	group 1 (n=77) hsCRP <2 mg/l	group 2 (n=76) hsCRP ≥2 mg/l	p Value
Age (years)	69 (6)	70 (6)	NS
Male sex	62/77 (81%)	57/76 (75%)	NS
BMI (kg/m^2)	28 (4)	28 (5)	NS
NYHA class	51 (66%) class I 26 (34%) class II-III	40 (53%) class I 36 (47%) class II-III	<0.05
LVEDV (ml)	120 (52)	122 (60)	NS
LVESV (ml)	56 (44)	64 (53)	NS
Ejection fraction (%)	58 (13)	53 (14)	<0.05
GFR (ml/min/1.73 m^2)	77 (18)	73 (15)	NS
Arterial hypertension	47 (61%)	54 (72%)	NS
Diabetes mellitus	25 (33%)	24 (32%)	NS
Smoking	5 (7%)	12 (9%)	NS
Total cholesterol (mmol/l)	4.31 (0.83)	4.57 (1.04)	NS
HDL-cholesterol (mmol/l)	1.27 (0.33)	1.30 (0.31)	NS
LDL-cholesterol (mmol/l)	2.36 (0.70)	2.52 (0.91)	NS
Triglycerides (mmol/l)	1.45 (0.85)	1.49 (0.72)	NS
Fasting glucose (g/l)	1.08 (0.28)	1.19 (0.50)	NS
Leuocytes (10 E^3/µl)	6452 (1569)	6782 (1571)	NS
Neutrophils (/µl)	3623 (1085)	4069 (1266)	<0.05
Log(IL6)	0.26 (0.29)	0.50 (0.31)	<0.001
Log(sTNFr1)	0.44 (0.12)	0.49 (0.14)	<0.05
Log(sTNFr2)	0.90 (0.13)	0.96 (0.13)	<0.01
Log(NT-proBNP)	2.36 (0.41)	2.52 (0.48)	<0.05

Values are mean (SD) or number (%).
BMI, body mass index; GFR, glomerular filtration rate; HDL, high density lipoproteins; IL-6, interleukin-6; LDL, low density lipoproteins; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NS, not significant; NYHA, New York Heart Association; sTNFr, soluble tumour necrosis factor.

Ray *et al* evaluated 2885 patients and found that several risk factors were weakly associated with higher CRP levels: age, sex, obesity, smoking, LDL-cholesterol ≥1.8 mmol/l, glucose >110 mg/dl and triglycerides >1.65 mmol/l.[5] In the present study, lipids and glucose were higher in group 2 but not significantly. The lack of association between risk factors and inflammation is probably due to the limited sample size. Patients with hsCRP levels ≥2 mg/l had a considerably lower LVEF and more symptoms. They had full activation of the inflammatory system with recruitment of neutrophils and higher proinflammatory cytokine levels. The higher NT-proBNP levels in group 2 patients reflect activation of the neurohumoral system. Moreover NT-proBNP was an independent predictor of hsCRP and cytokines. Using a multimarker approach, the combination of raised hsCRP, IL-6, sTNFr1 and 2 was associated with increased NT-proBNP levels. These findings suggest that patients with higher CRP levels despite standard statin treatment are in fact ''sicker'' patients; showing activation of different pathophysiological pathways that could explain worse clinical outcome in these patients. The observed correlations by Ray *et al*[5] between CRP levels and presence of cardiovascular risk factors might be accompanied by activation of neurohumoral and additional inflammatory pathways or might favour conditions causing this activation such as diastolic dysfunction. Intensive statin treatment will certainly diminish inflammatory activation, but additional (non)-pharmacological measures targeting risk factors could be mandatory in effectively treating the underlying pathophysiology and improving outcome.

In conclusion, statin treated stable CAD patients with higher CRP levels show activation of cytokines. The study shows an association between hsCRP and NT-proBNP suggesting a link between neurohumoral and inflammatory activation in these patients.

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