Brief Rapid Communication

Increased Plasma C-Reactive Protein in Familial Hypoalphalipoproteinemia
A Proinflammatory Condition?

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Background—HDL molecules have an established role in the regression processes of atherosclerosis as well as a putative role as antiinflammatory agents. Our study investigated whether familial hypoalphalipoproteinemia, a genetic form of dyslipidemia characterized by very low HDL levels, might be associated with increased inflammation markers such as C-reactive protein.

Methods and Results—A total of 50 subjects with hypoalphalipoproteinemia (age, 53.1±16.7 years) were compared with 64 healthy controls (age, 51.9±12.4 years). Apart from significantly lower values of HDL cholesterol (30.2±4.0 versus 52.5±12.7 mg/dL, \( P<0.0001 \)) and apolipoprotein AI (113.3±20.0 versus 155.4±24.9 mg/dL, \( P<0.0001 \)) and higher levels of triglycerides (141.3±62.9 versus 73.5±39.9 mg/dL, \( P<0.0001 \)), patients did not show different plasma values of total cholesterol and LDL cholesterol when compared with healthy controls (181.5±36.6 versus 186.3±32.6 mg/dL; 123.0±31.5 versus 119.1±30.3 mg/dL). CRP plasma values were significantly higher in patients than in controls (median 0.34 [range 0.02 to 4.66] versus 0.07 [0.02 to 0.85] mg/dL, \( P<0.0001 \)). In the patient group, CRP values were significantly higher in subjects with angiographically documented coronary atherosclerotic disease than in those without. Moreover, CRP concentrations were inversely correlated with both HDL cholesterol (\( r=-0.44, P=0.0006 \)) and apolipoprotein AI (\( r=-0.45, P=0.0006 \)) values.

Conclusions—Elevation of C-reactive protein values in familial hypoalphalipoproteinemia, in the absence of signs and symptoms of local or systemic inflammation or systemic or recurrent disease, may suggest an upregulation of proinflammatory mechanisms, which is further exacerbated by the presence of coronary atherosclerotic disease. (Circulation. 2002;105:11-14.)

Key Words: lipoproteins ■ C-reactive protein ■ hypolipoproteinemia ■ inflammation ■ atherosclerosis

The hypothesis that elevated levels of plasma high-density lipoprotein (HDL) protect against coronary atherosclerotic disease (CAD) was initially proposed by Barr et al in the 1950s and is now firmly established. Conversely, equally well-established evidence shows that low plasma HDL levels lead to atherosclerosis and are also recognized to be a major independent risk factor for CAD. Thus, HDL molecules can be considered the 2-faced Janus of the atherosclerotic process, which, in turn, is increasingly believed to be an inflammatory phenomenon. Atherosclerotic lesions show activation and proliferation of macrophages and T-lymphocytes, cytokine production, and oxidized low-density lipoprotein (LDL) accumulation.

We hypothesized that the link between low HDL levels and atherosclerosis may depend on an upregulation of inflammation mechanisms putatively induced by low HDL, which has been shown to act as a proinflammatory agent. Therefore, we measured C-reactive protein (CRP) in a group of patients affected by familial hypoalphalipoproteinemia (Hypoalpha), an autosomal-dominant genetic trait. Hypoalpha subjects are characterized by extremely low plasma levels of HDL (<10th percentile), together with reduced or normal LDL levels and normal or high triglyceride (TG) levels. Hypoalpha patients have greater susceptibility to early, severe coronary atherosclerosis. In the general population this trait has a prevalence of ~0.5%, and it is 10 to 20 times more frequent in subjects with CAD who are <60 years of age. CRP is a well-established, sensitive marker of systemic inflammation and represents an independent risk factor for cardiovascular events in population studies as well as in angina patients. Also, CRP seems to add predictive value to total cholesterol (TC) and HDL levels with regard to the risk of future myocardial infarction in subjects with hyperlipidemia and elevated concentrations of CRP. The hepatic synthesis of CRP is induced by cytokines such as interleukin-6; it accumulates in the arterial wall during the atherosclerotic...
rotic process, stimulates production of the tissue factor by monocytes, and induces the synthesis of adhesion molecules in endothelial cells.

Hypoalpha subjects were compared with a group of healthy controls and divided according to the presence or absence of CAD, as documented by coronary angiography, to provide a model in which to photograph the inflammatory state before and after the occurrence of clinical vascular damage.

Methods

Patients

The patients recruited for the study consisted of 50 consecutive subjects affected by Hypoalpha (43 men and 7 women; mean age 53.1 ± 16.7 years), who had been referred to our lipid clinic. The Hypoalpha diagnosis had been based on at least 3 consecutive analyses indicating HDL values <10th percentile, as well as on documentation of the vertical transmission of the trait through 2 (15 kindreds) or 3 (4 kindreds) generations. All subjects were of normal weight and free from other forms of organic, systemic, chronic, or recurrent disease and additional risk factors for atherosclerosis; none had experienced acute myocardial infarction in the previous 6 months. Subjects were excluded from the study when CRP values >5.00 mg/dL and other markers of inflammation indicated the presence of intervening infections. No subject from either the control or patient group was undergoing hormone or -blocker therapy at the time.

Laboratory Analysis

Serum TC, TG, and HDL were assessed by standard procedures; LDL was calculated according to Friedewald et al. Apolipoprotein AI (apoAI), lipoprotein (a) (Lp[a]) and high-sensitivity CRP (Hs-CRP) (0.02 to 6.00 mg/dL) were assayed on serum stored at −80°C in 1 batch by rate nephelometry (Beckman BN 100, Dade, Behring, Italy). Routine chemical clinical analyses were performed by standard methods subjects to strict quality control. The interassay coefficients of variation were <5% for every type of measurement.

Statistical Analysis

Data are expressed as mean ± SD or median (range) for nonnormal distributed variables. Variables not showing a normal distribution were logarithmically transformed. Any differences between mean values of cases and controls, as whole groups or when divided by sex, were tested by unpaired t test, whereas the nonparametric Mann-Whitney test was used for comparison of the median. ANOVA and multiple comparisons by Bonferroni test were performed in order to evaluate differences in age, body mass index, lipid profiles, and CRP levels among the 3 groups (ie, the control groups and the 2 Hypoalpha subgroups of patients with and without CAD). Variables able to influence CRP concentrations were analyzed by stepwise backward multiple regression. The relationships between the CRP and the other variables considered were assayed by logarithmic regression analysis.

Results

The physical characteristics, complete lipid profile, and prevalence of CAD in Hypoalpha subjects and in the control group are reported in the Table. The 2 groups differed significantly with regard to HDL-C levels, as well as triglyceride and apoAI levels and the ratios of TC/HDL-C and HDL-C/apoAI, although not for the TC and LDL concentrations.

HDL values of patients and controls differed not only quantitatively (30.3 ± 4.1 mg/dL, P < 0.0001) but also with regard to their composition; in Hypoalpha patients, a decreased HDL-C/apoAI ratio was found (0.27 versus 0.34, P < 0.0001), possibly indicating that in these subjects apoAI is less able to transport cholesterol.

CRP plasma values were significantly higher in patients than in controls (0.34 [0.02 to 4.66] mg/dL, P < 0.0001). Differences between CRP and lipid values were comparable after dividing patients and controls by sex. Figure 1 shows the distribution of CRP concentrations in controls, in patients as a whole, and in the 2 Hypoalpha subgroups: Patients without (no-CAD) coronary atherosclerotic disease had CRP values 3-fold higher than did controls (0.19 [0.02 to 3.41] mg/dL, P < 0.0001); patients with CAD had levels nearly 7-fold higher than did controls (0.54 [0.04 to 4.66] mg/dL, P < 0.0001) and nearly 3-fold higher than no-CAD patients (0.54 [0.04 to 4.66] versus 0.19 [0.02 to 3.41] mg/dL, P = 0.0420).

Stepwise multiple regression analysis revealed that factors influencing CRP concentrations included age (r = 0.45,
P=0.0044) and HDL-C (r=-0.39, P=0.0558), but not triglycerides (r=-0.33, P=NS), CAD condition (r=0.32, P=NS), sex (r=-0.09, P=NS), or body mass index (r=-0.07, P=NS). Furthermore, the logarithmic regression analysis (Figure 2) showed an inverse correlation between CRP and HDL-C (a) and apoAI (b) (r=0.44, P=0.0006 and r=0.45, P=0.0006, respectively).

Discussion

Several lines of evidence indicate that inflammation may play an important part in the initiation and progression of atherosclerosis. HDL molecules have an intriguing role in the development of atherosclerosis because they can either protect from or accelerate that process. The latter function may be explained by the fact that HDL can act as a proinflammatory agent, as has been shown experimentally.

Reduced concentrations of HDL may be found in a number of clinical conditions characterized or complicated by inflammatory phenomena; indeed, HDL molecules themselves are considered to be components of acute-phase response. The condition known as Hypoalpha is a genetic trait characterized by extremely low plasma levels of HDL and by increased risk of developing early, severe cardiovascular disease. Because these subjects’ HDL levels are congenitally low, this condition represents a clinical model for investigation into whether the possible association between Hypoalpha and an upregulated inflammatory state represents a major mechanism in the genesis of the severe atherosclerosis that develops in this condition. The patients recruited for the present study were carriers of congenitally low HDL levels, who did not present clinical or laboratory evidence of current inflammation.

The present study’s evidence of a greater concentration of CRP in Hypoalpha patients, compared with control subjects, in the absence of other inflammatory signs, suggests that Hypoalpha itself may be an inflammatory condition; this is further supported by the inverse relation between HDL molecules and CRP. The significantly higher CRP values in Hypoalpha subjects with angiographic evidence of CAD, compared with those without CAD, could in turn be interpreted as an index of a more severe inflammation caused by atherosclerotic damage in the vascular wall.

Conclusion

Although the limited number of subjects in this study suggests that we should proceed with the caution, the (1) higher CRP values in Hypoalpha patients, (2) inverse correlation between HDL and CRP in Hypoalpha patients, and (3) higher CRP concentration in Hypoalpha patients with CAD indicate that Hypoalpha may prove to be a useful clinical model for investigating the relationship between low HDL levels (the unique variable in Hypoalpha), inflammation, and atherosclerosis.

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