Plasma C-Reactive Protein in Subjects With Hypo/Hyperalphalipoproteinemias

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Hypoalphalipoproteinemia (Hypo-A), a lipid disorder characterized by low high-density lipoprotein (HDL)-cholesterol (HDL-C) levels, is frequently associated with an increased risk of suffering future coronary heart disease (CHD). Conversely, hyperalphalipoproteinemia (Hyper-A) is a characterized by high HDL-C concentrations and is possibly associated with longevity and protection against CHD. Whether plasma C-reactive protein (CRP) level, an emerging marker of CHD risk, may be influenced by either extremely low or high HDL-C concentrations is yet to be determined. Plasma levels of lipids and CRP have been measured in 52 middle-aged men and women, clinically free of CHD, including 20 subjects with Hypo-A, 12 with Hyper-A, and 20 healthy normolipemic age-matched controls. CRP levels were the highest in Hypo-A [0.22 mg/dL (interquartile range, 0.15 to 0.44)], the lowest in Hyper-A [0.03 mg/dL (0.02 to 0.07)], and intermediate in the control group [0.10 mg/dL (0.05 to 0.20)]. Differences in plasma CRP concentrations were significant between Hypo-A and the other 2 groups, as well as between Hyper-A and controls. Plasma CRP levels showed a particularly strong correlation with plasma HDL-C concentrations ($r = -.66$, $P < .001$). In multivariate models, HDL-C represented the only significant predictor of circulating levels of CRP. In conclusion, in subjects with Hypo-A or Hyper-A, HDL-C levels may account for plasma CRP variations independent of other potential cardiovascular risk factors.

PRIMARY HYPOALPHALIPOPROTEINEMIA (Hypo-A) is a dyslipidemia characterized by very low high-density lipoprotein-cholesterol (HDL-C) levels that may frequently result from defects either in the apolipoprotein-AI (apo-AI) genes or in the enzymes involved in the synthesis and remodeling of HDLs.[1-3] Conversely, primary hyperalphalipoproteinemia (Hyper-A) is characterized by very high HDL-C levels, which may be due to a variety of genetic factors,[4-8] one being plasma cholesteryl ester transfer protein deficiency, a frequent cause mainly among native Japanese.[9] Although subjects with very low HDL-C levels are not necessarily exposed to an increased coronary heart disease (CHD) risk[1,10] and very high HDL-C levels do not always protect against atherosclerosis,[4] a very large amount of evidence from epidemiologic studies established that HDL-C levels are inversely related to risk of CHD.[11-13] Several mechanisms have been proposed to explain the HDL cardioprotective effects, including reverse cholesterol transport, inhibition of the formation and neutralization of the effects of oxidized low-density lipoprotein (LDL), and inhibition of endothelial cell adhesion molecule expression.[14-16] A recent study by Sampietro et al[17] suggested that HDL-C levels below the 10th percentile would upregulate the synthesis of C-reactive protein (CRP), a nonspecific marker of inflammation and possibly an independent risk factor for CHD.[18-22] Thus, the presence of a low-grade systemic inflammation, as documented by even slight increases in plasma CRP concentrations, might induce an increased risk of CHD in patients with Hypo-A. Indeed, the ability of HDLs produced during inflammatory conditions to remove cholesterol from cells is less efficient than that of normal HDLs.[23]

On the other hand, HDLs have been shown to bind and neutralize lipopolysaccharide, thus playing an important role in modulating both acute and chronic inflammation.[24,25] Moreover, flow cytometry analyses showed that HDL-associated apo-AI inhibits contact-mediated activation of monocytes by binding to stimulated T lymphocytes, inhibiting the production of tumor necrosis factor-α and interleukin-1β, essential components in the pathogenesis of immunoinflammatory diseases.[26] Thus, it could be hypothesized that an increased plasma HDL concentration might exert an anti-inflammatory action.

In the study presented herein, we measured plasma CRP levels in subjects with Hypo-A and Hyper-A without any present or past clinical sign of cardiovascular disease, as well as in a control group of apparently healthy age-matched subjects. Our specific objective was to define whether decreases or increases in HDL-C levels might be associated with significant variations in plasma CRP levels, independent of the influence of other major cardiovascular risk factors.

MATERIALS AND METHODS

Subjects

The demonstration of either plasma HDL-C levels $<$ 5th percentile ($<$ 25 mg/dL in men and $<$ 30 mg/dL in women) or $>$ 95th percentile ($>$ 80 mg/dL in men and $>$ 90 mg/dL in women) in the Italian population on at least 3 consecutive measurements was fulfilled to make a diagnosis of Hypo-A in 20 subjects and Hyper-A in 12 subjects, all without history of cardiovascular events. Absence of secondary causes of plasma HDL-C level deficiency was documented in 12 Hypo-A subjects, which met all the criteria for diagnosis of primary Hypo-A; the remaining 8 Hypo-A subjects having plasma triglyceride concentration above 200 mg/dL did not fulfill criteria for the diagnosis for primary Hypo-A. Absence of secondary causes of plasma HDL-C level excess was documented in 20 Hyper-A subjects. At study entry,

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Table 1. Clinical Characteristics and Blood Measurements of Patients and Control Study Participants

	Hypo-A (n = 20)	Hyper-A (n = 12)	Controls (n = 20)
Age (yr)	50 ± 9	52 ± 9	49 ± 10
BMI (kg/m^2)	26.9 ± 2.4*	24.0 ± 2.3	26.5 ± 2.4*
Total cholesterol (mg/dL)	214 ± 35*	253 ± 29	207 ± 37*
Triglycerides (mg/dL)	261 ± 124*†	95 ± 35	151 ± 84*
HDL-C (mg/dL)	26.9 ± 2.8*†	95 ± 17	48 ± 13*
LDL-C (mg/dL)	120 ± 42	127 ± 32	129 ± 27
Apo-AI (mg/dL)	110 ± 9*†	205 ± 18	147 ± 22*
Apo-B (mg/dL)	139 ± 19*†	117 ± 17	108 ± 23
CRP (mg/dL) (25% to 75%)	0.22 (0.15–0.44)*†	0.03 (0.02–0.07)	0.10 (0.05–0.20)*

NOTE. Values are mean ± SD except for plasma CRP levels expressed as median and interquartile range. Differences between groups: *$P <$ .05 *v* Hyper-A, †$P <$ .05 *v* controls.

we excluded subjects with additional conditions that might alter plasma HDL cholesterol or CRP levels including cardiovascular disease, diabetes, hypertension, obesity (body mass index [BMI] $\geq$ 30 kg/m^2), renal, liver, or thyroid diseases, and infections up to 3 months before the study entry. None of the subjects were smokers or taking hormone replacement therapy, androgenic steroids, statins, aspirin, β-blockers, or other drugs potentially affecting either plasma HDL or CRP concentrations. No clinical signs, symptoms, or laboratory evidence of inflammation were present at all times of the study. Twenty sex- and age-matched subjects were also recruited in the study as controls. Information about alcohol consumption among participants was obtained by asking whether they drank alcohol and, if so, how many glasses of various types of alcoholic beverages they consumed a week. There were 16 nondrinkers among Hypo-A subjects (80%), 10 among Hyper-A subjects (83%), and 15 among controls (75%). The remaining 4 Hypo-A subjects, 2 Hyper-A subjects, and 5 controls all drank less than 2 oz/wk, 1 oz of alcohol being the equivalent of approximately 2 to 2.5 standard drinks, with a drink being defined as 12 oz of beer, 4 to 5 oz of wine, or 1.25 oz of 80 proof spirits. Thus, at the beginning of the study, Hypo-A subjects, Hyper-A subjects, and controls were matched for alcohol consumption. All subjects gave their informed consent, and the local ethics committee approved the study protocol.

Procedures

Total cholesterol, triglycerides, and HDL-C were determined by enzymatic-colorimetric methods (Dimension Autoanalyzer; DADE, Newark, NJ); LDL-C was calculated by the Friedewald equation.[27] Apo-AI and apo-B were determined by nephelometry (Beckman BN 100; DADE- Behring, Milano, Italy). Plasma CRP levels were measured using the Latex-Enhanced CRP assay (Dade-Behring High Sensitivity CRP Assay, Marburg, Germany) on the same nephelometer. Subanalysis of repeated measures indicated that the interassay coefficient of variation for plasma apo-AI and apo-B levels was 3% for both, and 2% for plasma CRP at both low and high concentrations.

Statistical Analysis

Means ± SD are given for all continuous variables. Because plasma CRP levels were not normally distributed, the values are reported as median and interquartile range. Comparisons between the 3 classes of plasma HDL-C levels were assessed by Kruskal Wallis H test with post hoc analyses. Analysis of variance (ANOVA) and post hoc analyses were used to test the differences between parametric variables in the 3 groups. Correlation analyses were performed using the Pearson and Spearman coefficients of correlation for parametric and nonparametric variables, respectively. Linear regression models were used to estimate prediction of plasma CRP levels in the entire study population by including simultaneously in the model the following variables: age, gender, BMI, total cholesterol, HDL-C, LDL-C, triglycerides, and apolipoproteins. All models were examined in both forward and backward regression, as well as for blocks, with comparable results. Plasma CRP levels were logarithmically transformed when appropriate and geometric means calculated. A value of $P < .05$ was considered significant. We used SPSS statistical package, release 8.0 (SPSS, Chicago, IL) for all statistical analyses.

RESULTS

The main characteristics of patients with either Hypo-A or Hyper-A and those of 20 healthy controls are listed in Table 1. Mean age was comparable in the 3 groups. Subjects with Hypo-A were matched with controls for BMI, which was higher than in Hyper-A. Comparisons between Hypo-A and controls showed that plasma triglycerides and apo-B concentrations were higher, whereas plasma HDL-C and apo-AI levels were lower in the former group. Subjects with Hyper-A had lower BMI and plasma triglyceride levels, as well as higher total cholesterol, HDL-C, and apo-AI concentrations compared with Hypo-A and controls. No difference in LDL-C was noted between the 3 groups. CRP levels were significantly higher in Hypo-A group [0.22 mg/dL (0.15 to 0.44)] both versus controls [0.10 mg/dL (0.05 to 0.20), $P = .008$] and versus Hyper-A subjects [0.03 mg/dL (0.02 to 0.07), $P < .001$] (Table 1 and Fig 1A). Moreover, plasma CRP concentration was lower in Hyper-A than in normolipemic controls ($P = .007$). Table 2 shows plasma triglycerides, HDL-C, and CRP levels in subjects with Hypo-A. Eight Hypo-A subjects had plasma triglyceride concentration above 200 mg/dL, thus not fulfilling criteria for primary Hypo-A; the remaining 12 Hypo-A subjects met all the criteria for diagnosis of primary Hypo-A (see also Materials and Methods). Figure 1A shows plasma CRP concentrations stratified by study group and by HDL-C concentration quintiles (Fig 1B). There was a clear gradient of plasma CRP concentration for different quintiles of HDL-C concentrations, plasma CRP levels being progressively increased for decreasing HDL-C levels (P for trend $< .001$). Logarithmic transformation and geometric mean calculation for plasma CRP levels did not materially affect the difference between study groups (data not shown). The same analysis was performed after 8 Hypo-A subjects with baseline plasma triglycerides above 200 mg/dL were excluded. Among Hypo-A subjects with plasma triglyceride below 200 mg/dL, median CRP levels and the corresponding interquartile range were 0.22 mg/dL (0.15 to 0.44),

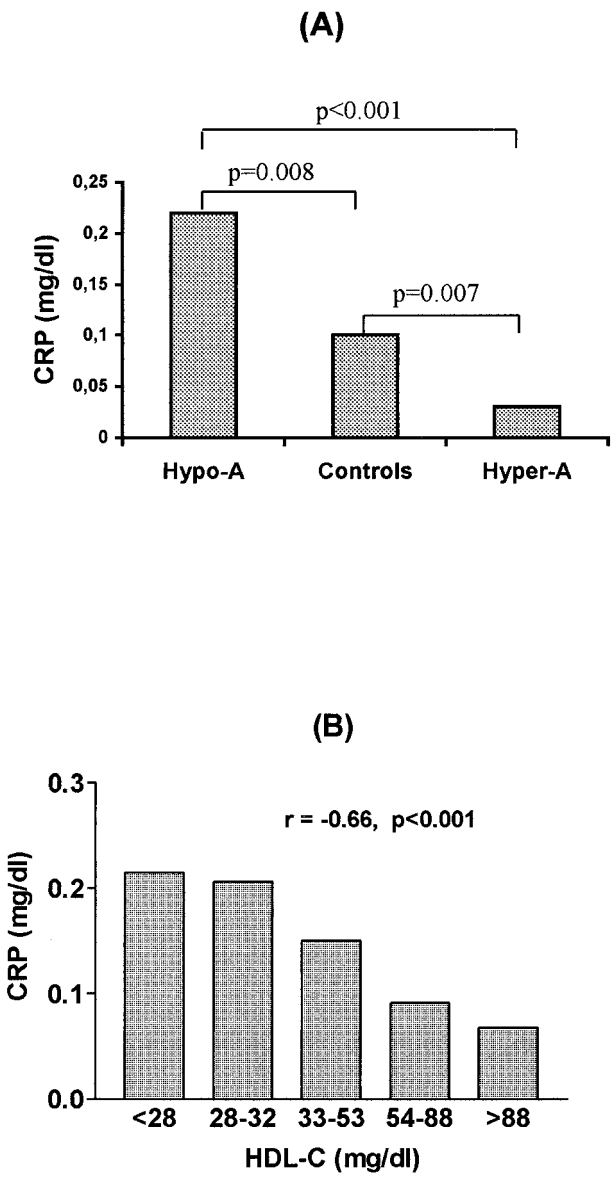

Fig 1. (A) Plasma CRP concentrations in subjects with Hypo-A, Hyper-A, and controls and (B) CRP level distribution in the entire cohort according to quintiles of plasma HDL-C levels.

which resulted still significantly higher than plasma CRP concentrations in Hyper-A and control subjects ($P < .05$ for both comparisons).

In the entire cohort, there was a statistically significant inverse correlation between CRP and HDL-C ($r = -.66$, $P < .001$) (Fig1B) and between CRP and apo-AI ($r = -.51$, $P = .001$) (Fig 2A). In addition, we found a statistically significant direct association between CRP, on one hand, and triglycerides ($r = .42$, $P = .008$) (Fig 2B) and BMI ($r = .40$, $P = .01$) (Fig 2C) on the other hand. Correlations were not influenced after log transformation of plasma CRP levels.

Using multivariate regression models, we tested the relationship between all variables considered in the study and plasma CRP concentrations. Regression analysis, both for blocks and stepwise, showed plasma HDL-C being the only independent predictor of plasma CRP concentrations even when potential confounders such as age, gender, BMI, total cholesterol, LDL-C, triglycerides, and apolipoproteins were simultaneously included in the models ($\beta = -.48$ and $-.51$, respectively, $P < .05$ for both). Inclusion of alcohol intake in the multivariate analysis did not affect results significantly. Similarly, HDL-C continued to predict plasma CRP concentrations also when Hypo-A subjects with plasma triglycerides above 200 mg/dL were excluded.

DISCUSSION

A relative large number of epidemiologic studies have found an inverse association between plasma HDL-C and CRP concentrations.[19] Although multiple changes in lipid metabolism occur during inflammation, which may lower HDL-C levels,[28] recent evidence suggests that low HDL-C levels may represent a potential inflammatory stimulus per se.[17] The objective of the present study was first to test whether subjects with HDL-C deficiency have evidence of systemic inflammation. In addition, we wanted to investigate whether plasma HDL-C excess in subjects with Hyper-A has a role in the low-grade inflammatory process regulation by reducing plasma CRP concentrations.

In the present study, we have demonstrated that apparently healthy subjects with Hypo-A (HDL-C < 5th percentile of a healthy Italian population) have plasma CRP levels more than doubled compared with normolipemic healthy controls and 7 times higher than subjects with Hyper-A (HDL-C > 95th percentile). Similar differences were found when Hypo-A subjects with high triglyceride levels (above 200 mg/dL) were excluded from the study. In addition, plasma HDL-C levels explained more than 40% of the variability of plasma CRP concentration in the whole population studied and represented

Table 2. Plasma Triglycerides, HDL-C, and CRP Levels in Subjects With Hypo-A

Subject No.	Triglycerides (mg/dL)	HDL-C (mg/dL)	CRP (mg/dL)
1	100.00	26.00	0.11
2	150.00	23.00	0.22
3	156.00	30.00	0.73
4	162.00	30.00	0.16
5	175.00	31.00	0.52
6	176.00	26.00	0.10
7	180.00	27.00	0.15
8	180.00	26.00	0.45
9	183.00	30.00	0.43
10	190.00	30.00	0.18
11	194.00	25.00	0.43
12	198.00	30.00	0.23
13	298.00	30.00	0.14
14	327.00	26.00	0.21
15	352.00	21.00	0.34
16	400.00	24.00	0.49
17	405.00	26.00	0.29
18	410.00	25.00	0.45
19	444.00	27.00	0.07
20	535.00	26.00	0.16

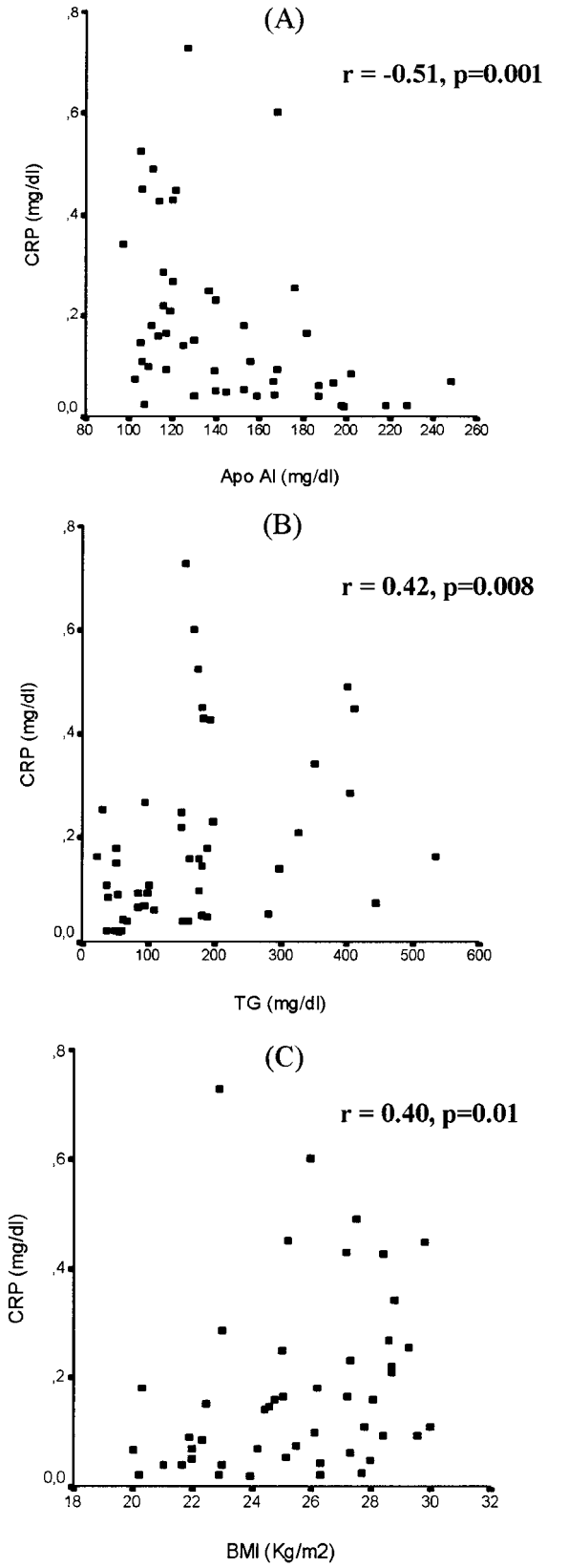

Fig 2. Nonparametric correlation coefficients between plasma CRP concentrations and (A) apo-AI, (B) triglycerides, and (C) BMI in the entire study population.

a powerful predictor of CRP levels after a consistent number of potential confounders were controlled for. Thus, our results provide further support to recent observations of a role of HDLs in the regulation of a low-grade systemic inflammatory status. Indeed, results of the present study agree with recently reported data by Sampietro et al,[17] showing increased plasma CRP levels in subjects with familial Hypo-A (HDL-C $<$ 10th percentile) compared with those in normolipidemic subjects.

Although our results in subjects with Hypo-A and those by Sampietro et al[17] may suggest a potential for low HDL-C levels to upregulate CRP synthesis, the supposed effect of HDLs to reduce plasma CRP levels would remain a hypothetical deduction according to these data. Particularly, whether considerably increased HDL-C levels may be associated with significant reduced plasma CRP levels has yet to be demonstrated.

The data reported here indicated that subjects with Hyper-A have normal CRP levels, reduced compared with Hypo-A subjects, and lower than in normolipemic healthy controls. Hence, low HDL-C levels may have a role in reducing plasma CRP levels, which in turn, appear to be decreased from an HDL-C excess in plasma. The latter supposition may be further supported by some recent findings.[26,29-31] Indeed, several potential anti-inflammatory activities have been suggested for HDLs, which might possibly suppress liver CRP synthesis. HDLs and apo-AI have been shown to inhibit the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β,[26] which have been demonstrated to modulate acute phase plasma protein synthesis in adult humans.[32] Moreover, overexpression of human apo-AI increases HDL-associated platelet-activating-factor-acetylhydrolase and paraoxonase-1 activities,[29] which have well known anti-inflammatory effects. It is also of interest that HDL may inhibit complement activation,[30] which has also been shown may result from interaction with CRP.[31]

The presence of very low plasma CRP concentration in Hyper-A subjects as compared with normolipemic healthy controls deserves more discussion, in that subjects with Hyper-A had significantly lower BMI and triglyceride levels than controls and Hypo-A subjects. It might eventually represent a bias of the present study, because adipose tissue is an important source of proinflammatory cytokines,[33,34] and triglycerides are an important positive correlate of plasma CRP in most studies.[19,35] In this sense, the lower BMI and triglyceride levels in Hyper-A than in controls and Hypo-A subjects may have had an influence on plasma CRP concentrations. However, it did not happen to a significant extent in the present study, because CRP differences between groups remained significant even after correction for BMI and triglyceride levels. Thus, the higher triglyceride concentration in subjects with Hypo-A compared with those in controls and Hyper-A subjects, as well the presence of overweight subjects among Hypo-A, may not be claimed as responsible for the different plasma CRP levels observed among HDL-C subgroups. Indeed, multivariate analysis, including also triglycerides and BMI as potential confounders, clearly shows an independent association between plasma CRP concentrations and HDL cholesterol levels. In addition, after Hypo-A subjects with triglycerides above 200 mg/dL were excluded, plasma CRP levels were still signifi-

cantly higher than in subjects with normal/high HDL-C concentrations.

In conclusion, despite the lack of direct evidence for CRP synthesis stimulation by HDLs, the present results may support, on one hand, previous findings of a possible role of Hypo-A in favoring a proinflammatory state and, on the other hand, suggest a HDL-mediated downregulation of CRP production.

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