C-Reactive Protein in Young, Apparently Healthy Men: Associations With Serum Leptin, QTc Interval, and High-Density Lipoprotein-Cholesterol

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To determine which anthropometric, biochemical, and cardiovascular variables are associated with serum levels of C-reactive protein (CRP) in young, apparently healthy men, a cross-sectional study of 179 male college students aged 18 to 22 years was performed. Multiple regression analysis was used to derive models for serum CRP concentrations in terms of the other variables measured. Although CRP was positively correlated with body mass index (BMI), percent fat mass, and serum leptin, correlations with BMI ($r = 0.15$, $P = .05$) and percent body fat ($r = 0.16$, $P = .003$) were not as strong as the correlation with leptin ($r = 0.28$, $P = .0002$). CRP was also associated with resting heart rate ($r = 0.14$, $P = .05$), heart-rate corrected QT (QTc) interval ($r = 0.22$, $P = .003$) and several components of the insulin resistance (IR) syndrome. CRP showed a strong and negative association with high-density lipoprotein (HDL)-cholesterol ($r = -0.26$, $P = .0005$) and a marginal and positive association with triglyceride ($r = 0.14$, $P = .05$). Although CRP was associated with fasting insulin ($r = 0.15$, $P = .04$), it was not related to serum adiponectin or IR index estimated using homeostasis model assessment (HOMA). MItiple regression analysis indicated that serum CRP was positively related to serum leptin ($P = .003$) and QTc interval ($P = .01$), and negatively correlated with HDL-cholesterol ($P = .01$, $R^2 = 0.15$). In young, apparently healthy men, serum leptin but not BMI was independently associated with serum CRP, suggesting that amount of body fat may be the most significant predictor of CRP. Although low-grade inflammation was associated with long QTc interval and low HDL-cholesterol, the mechanism underlying these associations is an important question to be addressed.

OBESITY is a pan-endemic health problem in both developed and developing countries. It predisposes to a host of complications including such major sources of morbidity and mortality as coronary artery disease, type 2 diabetes, and cancer. The pathogenesis of obesity-related complications remains the subject of much research. An interesting line of research is the role of obesity in the production of cytokines. Adipose tissue is now acknowledged to be a source of cytokines such as tumor necrosis factor-α and interleukin-6.[1,2] Inteleukin-6 stimulates hepatocytes to produce a variety of acute phase reactants.[3-5] Several studies have found that body mass index (BMI) is strongly associated with C-reactive protein (CRP), one such acute-phase reactant, suggesting that obesity may be a state of low-grade inflammation.[6-13]

Recently, CRP has been revealed to show a strong independent association with risk of coronary heart disease and other atherothrombotic events.[14-17] CRP levels have also been found to correlate with some features of insulin resistance (IR) symdrome.[13,17-21] Therefore, the aim of the present study was to examine whether CRP levels are driven by parameters related to the IR syndrome, including serum leptin and adiponectin, both of which have been reported to be associated with insulin resistance.[22,23] The analyses were done in apparently healthy men aged 18 to 22 years.[24]

MATERIALS AND METHODS

One hundred ninety-eight men entered Kobe University of Merchantile Marine, Kobe, Japan, in 1997. They all were Japanese and were aged 18 to 22 years. One hundred seventy-nine serum samples were available for CRP measurements and there were no significant differences between the 179 men and the remaining 11 men whose sera were not available for CRP determinations regarding the physical, biochemical, and cardiovascular variables described in Table 1 (data not shown).

Body weights and percent body fat were measured after the subjects fasted overnight and voided. This was done using an impedance fat meter (TBF-202, Tanita Corp, Tokyo, Japan). TBF-202 employs 2-foot pad electrodes with a corresponding digital scale, as previously reported.[25]

Blood pressure was measured with a standard mercury sphygmomanometer after the subjects had rested at least 10 minutes. Systolic blood pressure was recorded at the appearance of sounds and diastolic blood pressure was recorded at the disappearance of sounds (V-phase Korotkov). The measurements were repeated after 2 to 3 minutes and the average of the measurements were used in analysis.

Alcohol consumption and smoking habits were determined by an interview at the time of each participant's physical examination. Data with respect to diet and exercise were not available. Nobody received any medications.

Twelve-lead electrocardiograms were recorded at a 25 mm/s paper speed and at 10 mm/mV gain by means of an automated electrocardiogram (FCP-4266, Fukuda Denshi, Tokyo, Japan). A differential threshold technique[26] was used for determinations of QT interval and then QTc was calculated using Bazett's formula: QTc = QT/

The computer program uses successive R-R intervals between all ventricular muscle depolarization (QRS complexes) to calculate the mean heart rate within the recorded period of 10 seconds. Sinus rhythm was present in all participants and in none of the electrocardiograms were repolarization disturbances detectable.

Venous blood was sampled after an overnight fast and centrifuged at 3,000 rpm for 30 minutes at 4°C. Plasma glucose was measured by the glucose oxidase method. Insulin and leptin were assayed using commercially available kits (Pharmacia, Tokyo, Japan, and Linco Research, St Charles, MO, respectively). Cholesterol, triglyceride, HDL-cholesterol, and apolipoproteins were measured as previously reported.[25]

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Table 1. Despcriptive Data and Spearman's Correlation Coefficients (*r*) for CRP With Components of the IR Syndrome in 179 Apparently Healthy Men Aged 18 to 22 Years

	Mean	SD	Median	*r*
BMI (kg/m^2)	21.8	3.7	21.1	0.14*
Percentage body fat (%)	18.6	6.0	17.4	0.16*
Serum leptin (ng/mL)	2.3	2.9	1.4	0.28‡
Systolic BP (mm Hg)	121	13	122	0.10
Diastolic BP (mm Hg)	72	8	71	0.04
Resting heart rate (bpm)	65	10	65	0.14*
QTc duration (ms)	387	22	385	0.22†
Total cholesterol (mg/dL)	177	29	170	−0.02
LDL-cholesterol (mg/dL)	107	27	102	0.02
HDL-cholesterol (mg/dL)	57	10	56	−0.26‡
Triglyceride (mg/dL)	63	33	57	0.14*
Apolipoprotein A1 (mg/dL)	132	18	131	0.14*
Apolipoprotein B (mg/dL)	73	20	69	0.07
LDL diameter (nm)	270	5	269	0.02
Fasting glucose (mg/dL)	89	7	89	0.00
Fasting insulin (μU/mL)	8.4	3.6	8.0	0.15*
HOMA IR	1.87	0.84	1.75	0.12
HOMA β cell	6.66	3.09	6.08	0.15*
Serum adiponectin (μg/mL)	6.9	2.8	6.4	−0.08
CRP (mg/L)	0.51	1.45	0.16	—

*$P \leq .05$.

†$P < .01$.

‡$P < .001$ or less.

Abbreviations: BP, blood pressure; bpm, beats per minutes; QTc, heart-rate corrected QT; HOMA IR and β cell, insulin resistance and secretion estimated using homeostasis model assessment, respectively.

Low-density lipoprotein (LDL)-cholesterol was calculated using the formula of Friedwald et al.[27] The diameter of the major LDL fraction was determined by gradient gel electrophoresis on 2% to 16% polyacrylamide gels (Biocraft, Tokyo, Japan) according to the method of Nicolset al.[28]

IR and secretion (β cell) determined by homeostasis model assessment[29] (HOMA) were calculated using fasting plasma glucose and insulin levels in each participant. HOMA IR has been validated by comparison with results of glucose clamp studies,[29,30] intravenous glucose tolerance test,[29,31] and continuous infusion of glucose with model assessment.[31] The HOMA β-cell method has been validated by comparison with the intravenous glucose model assessment.[32] Application of HOMA has also been used in epidemiological studies.[29,33,34]

CRP and adiponectin concentrations were measured in sera stored at −70°C using a highly sensitive immunonephlometric assay[35] and an enzyme-linked immunosorbent assay (ELISA),[36] respectively. The intra-assay and interassay coefficients of variation of adiponectin were 3.3% and 7.4%, respectively, and those of CRP were less than 5%.

Statistical analysis was performed with the SAS statistical software system (SAS Institute, Cary, NC). Spearman's simple regression analysis and stepwise multiple regression analysis with backward elimination procedure were performed to discriminate variables affecting CRP. Because the distribution became normally distributed after log transformation, logarithmically transformed values of CRP (log CRP) were used. *P* values less than .05 were considered significant. Data are expressed as means ± SD unless otherwise stated.

RESULTS

Characteristics of these young men are shown in Table 1. CRP averaged 0.51 ± 1.45 mg/L with a median value of 0.16 mg/L. Spearman's rank correlation coefficients for CRP are also shown in Table 1. Although CRP was positively correlated with BMI, percentage body fat, and serum leptin, the correlation with serum leptin ($r = 0.28$) was stronger than the correlations with BMI ($r = 0.15$) and percent body fat ($r = 0.16$). CRP was also associated with resting heart rate and QTc interval, whereas it showed no association with systolic and diastolic blood pressure. HDL-cholesterol ($r = -0.26$) and apolipoprotein A1 ($r = -0.14$) showed significantly negative relationship with CRP. In contrast, triglyceride ($r = 0.14$) showed a positive correlation, and LDL-cholesterol and apolipoprotein B showed no correlation with CRP. CRP concentrations were related to fasting insulin levels ($r = 0.15$) and HOMA β-cell ($r = 0.15$) but not to HOMA IR or serum adiponectin concentrations.

Stepwise multiple regression analysis (Table 2), which included smoking status, HOMA IR, and all variables that showed significant univariate associations with CRP in Table 1, revealed that leptin, QTc duration, and HDL-cholesterol (inversely) were independently associated with log CRP and explained 15% of CRP variability. However, HOMA IR did not emerge as an independent determinant of CRP.

DISCUSSION

We have shown in the present study that CRP was independently related to serum leptin, QTc interval, and HDL-cholesterol (inversely) in young, apparently healthy men. It should be noted in the present study that the independent association of circulating CRP concentrations was found in a sample of male college students who had few confounding risk factors.

The reasons for the association between CRP and serum leptin, QTc interval, and HDL-cholesterol are not clear and it is clearly not possible, in a cross-sectional study, to attribute causality to one of a set of correlated variables, but several explanations are possible, which are not necessarily exclusive. As previously reported,[6-13] and confirmed in the present study, BMI was associated with CRP. In the present study, however, the association of CRP with leptin was stronger than that with BMI or percent body fat. Leptin is an extremely robust circulating marker of the percentage of fat mass. Thus, its correlation with CRP is biologically plausible because both leptin and cytokines, such as interleukin-6 which promotes CRP secretion from the liver, are produced by adipocytes.[1,2] Increases in serum leptin may be a consequence of low-grade inflammation.[37] This may be compatible with the recent observation by Limieux et al[38] who used hydrostatic weighing and computed tomography to make state-of-the-art assessments of body fat and found that the amount of total body fat was the best

Table 2. Stepwise Multiple Regression Analysis for Log CRP as the Dependent Variable

Independent Variable	β	SE (β)	*P* Values	Partial R^2 (%)
Serum leptin	0.086	0.029	.003	8.9
QTc duration	0.009	0.003	.014	11.8
HDL-cholesterol	−0.022	0.008	.010	14.8

NOTE. The model includes smoking status, HOMA IR, and all variables that showed significant relation to CRP in Table 1.

correlate of CRP levels in healthy middle-aged men with a wide range of BMI (21 to 41 kg/m^2).

QTc interval prolongation has been reported to be common in obesity[39] and people with an unfavorable balance between sympathetic and parasympathetic activity.[40] We have recently shown in young, apparently healthy men that fasting serum insulin concentrations are associated with QTc interval independent of serum leptin, percent body fat, and BMI,[41] suggesting that insulin-induced sympathetic activity is one of factors contributing to QTc prolongation. In the present study, however, QTc intervals were strongly associated with CRP, a sensitive marker of inflammation, independently of serum insulin and leptin concentrations, percent body fat, and BMI. These findings suggest that QTc prolongation commonly found in obesity[39] may be a result of sympathetic overactivity associated with low-grade inflammation, because inflammation has been shown to stimulate the central nervous system,[42] leading to activation of the sympathetic nervous system.

Insulin sensitivity measured by a frequently sampled intravenous glucose tolerance test was independently correlated with CRP in the Insulin Resistance and Atherosclerosis Study,[43] which included participants with a broad range of insulin sensitivity and diabetes status. However, in the present study performed in young healthy men, CRP was not associated with insulin sensitivity estimated using HOMA IR, which showed a surprisingly good correlation with insulin sensitivity measured using the hyperinsulinemic euglycemic clamp technique,[44] the gold standard in the measurement of insulin sensitivity. It is unlikely, therefore, that the discrepancy between the 2 studies is due to the difference in the measurement in insulin sensitivity. The striking difference between the 2 studies is in BMI and CRP levels in addition to their age. BMI averaged 21.8 and 28.4 kg/m^2 and CRP averaged 0.50 $\pm$ 1.45 and 3.53 $\pm$ 0.18 mg/L, respectively, in the present study and in the Insulin Resistance Atherosclerosis Study.[43] Recently, CRP concentrations have been reported to be associated with total fat mass,[38] as described earlier. This association was independent of insulin levels assessed over times during a 75-g oral glucose load (a crude marker of IR in nondiabetic subjects). In addition, there was no association between CRP and adiponectin, an insulin-sensitizing adipocytokine, replenishment of which has been reported to increase insulin sensitivity in different models of IR in vivo.[45,46] Therefore we believe that low-grade inflammation may be associated primarily with body fat, and then modified by IR, although the fact that the participants were all healthy and had a narrow range of CRP and HOMA-IR might make it impossible to associates CRP with abnormalities of IR in the present study.

Associations between CRP levels and lipoprotein profile have been observed in children and adults.[7,9,12,13,19,21] These associations between CRP and triglyceride and HDL-cholesterol have been reported to persist after adjustment for BMI.[7,13,19] However, in the report focusing on a detailed analysis of body composition using state-of-the-art assessments of body fat,[38] CRP levels were not associated with variables of the lipoprotein-lipid profile in middle-aged men with atherogenic dyslipidemia associated with the metabolic syndrome. We have previously shown that serum HDL-cholesterol concentrations are associated with triglyceride-rich lipoprotein metabolism and body fat in young healthy men.[25] Therefore, an inverse and independent association between HDL-cholesterol and CRP found in the present study suggests that low HDL-cholesterol may be related to chronic low-grade inflammation, as well as subtle abnormalities in triglyceride-rich lipoprotein metabolism[25] in young healthy men. Low HDL-cholesterol in low-grade inflammation in the present study may be compatible with the recent observation[47] that human secretory phospholipase A2, an acute-phase protein, decreased HDL-cholesterol in response to inflammation.

Several limitations of this study deserve mention. First, because the study is cross-sectional, the directionality of associations cannot be conclusively established. Second, study results might be a chance or bias and could be explained by possible confounders that were not included. Third, we used a single CRP measurement that may not accurately reflect long-term inflammation status. However, because random misclassification due to biological variability will lead to underestimation of true associations, this limitation is unlikely to explain our findings.

In conclusion, in young, apparently healthy men, we found significant relationships between CRP concentrations and serum leptin, QTc interval, and HDL-cholesterol (inversely). However, there was not a relationship with BMI and other components of IR, possibly due to the healthy status of the participants.

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