Obesity Is an Important Determinant of Baseline Serum C-Reactive Protein Concentration in Monozygotic Twins, Independent of Genetic Influences

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Background—C-reactive protein (CRP) values predict atherothrombotic cardiovascular disease and type 2 diabetes mellitus. Associations between CRP and obesity, predominantly assessed anthropometrically, may partly explain these observations. Previous studies have been unable to control for genetic influences on CRP and obesity. The aim of this study was to examine the relationship between CRP and accurately measured body fat, lipids, apolipoproteins, blood pressure, and environmental and behavioral factors, independent of genetic influences.

Methods and Results—One hundred ninety-four healthy female twins (age 57.2±7 years) were studied after excluding pairs with CRP values >10 mg/L. Total body fat and central abdominal fat (CAF) were measured by dual-energy x-ray absorptiometry. CRP concentration was strongly related to surrogate and direct measures of body fat (r=0.31 to 0.54, P<0.001), diastolic blood pressure (r=0.20, P=0.003), and lipid and apolipoprotein levels (r=0.21 to 0.51, P<0.008). Light-to-moderate alcohol consumers and nonusers of hormone replacement therapy (HRT) had lower CRP levels than abstainers and HRT users, respectively. In stepwise multiple regression analysis, CAF, triglycerides, apolipoprotein B, and HRT use explained 46% of the variance in circulating CRP. In analyses controlling for genetic influences in monozygotic twins, within-pair differences in CRP were associated with within-pair differences in total body fat (r=0.39, P<0.001), CAF (r=0.34, P=0.002), diastolic blood pressure (r=0.24, P=0.03), apolipoprotein Al (r=−0.33, P=0.01), HDL cholesterol (r=−0.42, P=0.001), and triglycerides (r=0.35, P=0.007).

Conclusions—CRP was strongly related to total and central abdominal obesity, blood pressure, and lipid levels, independent of genetic influences. These relationships are likely to contribute significantly to prospective associations between CRP and type 2 diabetes and coronary events. (Circulation. 2004;109:3022-3028.)

Key Words: obesity ▪ inflammation ▪ syndrome X ▪ lipids

Low-grade inflammation plays an important role in the formation and progression of atherosclerotic plaques.1–3 Prospective studies have demonstrated associations between circulating levels of acute-phase proteins, such as C-reactive protein (CRP), and coronary events in healthy adult populations and patients with acute coronary syndromes and established macrovascular disease.4,5 CRP values have also been associated with the development of type 2 diabetes mellitus.5–7 Although the physiological mechanisms linking elevated CRP to these disorders are not known, it is possible that their association is partly mediated by adipose tissue, an important source of circulating inflammatory cytokines. CRP is synthesized in the liver under the control of interleukin-6 and other proinflammatory cytokines.2,3 Approximately 25% of basal circulating interleukin-6 originates in human adipose tissue,4 with production in intra-abdominal fat 3 times that of subcutaneous fat.9 CRP mRNA has also recently been demonstrated in human subcutaneous abdominal adipose tissue,10 suggesting that adipose tissue itself may contribute to basal plasma CRP levels. Furthermore, strong associations between CRP and obesity markers have been found in epidemiological studies, albeit predominantly estimated by anthropometric surrogates.11–19 Few studies have examined the relationship between CRP levels and direct
measures of body fat, and no study has used dual-energy x-ray absorptiometry (DXA) to investigate associations between CRP and central abdominal fat (CAF), the core component of the metabolic syndrome and a strong predictor of insulin resistance and atherosclerotic cardiovascular disease.20,21

Because genetic factors account for approximately 40% to 50%22–24 and 60%25 of the population variance in circulating CRP and body fat, respectively, it is possible that genetic influences explain associations between CRP levels and obesity. Indeed, several polymorphisms in the CRP gene that may influence CRP production have been described.26–28 Although a twin study reported a within-pair correlation coefficient for CRP of 0.40 in monozygotic (MZ) twins, formal heritability estimates could not be calculated because dizygotic (DZ) twins were not included.29 Our own study in MZ and DZ twins showed significant heritability of baseline CRP values, even after adjustment for body mass index (BMI).24 A major advantage of studying twins is the ability to control for potential confounding genetic factors. Because MZ twins are genetically identical, any differences between same-pair MZ twins must be attributable to environmental factors for which the twin pair is discordant. To our knowledge, no previous study has simultaneously examined the relationship between circulating CRP and blood pressure, lipids, apolipoproteins, and body fat distribution, independent of potential genetic confounding. In this study of healthy female twins, we (1) examined relationships between CRP and metabolic syndrome phenotypes, including central obesity, lipids, and blood pressure; (2) investigated the influence of environmental and behavioral factors (smoking, alcohol consumption, physical activity, and hormone replacement therapy [HRT]) on circulating CRP; and (3) additionally examined relationships between CRP and these metabolic syndrome parameters, independent of genetic influences, by studying MZ twins.

Methods

Study Cohort and Lifestyle Variables

The study cohort comprised 210 healthy white female twins, recruited through St Thomas’ UK Adult Twin Registry (TwinReg) via a media campaign as previously reported.24 Because the 99th centile of the CRP distribution in thoroughly screened healthy subjects is 10 mg/L,30 8 twins whose CRP values were >10 mg/L and their co-twins were excluded to limit analyses to subjects without infection or inflammatory disease. A total of 194 twins were studied (83 MZ and 14 DZ pairs). No subject reported a history of coronary disease or diabetes. Zygosity was ascertained by questionnaire and confirmed (if necessary) by multiplex DNA fingerprinting (PE, Applied Biosystems). Subjects provided written informed consent. Research and ethics committees at St Thomas’ Hospital, UK, and St Vincent’s Hospital, Australia, approved the study. Use of HRT, smoking history, alcohol consumption, and participation in leisure-time physical activity were ascertained by nurse-administered standardized questionnaires.

Metabolic and Body Composition Measures

Blood pressure was measured in the supine position using an automated cuff sphygmomanometer after a 10-minute rest. BMI (kg/m²) and waist-to-hip ratio (WHR) were calculated. DXA (Hologic QDR-2000) was used to measure total body fat (TBF) and CAF as previously described.25,31,32

Biochemical Measurements

CRP was measured by a highly sensitive automated microparticle capture enzyme immunoassay, standardized on the World Health Organization International Reference Standard for CRP immunoassay 85/506.3 as previously reported.34 Apolipoproteins were assayed using an immunoturbidimetric method (n=126). Total cholesterol, triglyceride, and HDL cholesterol were measured by a colorimetric enzymatic kit (n=132). The Friedewald equation was used to calculate LDL cholesterol in subjects with triglycerides ≤4.5 mmol/L.

Statistical Methods

Data are mean±SD or median (interquartile range). When analyzing the relationship between categorical variables and CRP levels, mean (95% CI) is presented. CRP and triglycerides were loge-transformed for analysis and back-transformed for presentation because of skewed distribution. Simple and forward stepwise multiple regression analyses were used to determine relationships between loge-CRP and metabolic and body fat measures. ANOVA was used to analyze the effect of categorical variables on CRP. Because of the phenotypic correlation between same-pair twins, standard statistical techniques may underestimate standard errors and overestimate significance. Therefore, the generalized estimating equation was used to correct for within-pair phenotypic correlations in analyses including both twins of a pair. Statistical significance was set as P<0.05. Data were analyzed using Statview 5 (SAS Institute Inc) and Stata Statistical Software, release 7.0 (StataCorp).

A major advantage of studying MZ twins is the ability to examine relationships independent of genetic influences. These analyses were performed for variables significantly associated with CRP in univariate analysis using previously published methods.31,35 First, to assess whether associations found in univariate analyses were significant after accounting for genetic effects, we examined relationships between within-pair differences in loge-CRP and within-pair differences in body fat, blood pressure, and lipid and apolipoprotein levels. Second, in MZ twin pairs discordant for these factors (defined as a within-pair difference greater or equal to the median), we compared CRP levels in twins with the higher adiposity or metabolic parameters to twins with the lower levels using paired t tests. Because MZ twins have 100% genetic concordance, any difference between same-pair twins must be attributable to nongenetic factors for which the twin pair is discordant.

Results

Cohort Characteristics

Mean age was 57.2±7 years (range, 40.1 to 70.7); 91% of subjects were postmenopausal. HRT was used by 22 subjects for a mean of 2.6 years. Thirty-one subjects (16%) were current smokers; 53 (27%) were former smokers. The numbers of abstainers, social drinkers, and consumers of 1 to 5, 6 to 10, and >10 U of alcohol per week were 19, 47, 59, 32, and 18, respectively (19 unrecorded; 1 U=8 g of alcohol). Ninety-one subjects (47%) participated in leisure-time physical activity. Mean adiposity and metabolic measures are summarized in Table 1.

Univariate Associations

CRP values were not significantly related to age (r=0.1, P=0.28). In univariate analysis, CRP concentration was strongly related to all adiposity measures (Table 2). CRP values were directly related to diastolic blood pressure, apolipoprotein B, total and LDL cholesterol, and triglyceride levels and inversely to apolipoprotein A1 and HDL cholesterol levels (Table 2).
TABLE 1. Adiposity and Metabolic Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, m</td>
<td>-0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBF, kg</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% TBF</td>
<td>0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAF, kg</td>
<td>0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>0.02</td>
<td>0.69</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.16</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.20</td>
<td>0.003</td>
</tr>
<tr>
<td>Apolipoprotein AI, g/L</td>
<td>-0.21</td>
<td>0.007</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dL</td>
<td>-0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.31</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>0.33</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>-0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD or median (interquartile range).

Lifestyle Factors

Compared with alcohol abstainers (CRP, 1.6 [0.9 to 2.8] mg/L), CRP levels were lower in social drinkers (0.5 [0.3 to 0.7] mg/L, P=0.004) and consumers of 1 to 5 U/week (0.8 [0.6 to 1.2] mg/L, P=0.049) and 6 to 10 U/week (0.6 [0.4 to 1.0] mg/L, P=0.06). Because we have previously shown that alcohol consumption is associated with lower adiposity measures, TBF and CAF were included as covariates; however, differences between alcohol consumption categories persisted. Subjects drinking >10 U/week had similar CRP levels to abstainers (1.4 [0.8 to 2.4] mg/L, P=0.89).

CRP levels were similar in smokers and nonsmokers (0.6 [0.4 to 1.0] versus 0.8 [0.6 to 1.0] mg/L, P=0.68) and were unrelated to pack-year history among smokers (P=0.25). There was no difference in CRP between never smokers and former smokers (P=0.62). HRT users had higher levels of CRP than nonusers (1.1 [0.6 to 2.0] versus 0.7 [0.6 to 0.9] mg/L, P=0.02). Physically active subjects tended to have lower CRP values than nonactive subjects, although the difference was not statistically significant (0.6 [0.5 to 0.8] versus 0.9 [0.7 to 1.1] mg/L, P=0.06).

Stepwise Multiple Regression

In stepwise multiple regression analysis (n=116 twins), 46% of the variance in loge-CRP concentration was explained by CAF (β=0.41, P<0.001), loge triglycerides (β=0.17, P=0.03), apolipoprotein B (β=0.30, P<0.001), and HRT use (β=0.29, P<0.001). Variables entered but not retained in this model were total, LDL, and HDL cholesterol, apolipoprotein AI, diastolic blood pressure, physical activity, and alcohol consumption.

MZ Twin Analysis

In analyses controlling for genetic influences on CRP and metabolic variables in MZ twins, within-pair differences in loge-CRP were significantly related to within-pair differences in weight (r=0.42, P<0.001), BMI (r=0.46, P<0.001), waist circumference (r=0.43, P<0.001), hip circumference (r=0.33, P=0.002), WHR (r=0.28, P=0.01), TBF (r=0.39, P<0.001), percent TBF (r=0.27, P=0.02), and CAF (r=0.34, P=0.002) (Figure). Relationships were also found between within-pair differences in loge-CRP and within-pair differences in diastolic blood pressure (r=0.24, P=0.03), apolipoprotein AI (r=0.33, P=0.01), HDL cholesterol (r=0.42, P=0.001), and loge triglycerides (r=0.35, P=0.007). Relationships with within-pair differences in apolipoprotein B (r=0.22, P=0.11), total cholesterol (r=0.08, P=0.57), and LDL cholesterol (r=0.13, P=0.35) were not significant.

We also examined CRP concentrations in MZ twin pairs discordant for body fat, blood pressure, lipid, or apolipoprotein levels. Compared with twins with the lower adiposity measures, twins with the higher waist circumference, hip circumference, weight, BMI, TBF, and CAF had significantly higher CRP values than their co-twins (Table 3). Similarly, twins with higher triglyceride and lower HDL cholesterol levels had significantly higher CRP values than their co-twins (Table 3). Because MZ twins have 100% genetic concordance, this implies that associations between CRP levels and these adiposity and lipid parameters are independent of genetic influences. Within each MZ twin pair, twins with the higher WHR, apolipoprotein AI levels, and diastolic blood pressures had similar CRP concentrations to twins with lower levels of these variables (Table 3), demonstrating no relationship after controlling for genetic influences.
Discussion

Atherosclerosis and atherothrombosis are inflammatory conditions, and many studies have demonstrated an association between systemic markers of low-grade inflammation, especially CRP, and future cardiovascular events. However, as recently reviewed, the triggers for the very low-grade acute-phase response of CRP that predict such events in the general population are not known. It is not even clear that marginally increased CRP concentrations reflect inflammation rather than metabolic differences. There is also speculation whether CRP is only a marker or may itself actively contribute to atherothrombosis.

Our main findings were the following: (1) CRP was strongly related to all anthropometric and direct measures of total and central abdominal obesity, diastolic blood pressure, and apolipoprotein and lipid levels; (2) light-to-moderate alcohol consumers had lower CRP levels than abstainers, independent of body fatness; (3) HRT users had higher CRP levels than nonusers; (4) 46% of the variance in CRP was explained by CAF, elevated triglyceride and apolipoprotein B levels, and HRT use; and (5) relationships between CRP and direct and surrogate measures of obesity, HDL cholesterol, and triglycerides remained statistically significant after controlling for genetic influences in MZ twins.

The observation that CRP levels were strongly and independently related to directly measured total and central obesity in our study is consistent with the finding that adipocytes secrete interleukin-6, the main stimulus for CRP biosynthesis, and the recent demonstration that human subcutaneous adipose tissue expresses CRP mRNA. Our findings confirm the few reports demonstrating significant associations between CRP and DXA-measured total adiposity. They are also consistent with studies measuring abdominal fat by computed tomography, albeit using single-slice scanning, which, as we have reported, has its limitations. Although a relationship has previously been found between CRP and DXA-measured trunk fat, the current study is the first to demonstrate a significant association with DXA-measured central fat, a core component of the metabolic syndrome and a stronger predictor of insulin resistance than trunk, limb, or total fat. Our study extends previous reports by demonstrating, in MZ twins, that associations between CRP and adiposity measures persisted after controlling for potentially confounding genetic influences.

### TABLE 3. CRP Levels in MZ Twin Pairs Discordant for Adiposity or Metabolic Variables

<table>
<thead>
<tr>
<th>Variable (No. Discordant Pairs)</th>
<th>Twins With Higher Adiposity or Metabolic Variables (CRP Levels, mg/L)</th>
<th>Twins With Lower Adiposity or Metabolic Variables (CRP Levels, mg/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (46)</td>
<td>1.3 (0.9, 1.9)</td>
<td>0.6 (0.5, 0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip circumference (48)</td>
<td>1.4 (1.0, 1.9)</td>
<td>0.7 (0.5, 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR (43)</td>
<td>0.9 (0.6, 1.3)</td>
<td>0.7 (0.5, 0.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (41)</td>
<td>1.5 (1.0, 2.2)</td>
<td>0.7 (0.5, 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (41)</td>
<td>1.5 (1.1, 2.2)</td>
<td>0.6 (0.4, 0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBF (42)</td>
<td>1.4 (0.9, 2.0)</td>
<td>0.7 (0.5, 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% TBF (41)</td>
<td>1.0 (0.7, 1.5)</td>
<td>0.6 (0.4, 0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>CAF (42)</td>
<td>1.3 (0.9, 1.8)</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic blood pressure (41)</td>
<td>0.9 (0.6, 1.3)</td>
<td>0.6 (0.4, 0.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Apolipoprotein Al (29)</td>
<td>1.0 (0.6, 1.6)</td>
<td>1.3 (0.9, 2.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>HDL cholesterol (31)</td>
<td>0.7 (0.5, 1.2)</td>
<td>1.3 (0.9, 2.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides (30)</td>
<td>1.4 (0.9, 2.3)</td>
<td>0.7 (0.4, 1.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean (95% CI).
The strong and independent relationship between CRP and obesity may explain the observation that weight loss induced by caloric restriction may reduce CRP levels in studies of obese subjects. Although reductions in CRP levels were strongly correlated with the amount of weight or fat mass lost in some studies, others suggest that weight-induced decreases in CRP may be dependent on baseline insulin sensitivity. The CRP-obesity correlation in our study may also explain reports that adjustment for adiposity measures attenuated associations between CRP and metabolic syndrome parameters and incident type 2 diabetes mellitus.

Consistent with most, but not all, studies, we found strong relationships between CRP and total, LDL, and HDL cholesterol and triglyceride levels, and triglycerides, and HDL cholesterol and triglycerides, key components of the metabolic syndrome, showed the strongest relationships with CRP in univariate analysis, and the latter remained significant in multiple regression. Furthermore, after controlling for genetic influences in MZ twins, higher triglyceride and lower HDL cholesterol levels were significantly associated with higher CRP levels.

Few studies have examined the relationship between CRP and apolipoproteins, and none independent of genetic influences. Our results confirm previous reports demonstrating direct relationships with apolipoprotein B and inverse relationships with apolipoprotein AI, although the evidence is inconsistent. In the current study, the relationship with apolipoprotein B remained significant in multiple regression after controlling for the effect of body fat, triglycerides, and HRT use. However, neither apolipoprotein was consistently associated with CRP after controlling for genetic factors.

The observation that HRT users had higher CRP levels than nonusers supports results from epidemiological and randomized controlled studies that oral (but not transdermal) HRT, particularly estrogen, increases CRP levels. Although the route of HRT administration was not known in this study, our previous examination of other cohorts of postmenopausal twins suggests that most used oral preparations. Consistent with previous reports, HRT use remained a significant determinant of increased CRP levels in multiple regression analysis, even after accounting for adiposity. This may be relevant to recent reports of increased cardiovascular risk with HRT therapy, if, in fact, CRP contributes to atherothrombosis.

All categories of alcohol consumption, excepting >10 U/week, were associated with lower CRP levels than abstinence, suggesting a U-shaped relationship. This finding supports previous epidemiological studies. To our knowledge, only one small randomized study has examined the effect of alcohol on CRP levels, demonstrating a 35% reduction after 3 weeks, although only significant in women. In contrast to our recent report that increased insulin sensitivity in moderate alcohol consumers was partly mediated by lower central fat, the association between light-to-moderate alcohol consumption and lower CRP levels in the current study persisted after controlling for adiposity. Because CRP is a known predictor of cardiovascular risk, these observations raise the possibility that the reported cardioprotection associated with moderate alcohol consumption may be partly mediated through alcohol-induced downregulation of coronary artery inflammation, perhaps by reducing hepatic CRP production.

The strengths of our study include the simultaneous examination of multiple CRP determinants in a single model, a large cohort of predominantly normal-weight female twins; the direct measurement of total and central obesity by DXA; the use of a highly sensitive assay to measure CRP; and, by specifically studying MZ twins, the examination of these relationships independent of genetic influences. Limitations include its cross-sectional design and the self-report of lifestyle factors. Because our cohort comprised predominantly healthy postmenopausal white women, our results may not be extrapolated to premenopausal or nonwhite women, men, or patients with type 2 diabetes mellitus or coronary artery disease.

In conclusion, in a large cohort of female twins, using direct measures of adiposity, we demonstrated strong relationships between circulating CRP concentrations and adiposity measures, lipid levels, and lifestyle factors. The novelty of the study relates to our ability to examine relationships independent of genetic influences in MZ twins. Our data highlight the importance of adiposity in determining circulating CRP levels and raise the possibility that part of the relationship between circulating CRP and incident type 2 diabetes mellitus, and even cardiovascular disease, may be attributable to the strong association between CRP and obesity.

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References


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