C-Reactive Protein in Healthy Subjects: Associations With Obesity, Insulin Resistance, and Endothelial Dysfunction

A Potential Role for Cytokines Originating From Adipose Tissue?

John S. Yudkin, C.D.A. Stehouwer, J.J. Emeis, S.W. Coppack

Abstract—C-reactive protein, a hepatic acute phase protein largely regulated by circulating levels of interleukin-6, predicts coronary heart disease incidence in healthy subjects. We have shown that subcutaneous adipose tissue secretes interleukin-6 in vivo. In this study we have sought associations of levels of C-reactive protein and interleukin-6 with measures of obesity and of chronic infection as their putative determinants. We have also related levels of C-reactive protein and interleukin-6 to markers of the insulin resistance syndrome and of endothelial dysfunction. We performed a cross-sectional study in 107 non-diabetic subjects: (1) Levels of C-reactive protein, and concentrations of the proinflammatory cytokines interleukin-6 and tumor necrosis factor-α, were related to all measures of obesity, but titers of antibodies to Helicobacter pylori were only weakly and those of Chlamydia pneumoniae and cytomegalovirus were not significantly correlated with levels of these molecules. Levels of C-reactive protein were significantly related to those of interleukin-6 (r=0.37, P<0.0005) and tumor necrosis factor-α (r=0.46, P<0.0001). (2) Concentrations of C-reactive protein were related to insulin resistance as calculated from the homeostasis model assessment model, blood pressure, HDL, and triglyceride, and to markers of endothelial dysfunction (plasma levels of von Willebrand factor, tissue plasminogen activator, and cellular fibronectin). A mean standard deviation score of levels of acute phase markers correlated closely with a similar score of insulin resistance syndrome variables (r=0.59, P<0.00005), this relationship being weakened only marginally by removing measures of obesity from the insulin resistance score (r=0.53, P<0.00005). These data suggest that adipose tissue is an important determinant of a low level, chronic inflammatory state as reflected by levels of interleukin-6, tumor necrosis factor-α, and C-reactive protein, and that infection with H pylori, C pneumoniae, and cytomegalovirus is not. Moreover, our data support the concept that such a low-level, chronic inflammatory state may induce insulin resistance and endothelial dysfunction and thus link the latter phenomena with obesity and cardiovascular disease. (Arterioscler Thromb Vasc Biol. 1999;19:972-978.)

Key Words: C-reactive protein ▪ insulin resistance ▪ obesity ▪ endothelial dysfunction ▪ interleukin-6

Inflammatory processes have important roles in the etiology of coronary heart disease (CHD),1,2 but the mechanisms underlying this relationship are poorly understood. Several studies have shown that elevated plasma levels of fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6) are associated with the risk of CHD and the severity of atherosclerosis.3–6 Whether these molecules play a causative role, or simply act as markers of the acute phase reaction, is debatable. Elevated IL-6 levels have been reported in patients with unstable angina where inflammatory processes may facilitate the transition from the clinically stable to unstable atherosclerotic plaques.6 However, it has also been shown that CRP levels are associated with CHD in healthy subjects, both in a cross-sectional study in general practice,7 and longitudinally in the US Physicians Health Study,8 the MONICA-Augsburg Cohort Study,9 and the MRFIT Study,10 where CRP levels predicted cardiovascular events or CHD mortality during a follow-up of between 2 and 17 years. These observations imply that atheroma progression, as well as plaque rupture, may be predicted by raised CRP levels. It has nevertheless remained an issue of debate as to whether the relationship between CRP and cardiovascular disease reflects inflammation in the vascular wall, perhaps because of chronic infections such as Chlamydia pneumonia,11 or inflammation originating in a more remote site, with secondary effects on the vascular wall through cytokines and other mediators.

The synthesis of CRP by the liver is largely regulated by IL-6.12 Although the activated leukocyte is widely assumed to be the major source of circulating IL-6, with additional contributions from fibroblasts and endothelial cells,12 novel
observations from our laboratory have proposed a previously unsuspected source for this cytokine. Using the technique of arteriovenous difference measures across a subcutaneous adipose tissue bed and radio-xenon measures of adipose tissue blood flow, we have demonstrated IL-6 production by human subcutaneous adipose tissue in vivo. The production of IL-6, as well as systemic concentrations, increase with adiposity, and we have estimated that \( \approx 30\% \) of total circulatory concentrations of IL-6 originate from adipose tissue in healthy subjects. Both IL-6 and tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)) are expressed in adipose tissue and by adipocytes has been reported. Among the known effects of these cytokines are inhibition of insulin signaling and induction of both hypertriglyceridemia and endothelial activation.

These observations have led us to explore the links of levels of acute phase markers and concentrations of proinflammatory cytokines with two of their proposed determinants, ie, obesity and chronic infection with 3 organisms suspected of being a source of chronic low-level inflammatory state. We have also explored relationships of acute phase markers with features of the insulin resistance syndrome and of markers of endothelial dysfunction, ie, with the proposed consequences of a chronic low-level inflammatory state.

We hypothesized that: (1) If adipose tissue were responsible for production of proinflammatory cytokines, then circulating concentrations of C-reactive protein and of proinflammatory cytokines would be related to measures of obesity; (2) If IL-6 were responsible for the metabolic and vascular consequences of obesity, then measures of IL-6 and of CRP would relate to insulin resistance syndrome and endothelial markers, independently of measures of adiposity.

We have explored these relationships in a population of 107 healthy subjects in whom a large number of measures had been assessed, recognizing that this size of study, and its cross-sectional design, must, by its nature be hypothesis generating. We have explored associations both between individual measures of obesity, insulin resistance syndrome, endothelial and acute phase activation, as well as between predefined groups of these variables.

Methods

Subjects

We studied 107 white nondiabetic subjects as a follow-up investigation of cardiovascular risk factors. In summary, we originally investigated subjects aged 40 to 75 randomly selected from the age-sex register of a north London general practice, and 36 (SD5) months later restudied 125 of those with normal glucose tolerance. For some of the analyses, including those shown in Table 2, the age distribution was stratified by 5-year age bands.

For some analyses we also derived an obesity score as a mean standard deviation scores of insulin resistance variables, endothelial markers, and the insulin resistance syndrome, and endothelial activation, another approach has also been used. To explore the association between predefined clusters of variables, we created mean standard deviation scores for insulin resistance variables, endothelial markers, and acute phase markers for each subject. This approach was taken to reduce the influences of biological variability of each measure, which would make the usual multivariate approach less suitable, as well as to reduce the number of associations explored. We also preferred this approach to a formal factor analysis, as we were interested in possible etiological relationships between three pre defined, and ostensibly distinct, groups of variables. For each subject, each variable was expressed as standard deviations from the population mean, if necessary after logarithmic transformation, where a value that ranged from \( -2.5 \) to \( 2.5 \). The mean scores were calculated as the mean of these standard deviation scores as follows: (1) Insulin resistance score = [systolic blood pressure + diastolic blood pressure + triglyceride + [HDL cholesterol \( \times (1) \) ] + [insulin sensitivity \( (1) \) ] + body mass index + waist-to-hip ratio + subscapular-to-triceps ratio]. (2) Endothelial marker score = (thrombomodulin + cellular fibronectin + von Willebrand factor + mean albumin excretion rate)/4. (3) Acute phase marker score = (fibrinogen + C-reactive protein + IL-6 + TNF-\( \alpha \))/4.

For some of the analyses, including those shown in Table 2, the obesity variables were omitted from the insulin resistance score as follows: (systolic blood pressure + diastolic blood pressure + triglyceride + [HDL cholesterol \( \times (1) \) ] + [insulin sensitivity \( (1) \) ])/5.

For some analyses we also derived an obesity score as a mean standard deviation score: (body mass index + waist-to-hip ratio + subscapular-to-triceps ratio)/3.

Where results were missing, for insulin \( (n=2) \), albumin excretion rate \( (n=1) \), thrombomodulin \( (n=10) \), or fibrinogen \( (n=4) \), the mean standard deviation scores were calculated for the smaller denomina-
TABLE 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or Median (Interquartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M/F)</td>
<td>107 (59/48)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.0±10.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9±4.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.86±0.08</td>
</tr>
<tr>
<td>Subscapular-to-triceps ratio</td>
<td>1.31±0.59</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124.8±18.4</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.4±11.0</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.3 (1.0, 1.7)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.38±0.37</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.62±1.05</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>2-h plasma glucose (mmol/L)</td>
<td>4.9±1.1</td>
</tr>
<tr>
<td>PAI-1 activity (AU/mL)</td>
<td>8.1 (4.2, 15.9)</td>
</tr>
<tr>
<td>PAI-1 antigen (ng/mL)</td>
<td>95.6±58.9</td>
</tr>
<tr>
<td>tPA (ng/mL)</td>
<td>21.0±9.4</td>
</tr>
<tr>
<td>von Willebrand factor (%)</td>
<td>109.7±40.9</td>
</tr>
<tr>
<td>Thrombomodulin (ng/mL)</td>
<td>33.7 (10.9, 121.3)</td>
</tr>
<tr>
<td>Cellular fibronectin (%)</td>
<td>108 (71, 159)</td>
</tr>
<tr>
<td>Mean albumin excretion rate (µg/min)</td>
<td>10.2 (7.0, 20.6)</td>
</tr>
<tr>
<td>Fibrinogen (mg/L)</td>
<td>289.2±75.9</td>
</tr>
<tr>
<td>CRP (µg/mL)</td>
<td>1.35 (0.57, 2.18)</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>3.65 (2.98, 4.53)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>2.19 (1.18, 4.40)</td>
</tr>
</tbody>
</table>

Variables are presented as mean±SD, or as median (interquartile range) for skewed variables.

Results

The characteristics of these middle-aged white subjects with normal glucose tolerance are shown in Table 1. The low levels of CRP are similar to those found in other healthy populations.7,8

To explore the possible determinants of the acute phase markers and of the levels of proinflammatory cytokines, we explored their relationships with titers of IgG antibodies to 3 organisms which have been proposed as playing a potential role in atherogenesis.11,20–22 Concentrations of C-reactive protein correlated weakly with titers of H pylori, C pneumoniae, and cytomegalovirus antibodies (Table 2). However, the only significant correlation seen between titers of such antibodies and concentrations of cytokines was that of IL-6 with H pylori.

Both IL-6 and TNF-α are expressed in adipose tissue,14,15 and we have recently described the release of the former, but not the latter, from a subcutaneous adipose tissue bed in vivo.13 Concentrations of IL-6, TNF-α, and C-reactive protein were strongly related to measures of total, and particularly central, obesity (Table 2).

Concentrations of CRP correlated both with those of IL-6 (r=0.37, P<0.0005) and of TNF-α (r=0.46, P<0.0001). In Table 3 the relationships of concentrations of IL-6, TNF-α, and C-reactive protein with the components of the insulin resistance syndrome and with endothelial markers are shown. Univariate correlations are given as these were little affected by adjustment for age and gender. Concentrations of TNF-α were related to all insulin resistance variables, including proinsulin-like molecules, tPA, and PAI-1. Concentrations of IL-6 were also related to several of the insulin resistance syndrome and endothelial markers, including albumin excretion rate, although the relationships for C-reactive protein were generally stronger. Although there is a weak relationship between concentrations of low-density LDL cholesterol and those of CRP, no such relationships are seen with TNF-α or IL-6.

The population was dichotomized into those with high and those with low concentrations of CRP, based on the median

![Table 2. Relationships of Concentrations of Proinflammatory Cytokines and C-reactive Protein With Antibody Titers and Obesity](https://atvb.ahajournals.org/content/doi/10.1161/01.ATV.85.6.653.full)

Values are shown as Pearson correlation coefficients.

*P<0.05.
†P<0.01.
‡P<0.001.
§Data logarithmically transformed.

![Table 3. Relationship of Concentrations of Proinflammatory Cytokines and of C-reactive Protein With Components of Insulin Resistance Cluster and Endothelial Markers](https://atvb.ahajournals.org/content/doi/10.1161/01.ATV.85.6.653.full)

Values are shown as Pearson correlation coefficients.

*P<0.05.
†P<0.01.
‡P<0.001.
§Data logarithmically transformed.
TABLE 4. Characteristics of Subjects With Low (<1.35 μg/mL) and High (≥1.35 μg/mL) of C-Reactive Protein

<table>
<thead>
<tr>
<th></th>
<th>Low CRP</th>
<th>High CRP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M/F)</td>
<td>53 (27/26)</td>
<td>54 (32/22)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.9±11.0</td>
<td>62.1±9.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Smokers (non/ex/current)</td>
<td>37/3/13</td>
<td>26/6/22</td>
<td>0.17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±4.0</td>
<td>27.5±4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.84±0.08</td>
<td>0.89±0.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Subscapular-to-triceps ratio</td>
<td>1.15±0.51</td>
<td>1.47±0.62</td>
<td>0.004</td>
</tr>
<tr>
<td>H. pylori titer</td>
<td>1/10 (1/10, 1/48)</td>
<td>1/24 (1/10, 1/70)</td>
<td>0.57</td>
</tr>
<tr>
<td>C. pneumoniae titer</td>
<td>1/100 (1/100, 1/400)</td>
<td>1/200 (1/100, 1/200)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cytomegalovirus titre</td>
<td>1/20 (1/5, 1/80)</td>
<td>1/40 (1/10, 1/80)</td>
<td>0.11</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>21.4 (14.4, 42.9)</td>
<td>32.8 (19.1, 46.0)</td>
<td>0.032</td>
</tr>
<tr>
<td>Insulin sensitivity (HOMA) (%)</td>
<td>107.6 (55.9, 165.6)</td>
<td>73.8 (51.0, 127.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Fasting albumin excretion rate (g/min)</td>
<td>10.8 (7.3, 19.4)</td>
<td>9.6 (6.8, 21.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibrinogen (mg/mL)</td>
<td>275.2±68.7</td>
<td>301.8±80.4</td>
<td>0.22</td>
</tr>
<tr>
<td>PAI-1 activity (AU/mL)</td>
<td>6.5 (3.6, 12.2)</td>
<td>10.7 (4.8, 17.2)</td>
<td>0.051</td>
</tr>
<tr>
<td>PAI-1 antigen (ng/mL)</td>
<td>83.4±55.1</td>
<td>107.6±60.5</td>
<td>0.033</td>
</tr>
<tr>
<td>tPA (ng/mL)</td>
<td>17.1±8.6</td>
<td>24.9±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>von Willebrand factor (%)</td>
<td>101.5±37.8</td>
<td>117.8±42.6</td>
<td>0.038</td>
</tr>
<tr>
<td>Thrombomodulin (ng/mL)</td>
<td>33.2 (27.7, 39.6)</td>
<td>34.8 (28.1, 41.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Cellular fibronectin (%)</td>
<td>84.0 (62.0, 138.5)</td>
<td>130.0 (83.3, 178.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean albumin excretion rate (μg/min)</td>
<td>10.8 (7.3, 19.4)</td>
<td>9.6 (6.8, 21.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>1.35 (0.89, 3.11)</td>
<td>3.22 (1.79, 5.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Variables are presented as mean±SD, or as median (interquartile range) for skewed variables.

value of 1.35 mg/mL (Table 4). Subjects with high concentrations of CRP were more obese than those with lower levels, and had higher levels of blood pressure, triglyceride, von Willebrand factor, cellular fibronectin, PAI-1, tPA, and of the proinflammatory cytokines TNF-α and IL-6, but did not differ in titers of antibodies to Helicobacter, Chlamydia, or cytomegalovirus.

To overcome the problems of biological variability of the different measures, and to explore these inter-relationships further while controlling for potential confounds, we used summary scores for the insulin resistance syndrome variables, for endothelial dysfunction, and for acute phase markers by calculating a mean of a standard deviation score for each group of variables (see Methods). The relationships of these are shown in Figure 1. Whereas the insulin resistance syndrome and endothelial scores correlate with a coefficient of 0.32 (P=0.0008), there is a strong relationship between the insulin resistance syndrome and acute phase scores (r=0.59, P<0.00005). The third of these correlations, between endothelial and acute phase scores, is also significant (r=0.43, P=0.00005). A sum obesity score correlated with measures of both endothelial (r=0.33, P=0.001) and acute phase (r=0.54, P<0.0005) scores. Nevertheless, if the 3 measures of obesity are removed from the insulin resistance syndrome score, the relationship with the acute phase score was only slightly weakened (r=0.53, P<0.00005). Moreover, the strength of the relationship was not substantially affected by omitting any particular variable from either score. In multiple regression models, controlling for age, gender, smoking, and prevalent CHD, if the acute phase and endothelial scores were included in the same model, the former remained significantly associated with insulin resistance syndrome score (partial r=0.61, P<0.00005), but not the latter (partial r=−0.02, P=0.82). We have also approached the analysis of clustering of the variables using factor analysis, with generally similar results. The insulin resistance variables associate as two clusters, one comprising altered lipid concentrations with central obesity, and the other blood pressure with body mass index. Although both clusters correlate with acute phase markers, it is the second that relates more closely to endothelial dysfunction (data not shown).

Discussion

There has been much interest in the prognostic significance of raised levels of C-reactive protein in patients with angina, with the proposal that it points to release of IL-6 by activated macrophages in an unstable plaque. More recently, however, the observations that raised concentrations of CRP in
We report a relationship between circulating concentrations both of CRP and of two proinflammatory cytokines with a number of features of the insulin resistance syndrome, reflecting our previous report of a relationship between fibrinogen concentrations and measures of insulin resistance. Although relationships of CRP levels with triglycerides, HDL, glucose, and diabetes have been noted previously, no such relationship appears to have been reported with insulin concentrations or measures of insulin resistance. It is clearly not possible, in a cross-sectional study, to attribute causality to one of a set of correlated variables, but we have explored some hypotheses in this setting. The relationship between elevated concentrations of CRP and of the proinflammatory cytokines with the insulin resistance syndrome could represent associations produced by a confounding variable, such as adiposity. However, the relationships between a derived insulin resistance syndrome standard deviation score and one for the acute phase variables was only slightly weakened by removing all obesity measures from the former score. We also excluded PAI-1 from the calculation of an insulin resistance score, both because the measure of antigen may represent inactive PAI-1 (complexed to tPA or released from platelets), and also because PAI-1 is recognized to respond to acute phase stimuli.

Our observations could suggest that the cytokines, arising in part from adipose tissue, might themselves be partly responsible for the metabolic, hemodynamic, and hemostatic abnormalities that cluster with insulin resistance. Although not itself an inducer of acute phase proteins, TNF-α induces production of IL-6, which is itself the major determinant of the acute phase response. Among the known metabolic effects of TNF-α are inhibition of the action of lipoprotein lipase and stimulation of lipolysis, these actions being shared with IL-6. Furthermore, TNF-α impairs the function of the insulin signaling pathway by effects on phosphorylation of both the insulin receptor and its substrate, IRS-1.

In addition to their associations with insulin resistance syndrome variables, elevated levels of CRP and of cytokines were associated with a series of indicators of endothelial dysfunction. Tracy et al have previously reported associations of levels of CRP with a variety of measures of procoagulant activity and fibrinolysis, and have suggested that these represent consequences either of inflammation in underlying atherothrombotic disease or of inflammatory cells activated by products of ongoing coagulation processes. TNF-α is known to influence endothelial cell function, and a recent study suggests that IL-6 may also induce endothelial expression of chemokines and adhesion molecules in the presence of IL-6 soluble receptor, which is released in inflammatory states. If endothelial dysfunction, perhaps as a consequence of elevated concentrations of cytokines, resulted in impair-
ment of vasodilatation of resistance vessels, it could be postulated that the cluster of variables that have been attributed to insulin resistance (dyslipidemia, hypertension, and impaired fibrinolysis), as well as insulin resistance itself, might all result as consequences of a common antecedent. The strong relationship between concentrations of C-reactive protein and insulin resistance variables (Table 3), compared with those seen for IL-6, may simply reflect the longer half-life of C-reactive protein providing a more stable marker of acute phase mediators. Levels of C-reactive protein are predominantly modulated by hepatic effects of IL-6, which might all result as consequences of a common antecedent. The association of insulin resistance (dyslipidemia, hypertension, and not endocrine, metabolic effects of TNF-α) with a measure of insulin resistance and with markers of endothelial dysfunction. Furthermore, the association of acute phase markers with insulin resistance variables is independent of anthropometric measures of obesity, consistent with our finding of adipose tissue release of IL-6 in vivo and implicating adipose tissue as a major source for circulating IL-6. We have also found associations between levels of acute phase proteins and of proinflammatory cytokines not only with blood pressure and dyslipidemia, but also with a measure of insulin resistance and with markers of endothelial dysfunction. Furthermore, the association of acute phase markers with insulin resistance variables is independent of adipose tissue release of IL-6, both by TNF-α, and may thus be responsible for systemic effects on endothelium and lipids.

In conclusion, we have shown, in healthy subjects, relationships between levels of CRP and measures of obesity, consistent with our finding of adipose tissue release of IL-6 in vivo and implicating adipose tissue as a major source for circulating IL-6. We have also found associations between levels of acute phase proteins and of proinflammatory cytokines not only with blood pressure and dyslipidemia, but also with a measure of insulin resistance and with markers of endothelial dysfunction. Furthermore, the association of acute phase markers with insulin resistance variables is independent of adipose tissue release of IL-6, both by TNF-α, and may thus be responsible for systemic effects on endothelium and lipids.

Acknowledgments

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References

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