The Impact of Abnormalities in IGF and Inflammatory Systems on the Metabolic Syndrome

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OBJECTIVE — Low plasma levels of IGF-I, particularly when coupled with low levels of the potentially inhibitory IGF binding protein (IGFBP)-1 and higher levels of C-reactive protein (CRP), have been implicated in the pathogenesis of metabolic syndrome X and cardiovascular disease. We report the relative contributions of IGFBP-1 and CRP to the occurrence of the metabolic syndrome in a healthy population cohort to establish the extent to which these factors may contribute to subsequent risk of cardiovascular disease.

RESEARCH DESIGN AND METHODS — The volunteers in the study were all participants in the Ely study, a continuing population-based cohort in Ely, Cambridgeshire, U.K. Of 839 individuals studied, 154 (18.4%) fulfilled criteria for the metabolic syndrome.

RESULTS — Subjects with the metabolic syndrome had lower IGFBP-1 (14.4 μg/l [95% CI 12.9–16.0] vs. 25.4 [24.1–26.7], P < 0.001) and higher CRP (1.9 mg/l [1.6–2.2] vs. 1.0 [0.9–1.1], P < 0.001). Logistic regression, adjusted for age, sex, fasting insulin, and IGF-I, demonstrated a striking 14-fold increased risk for the metabolic syndrome (odds ratio 14.1 [95% CI 4.1–48.4], P < 0.001) in individuals with a CRP value in the highest tertile and IGFBP-1 levels below the median.

CONCLUSIONS — The combination of a high CRP concentration coupled with a low IGFBP-1 results in a dramatic increase in an individual’s risk of having the metabolic syndrome. Further elucidation of the biological processes linking the IGF and inflammatory systems may allow the identification of novel therapeutic targets for cardiovascular risk reduction.

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Both the IGF system and inflammatory mediators have been separately implicated in the pathogenesis of cardiovascular disease and glucose intolerance. A low IGF binding protein (IGFBP)-1 concentration has been linked (1–5) with characteristic features of the metabolic syndrome. The regulation of IGF-I bioavailability by IGFBP-1 provides a close link between IGFs and glucose homeostasis because hepatic IGFBP-1 production is potently suppressed by portal insulin (6,7). Furthermore, a low IGFBP-1 concentration coupled with low circulating IGF-I has been shown (8) to predict worsening of glucose tolerance. Many of the processes involved in the formation of atherosclerotic lesions are IGF dependent; IGF-1 promotes macrophage chemotaxis, endothelial cell migration (9), and vascular smooth muscle cell proliferation and migration (10). IGFBP-1 can also exert effects on cellular growth and migration independently of IGFs by binding to the cell surface via α5β1 integrins (11,12).

The acute-phase reactant C-reactive protein (CRP) is a systemic marker of inflammation. CRP has been shown to be an independent predictor of cardiovascular disease (13,14) and diabetes (15–17) and, in cross-sectional studies, to be associated with features of the metabolic syndrome (18–21). In addition to being a marker of vascular disease, it is thought that CRP may exert a direct proinflammatory effect on endothelial cells, promoting adhesion molecule and chemokine expression (22,23). Hepatic CRP synthesis is stimulated by proinflammatory cytokines, primarily interleukin (IL)-6, but also others, including tumor necrosis factor (TNF)-α and IL-1 (24,25).

The IGF and inflammatory systems have close biological links. Firstly, cytokines, in addition to being the main regulators of CRP, have stimulatory proinflammatory effects on hepatic IGFBP-1 production (26,27). Cytokines decrease circulating IGF-1, either by decreasing growth hormone levels or increasing growth hormone resistance (28,29). IGF-I promotes cytokine production from monocytes and macrophages (30). IGFBP-1, like CRP, may have a key role in atheroma secondary to α5β1 integrin binding (11). Inflamed atherosclerotic lesions, where such integrins are expressed (31), also produce a series of proteases with the ability to cleave IGFBPs, thereby increasing local IGF bioactivity (32,33).

This study examined the extent to which the known biological links between the IGF and inflammatory systems translated into increased cardiovascular risk, specifically the potential interplay between IGFBP-1 and CRP in determin-
ing the risk of an individual having the metabolic syndrome.

**RESEARCH DESIGN AND METHODS** — The volunteers in the study were all participants in the Ely study, a continuing population-based cohort in Ely, Cambridgeshire, U.K. The detailed methodology has been described previously (34). The original sample, comprising 1,122 patients without known diabetes, was recruited between 1990 and 1992 from a population-based sampling frame consisting of all people in Ely aged between 40 and 65 years. These subjects were asked to report to the local surgery at ~8:45 a.m. and underwent a standard 75-g oral glucose tolerance test, having fasted since 10:00 p.m. the previous evening. Fasting samples were available from 937 participants for assay of CRP and components of the IGF system. Of these, 839 people (89.5%) had a complete set of results available for IGF-I, IGFBP-1, and CRP and complete data for assessment of components of the metabolic syndrome.

Height and weight were measured with the participant wearing light indoor clothing. BMI was calculated using the formula weight (in kilograms)/height (in meters) (2). Waist and hip circumference were measured in duplicate using a metal tape. Diastolic and systolic blood pressure was recorded with the subject seated wearing a sphygmomanometer (Datascope, Cambridge, U.K.). Three sets of readings were taken in the right arm, 1 min apart, and mean systolic and diastolic readings were recorded.

The metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel III criteria, wherein individuals were identified as having the metabolic syndrome if three or more of the following criteria were present: waist circumference >102 cm (men) and >88 cm (women), triglycerides >1.69 mmol/l, HDL cholesterol <1.04 mmol/l (men) and <1.29 mmol/l (women), blood pressure ≥130/85 mmHg; and fasting glucose ≥6.1 mmol/l (35).

**Assays**

Blood samples were taken at fasting and 30 and 120 min after a 75-g oral glucose load. All samples were permanently stored at −70°C within 4 h. Plasma glucose was measured in the routine U.K. National Health Service laboratory at Addenbrooke’s Hospital by the hexokinase method (36), and total serum cholesterol, HDL, and triglyceride were measured using the RA 1000 (Bayer Diagnostics, Basingstoke, Hants, U.K.). Values for LDL cholesterol concentrations were calculated using the Friedewald formula (37). Plasma insulin was measured by two-site immunometric assays with either 125I or alkaline phosphatase labels (38,39). Cross-reactivity with intact proinsulin was <0.2%, and interassay coefficients of variation (CVs) were <7%. A measure of insulin secretion (the 30-min insulin increment) was calculated by dividing the difference between 30-min and fasting insulin concentrations by the 30-min glucose concentration (40). Plasma nonesterified fatty acid (NEFA) concentrations were enzymatically determined based on acyl-CoA synthetase activity as reported previously (40).

Baseline fasting concentrations of IGF-I, IGF-II, and IGFBP-1 (using monoclonal antibody 6303, which detects all IGFBP-1 phosphoforms) in plasma were measured by previously reported antibody-based assays (41–43). The assays have respective detection limits of 28 ng/ml, 30 ng/ml, and 3 μg/l and within- and between-assay CVs, respectively, of <6.3, <7.5, and <6.8%. IGFBP-3 was measured by solid-phase enzyme-labeled chemiluminescent immunometric assay using an Immulite Autoanalyzer (Diagnostics Products, Los Angeles, CA) with an analytical sensitivity of 0.02 mg/l and within- and between-assay CVs <7.4%. CRP was also measured by immunometric assay using an Immulite Autoanalyzer (Diagnostics Products) with an analytical sensitivity of 0.1 mg/l and within- and between-assay CVs <8%.

**Data analysis**

Individuals were divided into six groups based on their IGFBP-1 and CRP concentrations. The six groups were as follows:

1. IGFBP-1 above median, lowest tertile of CRP (n = 148);
2. IGFBP-1 above median, middle tertile of CRP (n = 134);
3. IGFBP-1 above median, highest tertile of CRP (n = 138);
4. IGFBP-1 below median, lowest tertile of CRP (n = 133);
5. IGFBP-1 below median, middle tertile of CRP (n = 145); and
6. IGFBP-1 below median, highest tertile of CRP (n = 141).

**Statistical analysis**

Data were analyzed using the statistical package SPSS version 9.0. Not all analyses were carried out on all subjects. All nonnormally distributed variables were logaritmically transformed to obtain nearnormal distribution, except for IGF-1, which was square-root transformed.

Differences in metabolic, anthropometric, and numerical demographic variables between individuals with and without the metabolic syndrome were assessed using independent samples t testing. The χ2 test was used to determine whether frequencies for categorical variables differed between these two groups of subjects. Comparisons between individuals with normal glucose tolerance and those with any form of glucose intolerance were made using the independent samples t test. Age-, sex-, and insulin-adjusted Pearson correlations were calculated to investigate the relation of IGFBP-1 and CRP with other metabolic and anthropometric variables. Multivariate logistic regression analysis was used to assess the relation between circulating IGFBP-1, IGF-I, and CRP and risk of having the metabolic syndrome.

**RESULTS**

**Characteristics of patients with the metabolic syndrome**

One hundred fifty-four patients (18.4% of the cohort) were identified as having the metabolic syndrome as defined by National Cholesterol Education Program Adult Treatment Panel III criteria. Of the 839 subjects included in the analysis, 537 were normoglycemic and 41 fulfilled the diagnostic criteria for diabetes. The remaining subjects were categorized by the presence of impaired fasting glycaemia (n = 134), impaired glucose tolerance (n = 67), and the combination of impaired fasting glycaemia and impaired glucose tolerance (n = 60). There was no significant difference in age distribution, anthropometric characteristics, or glycaemic tolerance status between the 98 excluded subjects and those included in the analysis.

Table 1 shows the demographic and metabolic characteristics according to the presence or absence of the metabolic syndrome. Subjects with the metabolic syndrome had a significantly lower concentration of IGFBP-1 (metabolic syndrome, 14.4 μg/l [12.9–16.0] versus no
IGF system and the metabolic syndrome

Table 1—Demographic and metabolic characteristics of individuals with and without the metabolic syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metabolic syndrome</th>
<th>No metabolic syndrome</th>
<th>P (difference between means)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>154 (18.4)</td>
<td>685</td>
<td>N/A</td>
</tr>
<tr>
<td>No. of patients</td>
<td>154 (18.4)</td>
<td>685 (81.6)</td>
<td></td>
</tr>
<tr>
<td>No. of males</td>
<td>73 (47.4)</td>
<td>276 (40.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.4 (55.2–57.6)</td>
<td>53.4 (32.9–54.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients with diabetes</td>
<td>23 (14.9)</td>
<td>18 (2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients with NGT</td>
<td>32 (20.8)</td>
<td>505 (73.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/l)*</td>
<td>1.9 (1.6–2.2)</td>
<td>1.0 (0.9–1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGFBP-1 (µg/l)*</td>
<td>14.4 (12.9–16.0)</td>
<td>25.4 (24.1–26.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF-I (ng/ml)*</td>
<td>141.6 (132.2–151.3)</td>
<td>151.3 (148.8–156.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>IGF-II (ng/ml)</td>
<td>655.6 (618.1–693.1)</td>
<td>577.2 (561.4–593.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGFBP-3 (µg/l)</td>
<td>4.1 (4.0–4.3)</td>
<td>3.9 (3.8–3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEFA (mmol/l)*</td>
<td>0.43 (0.39–0.43)</td>
<td>0.41 (0.39–0.47)</td>
<td>NS</td>
</tr>
<tr>
<td>0-h glucose (mmol/l)*</td>
<td>6.3 (6.2–6.5)</td>
<td>5.7 (5.6–5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-h insulin (pmol/l)*</td>
<td>61.6 (56.8–66.7)</td>
<td>36.1 (34.7–37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-min insulin increment</td>
<td>28.3 (25.6–31.3)</td>
<td>25.3 (24.1–26.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 (29.4–30.9)</td>
<td>24.9 (24.7–25.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are n (%), means (95% CI) for normally distributed variables, and *geometric means (95% CI) for nonnormally distributed variables. N/A, not applicable.

metabolic syndrome, 25.4 [24.1–26.7]; P < 0.001) and higher concentration of CRP (metabolic syndrome, 1.9 µg/ml [1.6–2.2 µg/ml] versus no metabolic syndrome, 1.0 [0.9–1.1]; P < 0.001). Patients with the metabolic syndrome also had a significantly higher IGF-II, IGFBP-3, fasting insulin concentration, and 30-min insulin increment and lower IGF-1 concentration. There was no difference in fasting NEFA concentration between the two groups. The exclusion of individuals found to have type 2 diabetes did not materially alter the finding that a low IGFBP-1 and high CRP value were independently associated with the presence of the metabolic syndrome. Of the 41 individuals with type 2 diabetes, 23 had the metabolic syndrome and 18 did not fit the criteria. The characteristics of the type 2 diabetic subjects with and without the metabolic syndrome were no different from each other.

IGFBP-1 and cardiovascular risk factors

The correlations between IGFBP-1, the IGF system, and established cardiovascular risk factors for all subjects are shown in Table 2. All correlations were adjusted for age, sex, and fasting insulin. Of the three measures of obesity assessed, namely waist circumference, BMI, and waist-to-hip ratio, IGFBP-1 showed the greatest negative correlation with waist circumference (r = −0.33, P < 0.001). IGFBP-1 concentration was significantly negatively correlated with other surrogate markers of cardiovascular risk, namely 2-h insulin concentrations, 30-min insulin increment, 2-h glucose, fasting triglycerides, and diastolic blood pressure. There was a significant positive association between IGFBP-1 and HDL cholesterol.

**Relationship of CRP with the IGF system and cardiovascular risk factors**

As evident in Table 2, there was a significant negative correlation when adjusted for age, sex, and fasting insulin between CRP and IGF-1 (r = −0.11, P < 0.01). As with IGFBP-1, CRP showed a greater correlation with waist circumference (r = 0.30, P < 0.001) than with other measures of obesity. CRP concentration was significantly and positively correlated with 2-h insulin concentration, fasting and 2-h glucose, total and LDL cholesterol, triglycerides, and systolic and diastolic blood pressure and negatively with HDL cholesterol. There was no correlation between CRP and NEFAs.

**Odds of metabolic syndrome according to IGFBP-1 and CRP concentrations**

Multivariate logistic regression analysis was used to determine the relative strength of IGFBP-1 and CRP as markers for the metabolic syndrome and also to establish the odds of having the metabolic syndrome if both low IGFBP-1 and high CRP were present in combination. In a model adjusted for age and sex, IGFBP-1 in the lowest tertile (≤17.0 µg/l) was associated with a 9.1-fold increased risk of having the metabolic syndrome com-

Table 2—Pearson correlation coefficients, partial r, for CRP and IGFBP-1-1 (adjusted for age, sex, and fasting insulin concentration)

<table>
<thead>
<tr>
<th>Variable</th>
<th>LogCRP</th>
<th>LogIGFBP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogIGFBP-1</td>
<td>0.00</td>
<td>—</td>
</tr>
<tr>
<td>√(IGF-I)</td>
<td>−0.11*</td>
<td>−0.12*</td>
</tr>
<tr>
<td>IGF-II</td>
<td>0.00</td>
<td>−0.04</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>−0.03</td>
<td>−0.12†</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28†</td>
<td>−0.29†</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.30†</td>
<td>−0.33†</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.23†</td>
<td>−0.24†</td>
</tr>
<tr>
<td>Log2-h insulin</td>
<td>0.10*</td>
<td>−0.22†</td>
</tr>
<tr>
<td>Log30-min insulin increment</td>
<td>0.02</td>
<td>−0.07†</td>
</tr>
<tr>
<td>0-h glucose</td>
<td>0.07†</td>
<td>−0.04</td>
</tr>
<tr>
<td>2-h glucose</td>
<td>0.18†</td>
<td>−0.12†</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.08†</td>
<td>−0.03</td>
</tr>
<tr>
<td>Logtriglycerides</td>
<td>0.25*</td>
<td>−0.09*</td>
</tr>
<tr>
<td>LogHDL</td>
<td>−0.16†</td>
<td>0.15†</td>
</tr>
<tr>
<td>LDL</td>
<td>0.07†</td>
<td>−0.05</td>
</tr>
<tr>
<td>LogNEFA</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.09*</td>
<td>−0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.09*</td>
<td>−0.08†</td>
</tr>
</tbody>
</table>

*P < 0.01; †P < 0.001; ‡P < 0.05.
Table 3—Pearson correlation coefficients, partial r, for CRP and IGFBP-1 (adjusted for age, sex, and fasting insulin concentration)

<table>
<thead>
<tr>
<th>Category</th>
<th>OR adjusted for age and sex</th>
<th>OR adjusted for age, sex, fasting insulin, and IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGFBP-1 ≥23.7 μg/l, CRP ≤0.67 mg/l</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>IGFBP-1 ≥23.7 μg/l, CRP 0.68–1.64 mg/l</td>
<td>2.65 (0.69–10.24)</td>
<td>2.14 (0.58–4.89)</td>
</tr>
<tr>
<td>IGFBP-1 ≥23.7 μg/l, CRP ≥1.66 mg/l</td>
<td>7.01 (2.02–24.28)</td>
<td>5.06 (1.43–17.87)</td>
</tr>
<tr>
<td>IGFBP-1 &lt;23.7 μg/l, CRP ≤0.67 mg/l</td>
<td>7.97 (2.26–28.07)</td>
<td>5.02 (1.39–18.04)</td>
</tr>
<tr>
<td>IGFBP-1 &lt;23.7 μg/l, CRP 0.68–1.64 mg/l</td>
<td>21.31 (6.39–71.06)</td>
<td>10.65 (3.12–36.37)</td>
</tr>
<tr>
<td>IGFBP-1 &lt;23.7 μg/l, CRP ≥1.66 mg/l</td>
<td>35.79 (10.82–118.32)</td>
<td>14.15 (4.14–48.37)</td>
</tr>
</tbody>
</table>

pared with a value in the highest tertile (≥32.6 μg/l) as compared with a 4.8-fold increased risk for the highest tertile of CRP (≥1.7 mg/l) (Table 3) compared with the lowest tertile of CRP (≤0.7 mg/l). Even after additional adjustment for fasting insulin and IGF-I, there was a 3.6-fold increase. The odds of the metabolic syndrome for the highest tertile of IGFBP-1 and 3-fold for elevated CRP. This suggests that low IGFBP-1 is as strongly associated with the metabolic syndrome as high CRP.

Subjects with both low IGFBP-1 (below the median) and high CRP (in the highest tertile) had a 35.8-fold increased risk of the metabolic syndrome (Table 3). In a model adjusted for fasting insulin and IGF-I (both profound negative regulators of IGFBP-1 and therefore potential confounders) as well as age and sex (Table 3 and Fig. 1), it is evident that although the magnitude of the odds ratios (ORs) are lower, those subjects with low IGFBP-1 and high CRP still have a 14.1-fold increased risk of having the metabolic syndrome compared with the reference category. Figure 1 demonstrates that for each tertile of CRP, low IGFBP-1 (below the median) significantly raises the odds of having the metabolic syndrome, independently of age, sex, and CRP concentrations.

In a separate multivariate logistic regression analysis, we examined the associated risk of the metabolic syndrome using IGFBP-1 and CRP as continuous variables. This showed that logIGFBP-1 (OR 0.49 [95% CI 0.35–0.68], P < 0.001) and logCRP (1.42 [1.17–1.73], P < 0.001) were both associated with the metabolic syndrome independently of fasting insulin (4.56 [2.83–7.34], P < 0.001) in a model that also included age, sex, and IGF-I. IGF-I showed no independent relationship with the metabolic syndrome in this model (0.92 [0.85–1.02], P = 0.10).

CONCLUSIONS — In this cross-sectional study, we have demonstrated that the combination of an IGFBP-1 level below the median and a CRP level in the highest tertile is associated with a dramatic increase in the risk for an individual having the metabolic syndrome. Independently, low IGFBP-1 is more strongly predictive of the presence of metabolic syndrome than high CRP. The absolute concentrations of CRP are similar to those in previous studies (14,15) and in the level of CRP associated with the presence of the metabolic syndrome and thus with an increased risk of the individual developing type 2 diabetes or cardiovascular disease in the future. Similarly, the lower circulating IGFBP-1 levels associated with the presence of the metabolic syndrome are comparable with those seen in subjects with impaired glucose tolerance in our previous study (3) in two different ethnic groups.

We have previously shown (19) an inverse correlation between CRP and circulating IGF-I in a multiethnic population without known type 2 diabetes at baseline. The present study, consisting of a much larger number of predominantly Caucasian subjects, has demonstrated a similar inverse association between CRP and IGF-I. The inverse association between CRP and IGF-I is important because we and others have previously established that high CRP and low circulating IGF-I levels are associated with an increased risk of the metabolic syndrome, cardiovascular disease (19,44,45), and the development of worsening glucose tolerance (8). Inflammatory cytokines (IL-6 and TNFα) increase CRP production and are known to decrease both circulating and tissue concentrations of IGF-I (28,29). They may be important...
mediators of the negative association seen between IGF-1 and CRP. A previous longitudinal study (8) in the Ely cohort demonstrated that increasing tertiles of circulating IGF-1 were inversely associated with 2-h glucose concentrations at a 4.5-year follow-up visit, but only in those individuals with an IGFBP-1 concentration below the median. Importantly, in this study the correlation between low IGFBP-1 and metabolic syndrome persists following adjustment for fasting insulin concentration. IGFBP-1 levels may therefore be a useful independent marker of cardiovascular risk and glucose intolerance. The low prevalence of the metabolic syndrome in the study may be related to the population residing in a semirural affluent part of the U.K., where a higher proportion of individuals pursue an overall healthy lifestyle than is the case in urban areas of the U.K. and where rates of obesity and type 2 diabetes are relatively low (46).

As previously reported in this and other cohorts (18–21,47), we found a close association of CRP with features of the metabolic syndrome. CRP was more strongly associated with waist circumference, a measure of central obesity, than overall obesity (BMI). Approximately 30% of circulating IL-6, the predominant cytokine regulating hepatic CRP production, is secreted by adipose tissue (48). In vitro data suggest (49) that most of this IL-6 comes from visceral rather than subcutaneous adipose tissue, perhaps explaining the greater association of CRP with waist circumference than with BMI.

This study has shown that the presence of low IGFBP-1 and elevated CRP in combination may be a powerful tool for identifying individuals at risk of the metabolic syndrome. In inflammatory and catabolic conditions, the stimulatory effect of IL-6 has been shown (26,27,50) to be dominant over the inhibitory influence of insulin on IGFBP-1 production. Inflammatory processes are also fundamental to atherosclerotic disease, and elevated cytokine concentrations are found in subjects at increased risk of cardiovascular disease (18). An elevated IL-6 level has been shown to be predictive of future cardiovascular events (14), and raised TNF-α postmyocardial infarction has been associated with an increased likelihood of recurrent coronary events (51). Cytokines cause insulin resistance by inhibition of insulin signaling (52). However, in the present study, IGFBP-1 concentrations were lower in individuals at risk of atherosclerotic disease, and indeed, this finding has been replicated in other studies of individuals known to be at risk of (1–3,5,8), or have established evidence of, cardiovascular disease (4).

It is interesting to speculate on the reason why a low IGFBP-1 concentration is associated with an adverse cardiovascular risk profile. The early phase of atherosclerosis involves recruitment of circulating inflammatory cells and their transendothelial migration. Adhesion molecules, including integrins, are necessary for the tethering of these inflammatory cells to the vessel wall (31). The expression of two of the integrins that are specifically known to bind IGFBP-1, namely α5β1 and αvβ3, is increased in atherosclerosis (53). A lower circulating concentration of IGFBP-1, and consequently decreased binding of IGFBP-1 to these integrins, may increase the potential for inflammatory cells to bind, with a resultant progression of the atheromatous plaque.

In summary, we have demonstrated important links between the IGF and inflammatory systems in relation to cardiovascular disease risk. Both IGFBP-1 and CRP are independently and increasingly recognized in the pathogenesis of impaired glucose tolerance and cardiovascular risk. We have shown that the combination of a high CRP concentration with a low IGFBP-1 concentration greatly enhances an individual’s risk of having the metabolic syndrome. Further elucidation of the biological processes linking the IGF and inflammatory systems will be important in facilitating the identification of novel therapeutic targets for cardiovascular risk reduction.

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