C-Reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (DM) is estimated to affect 15 million Americans, is dramatically increasing in incidence, and is associated with an augmented risk for cardiovascular disease, especially among women.1-3 Because of the risk for cardiovascular disease, especially among women.1-3 Because of the economic and functional burdens are greatest during mid-to-late adulthood. Compounding these issues, as many as one third of individuals with type 2 DM are undiagnosed, and approximately 20% have diabetic retinopathy or evidence of systemic vasculopathy at clinical presentation.4

Although the main physiological abnormalities are insulin resistance and impaired insulin secretion,5-7 the specific underlying determinants of these metabolic defects remain uncertain. An accumulating body of evidence suggests that inflammation may play a crucial intermediary role in pathogenesis, thereby linking diabetes with a number of commonly coexisting conditions thought to originate through inflammatory mechanisms. In this regard, substantial experimental evidence and more recent cross-sectional data suggest that interleukin 6 (IL-6) and C-reactive protein (CRP), 2 sensitive physiological markers of subclinical systemic inflammation, are associated with hyperglycemia, insulin resistance, and overt type 2 DM.8-15 Indeed, it recently has been postulated that type 2 DM may represent a disease of the innate immune system,16 a hypothesis of particular interest because both of these inflammatory biomarkers also are known to predict the development of cardiovascular disease in otherwise healthy populations.17-20

Interleukin 6, a major proinflammatory cytokine, is produced in a variety of tissues, including activated leukocytes, adipocytes, and endothelial cells. C-reactive protein is the principal downstream mediator of the acute phase response and is primarily derived via IL-6-dependent hepatic biosynthesis. In rodent models of glucose metabolism, the in vivo infusion of human recombinant IL-6 has been shown to induce gluconeogenesis, subsequent hyperglycemia, and compensatory hyperinsulinemia.21 Similar metabolic responses have been observed in humans after administration of subcutaneous recombinant IL-6.10 Cross-sectional investigations further support a role in inflammation in the etiology of diabetes;

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several studies have demonstrated elevated levels of IL-6 and CRP among individuals both with features of the insulin resistance syndrome and clinically overt type 2 DM.\textsuperscript{11-15}

Despite these observations, to our knowledge, there are no published prospective data evaluating the relationship between IL-6, CRP, and the development of type 2 DM. Therefore, we evaluated whether baseline plasma levels of these inflammatory markers might independently predict future risk for this disease among apparently healthy individuals.

**METHODS**

**Study Participants**

We designed a prospective, nested case-control study involving participants in the Women’s Health Study (WHS), an ongoing randomized clinical trial initiated in 1992 evaluating the use of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among female health professionals aged 45 years and older.\textsuperscript{22} Among participants in this primary prevention trial, 27,628 individuals (69% of the WHS cohort) also were free of baseline type 2 DM and provided whole blood samples at enrollment. These samples were centrifuged and then stored in liquid nitrogen until laboratory analysis. Plasma samples collected in EDTA were used for IL-6, CRP, and insulin level determination. Packed red blood cell samples were used for measurement of hemoglobin (Hb) A\textsubscript{1c}.

Case subjects were WHS participants who provided blood specimens, were free of reported diabetes at enrollment, and subsequently developed newly diagnosed diabetes during a 4-year observation period. Candidate cases were initially identified by self-report on yearly follow-up questionnaires and were subsequently verified through telephone interview conducted by a physician (A.D.P.). Based on revised American Diabetes Association diagnostic criteria,\textsuperscript{23} cases were confirmed if 1 or more of the following conditions were met: (1) presence of more than 1 classic symptom of hyperglycemia (ie, polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision) plus either a fasting plasma glucose of 126 mg/dL (7.0 mmol/L) or higher or random plasma glucose 200 mg/dL (11.1 mmol/L) or higher; (2) in the absence of symptoms, 2 or more elevated plasma glucose concentrations (fasting plasma glucose of $\geq 126$ mg/dL [7.0 mmol/L], random plasma glucose $\geq 200$ mg/dL [11.1 mmol/L], or 2-hour plasma glucose $\geq 200$ mg/dL [11.1 mmol/L] during oral glucose tolerance testing); or (3) use of insulin or an oral hypoglycemic agent. The primary care physician’s office was contacted for supporting documentation as necessary. Candidate cases who did not meet the diagnostic criteria, who were found to have prevalent diabetes at enrollment, who died, or who were otherwise lost to follow-up were excluded. In addition, to reduce misclassification bias that might be due to undiagnosed diabetes at study entry, individuals diagnosed within the first year of follow-up ($n=69$) also were excluded.

For each woman who developed confirmed type 2 DM, 2 control subjects were chosen at random among individuals free of self-reported DM at the time the case subject reported her event. Control subjects were matched by age and assayed for IL-6, CRP, and specific insulin levels. Hemoglobin A\textsubscript{1c} was measured by immunoassay (Hitachi 911 Analyzer; Roche Diagnostics, Indianapolis, Ind). The plasma concentration of IL-6 was measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn). C-Reactive protein was measured via a high-sensitivity latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Newark, Del).\textsuperscript{25} Double antibody systems (Linco Research, St Louis, Mo), with less than 0.2% cross-reactivity between insulin and its precursors, were used to measure specific concentrations of plasma insulin. In addition, as insulin levels may be falsely lowered in the presence of hemolysis,\textsuperscript{26} samples with free hemoglobin values higher than 50 mg/dL (spectrophotometric method, Hitachi 911 Analyzer) were excluded from fasting subgroup investigations. Blood samples were analyzed in randomly ordered case-control triplets so as to reduce systematic bias and interassay variation. Blinded quality control specimens were analyzed...
simultaneously with the study sample. The coefficients of variation for IL-6, CRP, and insulin were 12.7%, 12.0%, and 14.7%, respectively.

**Statistical Analysis**

We used repeated measures analysis (SAS PROC mixed; SAS Institute, Cary, NC) to evaluate differences in means and a matched χ² statistic to assess for differences in proportions, both approaches allowing for correlation within matched case-control sets. Because the distributions of IL-6, CRP, and insulin are skewed, differences in medians were tested with the Wilcoxon rank-sum test. Analysis of linear trends was used to assess associations between increasing level of each biomarker and risk of future diabetes after the sample was divided into quartiles based on the distribution of controls. Quartile-specific risk estimates were obtained through conditional logistic regression adjusting for BMI, family history of diabetes in a first-degree relative, smoking, physical activity, alcohol consumption, and use of HRT. Continuous and categorical variables were specified according to best fit through comparison of competing regression models. In particular, BMI was controlled for on a continuous linear scale and insulin was expressed using both categorical and continuous variables while controlling for age and BMI.

Conditional logistic regression was used to examine the joint role of IL-6 and CRP in predicting diabetes after dividing the primary sample into 4 groups based on the 75th percentile cutpoints for each biomarker. Finally, to assess consistency of risk relationships among obese and nonobese individuals, the study sample was divided into 6 groups based on a BMI cutoff value of 29 kg/m² (the upper tertile of BMI for our study population) and low, medium, and high tertiles of the inflammatory markers.

**RESULTS**

Baseline characteristics of women who were subsequently diagnosed with diabetes (case subjects) and those remaining free of diabetes (control subjects) are shown in Table 1. As would be predicted, women who subsequently developed diabetes had a higher mean BMI, were more likely to have a family history of diabetes in a first-degree relative, and were more likely to have a history of hypertension or hyperlipidemia. In addition, case subjects exercised less frequently and consumed less alcohol. There were no statistically significant differences in ethnicity, smoking, or HRT use.

Median baseline levels of IL-6 and CRP were significantly higher among cases than among controls (P<.001) (Table 1). Moreover, increasing levels

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Study Cohort*</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Mean age, y</td>
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<tr>
<td>Mean BMI, kg/m²†</td>
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<tr>
<td>Race, %</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Nonwhite/unknown</td>
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<tr>
<td>Family history of diabetes mellitus, %</td>
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<tr>
<td>History of hypertension, %</td>
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<tr>
<td>History of hyperlipidemia, %</td>
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<tr>
<td>Smoking status, %</td>
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<tr>
<td>Nonsmoker</td>
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<tr>
<td>Former smoker</td>
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<tr>
<td>Current smoker</td>
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<tr>
<td>Frequency of exercise, times/week, %</td>
</tr>
<tr>
<td>Rarely or never</td>
</tr>
<tr>
<td>&lt;1</td>
</tr>
<tr>
<td>1-3</td>
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<tr>
<td>≥4</td>
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<tr>
<td>Frequency of alcohol consumption, %</td>
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<tr>
<td>Rarely or never</td>
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<tr>
<td>Monthly</td>
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<td>Weekly</td>
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<tr>
<td>Daily</td>
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<tr>
<td>Hormone replacement therapy use, %</td>
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<tr>
<td>Never</td>
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<tr>
<td>Past only</td>
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<tr>
<td>Current</td>
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<tr>
<td>Interleukin 6, pg/mL, median (interquartile range)</td>
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<tr>
<td>C-Reactive protein, mg/dL, median</td>
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<td>Fasting insulin, pmol/L,† median (interquartile range)</td>
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<tr>
<td>Hemoglobin A₁c, %, median (interquartile range)</td>
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</tbody>
</table>

*Limited to subjects (N = 550) with hemoglobin A₁c of 6.5% or less at baseline.
†BMI indicates body mass index.
‡Among subjects providing fasting blood samples: 126 cases and 225 controls.
of both inflammatory markers were associated with a higher risk of developing future diabetes; in age-matched analyses, the RRs of incident type 2 DM for increasing quartiles of IL-6 were 1.0, 2.5, 4.1, and 7.5, respectively (P<.001 for trend) and the RRs for increasing quartiles of CRP were 1.0, 2.2, 8.7, and 15.7, respectively (P<.001 for trend) (TABLE 2). Adjustment for BMI markedly attenuated these relationships, although persistent positive effects of IL-6 (P=.008 for trend) and CRP (P<.001 for trend) were observed. Indeed, CRP remained a significant predictor in fully-adjusted models that included BMI, family history of diabetes, smoking, physical activity, alcohol consumption, and hormone replacement therapy. However, the risk relationship for CRP was not materially altered after adjustment for this factor. In addition, in this subgroup, Spearman partial correlation coefficients between inflammatory markers and both fasting insulin and BMI were statistically significant (P<.001) (TABLE 4). C-Reactive protein was more strongly correlated than IL-6 with each parameter tested. Hemoglobin A₁c of 6.5% or less was not strongly associated with either biomarker.

To assess potential joint effects, we computed the RR of DM after dividing the original sample into 4 groups based on the 75th percentile of control distributions for IL-6 and CRP (FIGURE 1). As shown, the RR of type 2 DM was highest among women with both high

### Table 2. Crude and Adjusted Relative Risks of Type 2 Diabetes Mellitus, According to Baseline Plasma Concentration of Interleukin 6 and C-Reactive Protein

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Quartile of Interleukin 6, Median (Interquartile Range), pg/mL</th>
<th>Quartile of C-Reactive Protein, Median (Interquartile Range), mg/dL</th>
<th>P for Trend</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude analysis</td>
<td>BMI-adjusted analysis</td>
<td>Adjusted for all risk factors†</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>Relative risk (95% CI)</td>
<td>Relative risk (95% CI)</td>
<td>Relative risk (95% CI)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.698 (.909)</td>
<td>0.050 (.100-0.26)</td>
<td>1.00 (.050-0.950)</td>
<td>1.90 (.80-4.2)</td>
</tr>
<tr>
<td>2</td>
<td>1.133 (.91-1.382)</td>
<td>0.170 (.27-0.61)</td>
<td>.90 (.27-0.3)</td>
<td>2.90 (1.3-6.7)</td>
</tr>
<tr>
<td>3</td>
<td>1.646 (1.383-2.050)</td>
<td>0.435 (.27-0.61)</td>
<td>.19 (.05-0.4)</td>
<td>4.30 (1.6-10.6)</td>
</tr>
<tr>
<td>4</td>
<td>2.709 (&gt;2.050)</td>
<td>0.930 (.27-0.61)</td>
<td>.73 (.04-0.004)</td>
<td>.61 (.007-0.007)</td>
</tr>
</tbody>
</table>

*Limited to subjects with hemoglobin A₁c of 6.5% or less; 188 cases, 362 controls. CI indicates confidence interval; BMI, body mass index.†Matched on age and fasting status, controlled for body mass index, family history of diabetes, smoking, physical activity, alcohol consumption, and hormone replacement therapy. Limited to subjects providing fasting blood specimens, the median insulin level also was significantly higher in case subjects than control subjects (77.5 vs 39.3 pmol/L; P<.001). Therefore, we evaluated whether relationships between IL-6, CRP, and the future risk of diabetes were independent of fasting insulin level. As shown in TABLE 3, adjustment for baseline fasting insulin level further attenuated the effects of IL-6 levels. However, the risk relationship for CRP was not materially altered after adjustment for this factor. In addition, in this subgroup, Spearman partial correlation coefficients between inflammatory markers and both fasting insulin and BMI were statistically significant (P<.001) (TABLE 4). C-Reactive protein was more strongly correlated than IL-6 with each parameter tested. Hemoglobin A₁c of 6.5% or less was not strongly associated with either biomarker.

To assess potential joint effects, we computed the RR of DM after dividing the original sample into 4 groups based on the 75th percentile of control distributions for IL-6 and CRP (FIGURE 1). As shown, the RR of type 2 DM was highest among women with both high
IL-6 and CRP levels, suggesting a multiplicative effect above that seen for either high IL-6 or high CRP levels alone.

To investigate effect modification by BMI, we determined the RR of incident diabetes among women with a BMI less than 29 kg/m² or 29 kg/m² and greater (Figure 2). After controlling for BMI within strata, higher baseline plasma levels of IL-6 and CRP were associated with increased risk of incident disease. Notably, even among non-obese women, increasing IL-6 and CRP levels conferred an augmented stepwise elevation in risk.

Among individuals with a baseline HbA1c of 6.5% or less, we performed secondary analyses to address the additional issues of potential surveillance bias, possible confounding by degree of baseline chronic hyperglycemia, and residual confounding by obesity. Case subjects were noted to have a higher baseline prevalence of diagnosed hypertension and hyperlipidemia and on this basis might have been screened more frequently for other major cardiovascular risk factors, including diabetes. We attempted to control for this potential surveillance bias by adjusting for history of hypertension and hyperlipidemia and found equivalent results; the BMI-adjusted RR in the highest vs the lowest quartile for IL-6 was 3.0 (95% CI, 1.3-7.0; \( P = .007 \) for trend) and for CRP was 4.0 (95% CI, 1.5-10.6; \( P < .001 \) for trend). To evaluate for confounding by chronic hyperglycemia, we controlled for baseline HbA1c in analyses simultaneously controlling for BMI, the adjusted RR for the highest compared with the lowest quartile of IL-6 was 2.0 (95% CI, 0.6-6.2; \( P = .77 \) for trend) and for CRP was 3.4 (95% CI, 0.9-12.1; \( P = .03 \) for trend). To assess residual confounding by obesity, we used waist-hip ratio (WHR) and waist circumference as alternate indices of adiposity among approximately two thirds of the study cohort for whom these parameters were available. The distribution of baseline characteristics in this subgroup was similar to those observed for the primary study sample. In statistical models controlling for WHR in addition to BMI, the RR in these analyses comparing the highest with the lowest quartile for IL-6 was 4.1 (95% CI, 1.4-11.8; \( P = .004 \) for trend) and for CRP was 3.1 (95% CI, 1.1-9.4; \( P = .001 \) for trend). Similar results were obtained after adjustment for waist circumference. In addition, after confining the study cohort to normal weight subjects (BMI ≤ 25 kg/m²), the median CRP level remained significantly elevated among case subjects vs control subjects (0.46 vs 0.15 mg/dL; \( P = .01 \)). Finally, we found that randomized treatment assignment to vitamin E or low-dose aspirin did not affect the observed risk relationships during the 4-year observation period.

**COMMENT**

In this prospective study of apparently healthy middle-aged women, 2 markers of systemic inflammation, CRP and IL-6, were found to be determinants of risk for type 2 DM. In particular, CRP was a powerful independent predictor after adjustment for obesity, clinical risk factors, and fasting insulin levels. Parallel associations were found for IL-6, although lower in magnitude and of borderline statistical significance after multivariate adjustments. These findings were robust in sensitivity analyses limited to subjects with a baseline HbA1c of 6.0% or less and were consistently noted in both obese and nonobese individuals.

To our knowledge, no prior epidemiologic evidence has been available linking baseline CRP and IL-6 levels to incident DM. However, across-sectional studies have reported increased concentrations of these inflammatory markers in both the insulin resistance syndrome and overt type 2 DM. Our data also extend prior work in which other inflammatory markers, such as white blood cell count, fibrinogen, and low serum albumin, and inflammation-associated hemostasis variables, such as factor VIII and von Willebrand factor, were associated with risk of diabetes; although in these latter investigations, risk relationships largely disappeared after adjustment for obesity.

The current prospective data support a possible role for inflammation in diabetogenesis and are in accord with previous hypotheses originated by Pickup and Crook, that type 2 DM may be a manifestation of an ongoing cytokine-mediated acute phase response initiated by the body's innate immune system. Of particular relevance to the current findings, CRP is thought to exhibit several characteristics that imply a fundamental role in natural host defense. Specifically, CRP is a member of the pentraxin family of oligomeric proteins involved with pattern recognition in innate immunity. Reported immunoregulatory functions of CRP include enhancement of leukocyte reactivity, complement fixation, modulation of platelet activation, and clearance of cellular debris from sites of active inflammation. Although our data support etiological associations, at this time explicit mechanisms remain speculative and require further study.

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Several alternative, perhaps coordinate, explanations for our results warrant further discussion. First, it is possible that the associations observed in this study of diabetes reflect underlying atherosclerosis among case subjects.17-20 However, it is worth noting that the 4-year cardiovascular event rate among our study cohort was low (1 case subject and 1 control subject with incident stroke, myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery), even among those individuals with greatest baseline elevations of either IL-6 or CRP levels.

Obesity-mediated cytokine production is another important and perhaps central mechanism for systemic elevations of both of these biomarkers. The primary cytokine involved in hepatic CRP synthesis is IL-6, also an important adipocyte signaling molecule released from visceral and subcutaneous fat stores. Indeed, approximately 25% of in vivo systemic IL-6 originates from subcutaneous adipose tissue34 and is thought to modify adipocyte glucose and lipid metabolism and body weight.35-37 Furthermore, omental fat cells have been shown to secrete as much as 2 to 3 times more IL-6 in vitro than cells derived from subcutaneous stores,24 an intriguing finding as venous drainage from omental fat provides direct access to the portal system, and abdominal adiposity is strongly linked to insulin resistance.36,37 Although we found a stronger relationship between baseline elevations of CRP and incident diabetes than that seen for IL-6, this may partially reflect the considerably longer plasma half-life of CRP that thereby may provide a more stable indication of subclinical inflammation. Furthermore, because of diurnal variation in IL-6 release and because study specimens were obtained at different times of the day, random misclassification of both cases and controls may have biased our results for IL-6 toward the null. In this regard, plasma CRP levels may represent a more appropriate integrated measure of basal IL-6 activity.

In the present analysis, BMI was used as the principal measure of obesity, and as expected, significantly attenuated RR estimates for both IL-6 and CRP. Adjustment for WHR or waist circumference, indices of abdominal adiposity, similarly weakened the observed risk relationships. However, significant associations for both IL-6 and CRP were nonetheless observed in multivariate models adjusting for these factors. In addition, a stepwise RR gradient was evident even among nonobese individuals (Figure 2). Regardless of the apparent diminution of effects in statistical models controlling for obesity, the graded crude association between increasing concentrations of these inflammatory markers and risk for diabetes suggests a possible role in disease expression whether this process is obesity-driven or autonomously mediated.

Another potential mechanism that may explain our results is the relationship between inflammation and endothelial dysfunction. Altered endothelial permeability and diminished peripheral blood flow may limit insulin delivery and promote insulin resistance in metabolically active tissues.43 Indeed, in the dynamic state, interstitial insulin concentration appears to be the rate-limiting step for determining insulin effectiveness.44 In this regard, the local administration of proinflammatory cytokines has been shown to impair endothelium-dependent vascular relaxation in human veins in vivo,45 and plasma IL-6 response to mild inflammatory stimuli is correlated with temporary but profoundly diminished response to both physical and pharmacological vasodilatory agents.46 Elevated CRP levels have been similarly associated with blunted endothelial vasoactivity and, perhaps more importantly, CRP normalization is associated with subsequent improvement of regional blood flow.47 In addition, cross-sectional analyses show that CRP is
strongly correlated with markers of endothelial activation and dysfunction.\textsuperscript{38} The increasingly recognized associations between endothelial dysfunction, inflammation, and insulin resistance provide an additional plausible physiological basis for our findings.

Finally, it is possible that elevated IL-6 and CRP levels may largely reflect adipocyte activation. For instance, IL-6 and downstream CRP production may be associated with the corelease of other pathogenic substances arising from otherwise stimulated adipocytes. Other potential mediators of insulin resistance deriving from adipose stores include tumor necrosis factor \(\alpha\), leptin, free fatty acids, and resistin. Nonetheless, under the assumption that elevated levels of IL-6 and CRP purely reflect altered adipocyte function, the ready availability of reliable and sensitive markers of this process may represent a novel approach for early identification of both obese and nonobese individuals at increased risk for the clinical development of this disease.

Several limitations of our study warrant further discussion. First, because our cohort was composed of primarily healthy middle-aged women, our results may not be generalizable to other age groups or to men who may be at risk for type 2 DM. Second, it is possible that undetected diabetes at study entry might have biased our results. However, to minimize the impact of this factor we excluded individuals with a baseline HbA\(_1c\) of greater than 6.5% from our primary sample and also conducted sensitivity analyses using a lower threshold for case and control inclusion. Furthermore, all women who were diagnosed with diabetes within the first year of follow-up were eliminated. A third limitation is potential residual confounding by obesity in our multivariate analyses. Although BMI, WHR, and waist circumference are the more common clinical measures of adiposity, multivariate adjustment on this basis may not fully account for the metabolic consequences of obesity. In this regard, it is important in analyses to note adjusting for WHR and waist circumference in addition to BMI, we found consistent results statistically significant and undiminished in magnitude. Finally, we used a single baseline plasma measurement of each biomarker. We therefore could not evaluate the effects of changes in plasma levels of inflammatory markers over time. However, several longitudinal analyses have found that levels of CRP are stable during long-term follow-up, as long as measurements are not made within 2 weeks of an acute infection.\textsuperscript{35,36}

In conclusion, in this prospective evaluation of 2 markers of systemic inflammation in the prediction of incident diabetes, elevated CRP was found to be a powerful independent risk determinant. Interleukin 6 levels also were elevated among individuals at risk, although these associations were markedly attenuated after multivariate adjustment. Our epidemiological observations, coupled with emerging experimental evidence, support a possible role for inflammation in the pathogenesis of type 2 DM. Our data also raise the possibility that inflammatory markers, like CRP, might provide an adjunctive method for early detection of risk for this disease.

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Financial Disclosure: Drs Ridker and Manson are listed as coinvestigators on patents filed by the Brigham and Women’s Hospital that relate to inflammatory markers in vascular disease and diabetes mellitus.

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Analysis and interpretation of data: Pradhan, Manson, Ridker.

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Administrative, technical, or material support: Manson, Rifai, Ridker.

Study supervision: Manson, Ridker.

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REFERENCES


CRP, IL-6, AND RISK OF TYPE 2 DIABETES MELLITUS


