Low-Grade Systemic Inflammation and the Development of Type 2 Diabetes

The Atherosclerosis Risk in Communities Study

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To examine the association of low-grade systemic inflammation with diabetes, as well as its heterogeneity across subgroups, we designed a case-cohort study representing the ~9-year experience of 10,275 Atherosclerosis Risk in Communities Study participants. Analytes were measured on stored plasma of 581 incident cases of diabetes and 572 noncases. Statistically significant hazard ratios of developing diabetes for those in the fourth (versus first) quartile of inflammation markers, adjusted for age, sex, ethnicity, study center, parental history of diabetes, and hypertension, ranged from 1.9 to 2.8 for sialic acid, orosomucoid, interleukin-6, and C-reactive protein. After additional adjustment for BMI, waist-to-hip ratio, and fasting glucose and insulin, only the interleukin-6 association remained statistically significant (HR = 1.6, 1.01–2.7). Exclusion of GAD antibody–positive individuals changed associations minimally. An overall inflammation score based on these four markers plus white cell count and fibrinogen predicted diabetes in whites but not African Americans (interaction \( P = 0.005 \)) and in nonsmokers but not smokers (interaction \( P = 0.13 \)). The fully adjusted hazard ratio comparing white nonsmokers with score extremes was 3.7 (\( P \) for linear trend = 0.008). In conclusion, a low-grade inflammation predicts incident type 2 diabetes. The association is absent in smokers and African-Americans. Diabetes 52:1799–1805, 2003

Type 2 diabetes is a leading cause of morbidity and mortality. Prevention of diabetes and its associated burden, primarily cardiovascular morbidity and mortality, have become major health issues worldwide (1). Obesity has also become a public health priority, given its growing worldwide epidemic and its vast health consequences. Thus, the pathogenesis of so-called “diabesity”—type 2 diabetes in the milieu of obesity—has recently received increased attention.

Although insulin resistance and \( \beta \)-cell failure continue to be recognized as the central causal processes in the development of type 2 diabetes, other paradigms have evolved. Influenced by findings indicating an inflammatory basis for cardiovascular diseases and following the “common soil” hypothesis of coronary heart disease and type 2 diabetes, we investigated the association between inflammation markers and incident diabetes, reporting in 1999 that a low-grade inflammation precedes and predicts diabetes development in adults participating in the Atherosclerosis Risk in Communities (ARIC) Study (2). Several reports investigating various markers of inflammation in different population groups have confirmed this association (3–11). The marked variation in magnitude of these reported associations and the frequently modest correlations found between markers of inflammation highlight the difficulty of characterizing this low-grade systemic inflammatory state on the basis of a single analyte.

Thus, the purpose of this study is to evaluate the association of incident type 2 diabetes with several markers of inflammation, examined individually and also jointly as a score composed of six markers. To gain insight into the sources of reported variation of the inflammation marker–diabetes association, we characterized the association with this score across sex, ethnicity, BMI, and smoking status, as well as its independence of measures of obesity, fasting glucose, and fasting insulin.

RESEARCH DESIGN AND METHODS

In 1987–1989, the ARIC study recruited a population-based cohort of 15,792 men and women 45–64 years of age from four U.S. communities (12). All subjects were invited to return to three clinic visits, at ~3-year intervals, at which incident diabetes was ascertained. Human subjects research review committees at the involved institutions approved the study, and all participants gave written consent.

We chose a case-cohort design to investigate our objectives in order to permit an efficient use of ARIC frozen biologic specimens. Before sampling, we excluded 2,018 participants with prevalent diabetes, 95 members of minority ethnic groups with small numbers, 853 not returning to any follow-up visit, 26 having no valid diabetes determination at follow-ups, 7 with restrictions on stored plasma use, 12 with missing baseline anthropometrics, and 2,506 participants in previous ARIC case-control studies involving cardiovascular disease for whom stored plasma was either previously exhausted or held in reserve. This resulted in a final sample of 10,275 individuals (75% of those in the full cohort without diabetes at baseline), of whom 1,155 (11.2%)
developed diabetes during follow-up. From these 10,275 eligible members of the cohort, we selected and measured analytes on ethnicity-stratified random samples of cases of incident diabetes and of eligible members of the full cohort (in total, 1,153 individuals). A few of the incident cases of diabetes overrepresented in the cohort sample, and a few were selected only via the cohort sample. Of those sampled, we excluded 45 for incomplete fasting (<8 h) or for not having values for all covariates, leaving a total of 1,153 subjects, including 581 diabetes cases and 572 noncases, for analysis.

We measured glucose at baseline and at follow-up visits by a hexokinase method, and we measured fasting serum insulin by nonspecific radioimmunoassay. We measured waist girth at the umbilical level and hip circumference at the maximum hip girth, defining waist-to-hip ratio (WHR) as the ratio between the two measurements. We defined parental history of diabetes as a report of diabetes in either parent. The definitions and methods for other baseline measurements (height, weight, smoking status, systolic blood pressure, hypertension, physical activity, triglycerides, HDL cholesterol, insulin, white cell count, fibrinogen, and mean carotid intimal-medial thickness) have been previously reported (2).

To characterize the acute-phase response, we chose to analyze three acute-phase markers, namely C-reactive protein (CRP), orosomucoid, and sialic acid, as well as interleukin (IL)-6, the main circulating mediator of the acute-phase response. To ensure the independence of the inflammation markers measured from inflammatory processes related to pancreatic autoimmunity, we also measured GAD antibodies. These determinations were performed on plasma specimens frozen at baseline at a central lab. We measured GAD antibodies by radioimmunoassay using human recombinant 115 kD GAD according to manufacturer’s protocol (Kronus, Boise, ID); IL-6 levels by high-sensitivity enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN); sialic acid by enzymatic determination using a colorimetric assay (13) (Roche Diagnostics, Indianapolis, IN); orosomucoid utilizing an immunoturbidimetric technique (Kamiya Biomedical, Seattle, WA); and high sensitivity CRP (Equal Diagnostics, Exton, PA) on a Hitachi 911 automated analyzer. Each analyte, with the exception of sialic acid, was measured in duplicate in the laboratory, with the mean of the duplicate measurements being taken as the value for that sample. Reliability coefficients, measuring between-person variance to the total variance, were obtained analyzing replicate pairs of samples obtained at baseline at one sitting on a subset of subjects. Reliability coefficients were 0.97 for orosomucoid, 0.94 for CRP, 0.98 for GAD, 0.82 for IL-6, and 0.50 for sialic acid. The correlation coefficient for duplicate measurements in separate assays of 61 plasma samples of sialic acid, the marker with the lowest reliability coefficient, was 0.84.

We created a score to indicate low-grade systemic inflammation ranging from 0 to 6, attributing one point for a value greater than the median of the cohort sample for each of the four newly measured inflammation markers (IL-6, CRP, orosomucoid, and sialic acid) and for each of the two inflammation markers available from the baseline cohort measurements (white cell count and fibrinogen).

We defined diabetes on the basis of 1) a reported physician diagnosis, 2) use of antidiabetes medications, 3) a fasting (≥8 h) glucose ≥7.0 mmol/l, or 4) a nonfasting glucose of ≥11.1 mmol/l. For incident diabetes ascertained on the basis of a glucose value, incident date was estimated by linear interpolation between orosomucoid and CRP. Correlations of these markers with elements related to the metabolic syndrome are shown in Table 2. Orosomucoid and CRP presented the highest correlations with these syndrome elements. Among noncases, equivalent numbers were 123 (22%), 203 (35%), 76 (13%), and 170 (30%), respectively.

Median (interquartile range) values in the cohort random sample were as follows: IL-6 1.98 pg/ml (1.32–2.96), CRP 1.41 mg/dl (0.64–3.33), orosomucoid 84 mg/dl (74–99), and sialic acid 90.1 mg/dl (77.3–106.5). Table 1 displays medians and proportions of covariates and of other markers of inflammation for those who developed, or did not develop, incident diabetes. Smokers constituted 21% of cases (21% of African Americans and 20% of whites) and 22% of noncases (28% of African Americans and 21% of whites).

Correlations of a wide, mostly modest range (0.17–0.57) were seen among inflammatory markers, the largest being between orosomucoid and CRP. Correlations of these markers with elements related to the metabolic syndrome are shown in Table 2. Orosomucoid and CRP presented the highest correlations with these syndrome elements. The syndrome elements that most strongly correlated with inflammation markers were waist circumference and BMI; those most weakly correlated were diastolic blood pressure and HDL cholesterol. Correlations of the inflammation score with syndrome elements were generally similar, though frequently slightly weaker, than those seen for orosomucoid and CRP.

Table 3 demonstrates positive associations with incident diabetes for the four newly analyzed inflammation
markers after adjustment for age, center, sex, ethnicity, parental history of diabetes, and hypertension (model 1). After additional adjustment for obesity indexes, glucose, and insulin (model 2), only that of IL-6 was of statistical significance, with those with values in the highest quartile having a 65% higher risk of developing diabetes than those in the lowest quartile (hazard ratio [HR] 1.65, 95% CI 1.01–2.68). In this model, HRs for second and third IL-6 quartiles were 1.18 (0.72–1.95) and 1.02 (0.62–1.71), respectively. With full adjustment, the HR comparing fourth with first quartiles of sialic acid was 1.54 (0.96–2.48) and for CRP was 1.23 (0.74–2.03). The HR comparing extreme quartiles of orosomucoid was close to unity. Removal of individuals positive for GAD antibodies produced little change, as, for example, it only raised the HR comparing extreme quartiles of IL-6 in the fully adjusted model to 1.67 (95% CI 1.01–2.74).

In the cohort random sample, the overall mean (SE) of the inflammation score, adjusted for age, sex, ethnicity, educational level, smoking status, and BMI, was 2.86 (0.08). Among noncases, 11.0% had no markers with above-median values (score = 0), and 8.8% had all markers with above-median values (score = 6). In contrast, among cases, only 2.6% had no markers with above-median values and 21.6% had all markers with above-median values. Values of this score varied considerably in subsets of the cohort random sample, as seen by adjusted means (SE): it was higher in smokers (3.85 ± 0.16) compared with nonsmokers (2.59 ± 0.09) (P < 0.001), in obese (3.82 ± 0.16) compared with overweight (2.93 ± 0.12) and nonoverweight (2.29 ± 0.13) (P < 0.001), and to a certain extent in African Americans (3.06 ± 0.11) compared with whites (2.81 ± 0.09) (P = 0.08). Lesser differences were noted across sex (men 2.79 ± 0.13 vs. women 2.90 ± 0.09, P = 0.48) and educational levels (less than high school graduate 2.79 ± 0.18 vs. high school completed 3.04 ± 0.12 vs. college completed 2.68 ± 0.12; P = 0.046 for high school vs. college completed, but P = 0.62 for less than high school vs. college completed).

Figure 1 displays the HR of developing diabetes across the range of this summary score. Associations were present only in whites (inflammation score–ethnicity

### TABLE 2
Correlations of inflammation markers and score with metabolic and vascular factors related to the metabolic syndrome

<table>
<thead>
<tr>
<th>Element</th>
<th>IL-6</th>
<th>CRP</th>
<th>Orosomucoid</th>
<th>Sialic acid</th>
<th>White blood cell count</th>
<th>Fibrinogen</th>
<th>Inflammation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.08</td>
<td>0.16</td>
<td>0.18</td>
<td>0.11</td>
<td>0.10</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.19</td>
<td>0.35</td>
<td>0.31</td>
<td>0.12</td>
<td>0.10</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.32</td>
<td>0.37</td>
<td>0.34</td>
<td>0.16</td>
<td>0.13</td>
<td>0.22</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI</td>
<td>0.29</td>
<td>0.40</td>
<td>0.32</td>
<td>0.19</td>
<td>0.07</td>
<td>0.24</td>
<td>0.34</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.14</td>
<td>0.20</td>
<td>0.26</td>
<td>0.21</td>
<td>0.20</td>
<td>0.01</td>
<td>0.23</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.12</td>
<td>−0.06</td>
<td>−0.19</td>
<td>−0.09</td>
<td>−0.18</td>
<td>−0.07</td>
<td>−0.14</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.12</td>
<td>0.21</td>
<td>0.21</td>
<td>0.11</td>
<td>−0.02</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.06</td>
<td>0.14</td>
<td>0.17</td>
<td>0.08</td>
<td>−0.04</td>
<td>0.09</td>
<td>0.09</td>
</tr>
</tbody>
</table>

### TABLE 3
Adjusted* associations (fourth vs. first quartile) of IL-6 and acute-phase proteins with incident diabetes: ARIC Study, 1987–1998

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 HR</th>
<th>95% CI</th>
<th>Model 2 HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>2.50</td>
<td>1.74–3.59</td>
<td>1.65</td>
<td>1.01–2.68</td>
</tr>
<tr>
<td>CRP</td>
<td>2.76</td>
<td>1.88–4.07</td>
<td>1.23</td>
<td>0.74–2.03</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>2.31</td>
<td>1.60–3.32</td>
<td>1.11</td>
<td>0.68–1.78</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>1.85</td>
<td>1.29–2.66</td>
<td>1.54</td>
<td>0.96–2.48</td>
</tr>
</tbody>
</table>

*Adjusted through proportional hazards modeling for the following covariates: age, center, sex, ethnicity, parental history of diabetes, and hypertension (model 1); model 1 covariates plus BMI, WHR, fasting glucose, and fasting insulin (model 2).
interaction, \( P = 0.001 \) in the less-adjusted model, \( P = 0.005 \) in the final model). In fact, HRs <1.0 were found when comparing extreme quartiles of five of the six inflammation markers among African-American men (data not shown). HRs of developing diabetes among whites with above-median values for four, shown). HRs of developing diabetes among whites with interaction markers among African-American men (data not

Additional adjustment for mean intimal-medial wall thickness, a measure of subclinical atherosclerosis, did not alter the association. The association was slightly weaker among those with above-median subclinical atherosclerosis (interaction HR = 0.85, interaction \( P = 0.24 \)).

The inflammation score–incident diabetes association was somewhat stronger in white nonsmokers when cases defined by only a fasting glucose of between 7.0 and 7.8 mmol/l were excluded (HR = 1.27, 95% CI 1.07–1.50 for a one-unit change in the score variable, \( P = 0.006 \)).

**DISCUSSION**

The present report, consistent with previous investigations of the inflammation-diabetes association (2–11,18), demonstrates that subclinical elevations of IL-6, CRP, orosomucoid, and sialic acid are related to the development of diabetes in middle-aged adults. An inflammation score composed of these four markers plus white cell count and fibrinogen showed the association of inflammation with diabetes to be heterogeneous across smoking and ethnicity categories. Among white nonsmokers, the association was large and generally graded. The association decreased considerably after adjustment for obesity indexes. Nevertheless, in fully adjusted models, those with above-median values for four or more of the six markers had a risk of developing diabetes two to four times that of those with no markers above median values. Adjustment for subclinical atherosclerosis did not alter the association, nor did it vary appreciably in those with more or less subclinical atherosclerosis. The findings do not appear to be explained by pancreatic autoimmune disease, as the exclusion of GAD antibody–positive cases did not change the results.

More detailed examination of the association revealed remarkable heterogeneity, associations being present in whites but not in African Americans and in nonsmokers but not in smokers. The association, though present in those with BMI <25 kg/m\(^2\), was strongest in the obese. This heterogeneity in association may in part explain the variation seen across previously reported studies. The two studies reporting the largest association with high CRP levels were the Women’s Health Study (3) and the West of Scotland Coronary Prevention Study (8), both of which were predominantly composed of white subjects (91% and close to 100%, respectively). Moreover, the rate of smoking was low (~12%) in the former study, and although high (~43%) at baseline in the latter one, as it was a clinical trial to prevent coronary disease, the fraction of smokers who quit during follow-up may have been large. Finally, the Insulin Resistance Atherosclerosis Study (IRAS) (11), which did not find an association of diabetes with CRP, had a relatively low percentage of whites (40%) and a large contingent of African Americans (27%).

It is increasingly recognized that a low-grade systemic inflammation precedes and predicts the development of both diabetes and atherothrombotic diseases. New facts that may explain this association are emerging. The mild inflammatory state is closely related to obesity and insulin resistance. Adipocytes, especially in the obese, secrete a
number of proinflammatory cytokines (19), some of which have been shown to directly inhibit insulin signaling (20). Adipocytokines probably act through master proinflammatory regulators such as those of the nuclear factor-κB (21) and the c-Jun NH2-terminal kinase (JNK)/AP-1 signaling pathways (22) to modulate the expression of genes coding for many inflammatory proteins and to alter insulin signaling. These actions have two basic consequences: first, to augment and perpetuate the proinflammatory diathesis, and second, to decrease insulin sensitivity. Some adipocytokines may also cause vasoconstriction (19). Vasoconstriction appears to diminish insulin action (23). In fact, arteriolar constriction, seen in the retina, has recently been shown to predict diabetes (24).

Capturing these pathophysiologic processes and others potentially involved in the generation of a chronic mild inflammatory state through measurement of circulating factors has, to date, mostly involved nonspecific markers of inflammation, with analytes being investigated one at a time. We have chosen to characterize this inflammatory state with a score. Our score, a mix of one cytokine, several acute-phase reactants (some produced by adipocytes), and the leukocyte count, is admittedly ad hoc. Given that multiple pathways are probably involved in the interaction between insulin action and the innate immune system (25), the use of a summary measure of several markers conceptually makes sense. As new knowledge becomes available, more conceptually based summary measures should be better able to capture the nature and scope of this inflammatory state.

Obesity also decreases adipocyte expression of adiponectin, which has anti-inflammatory and insulin-sensitizing effects (26). The important role for adipocytokines in this process may explain the somewhat stronger inflammation score–incident diabetes association we found with higher BMI.

Insulin, on the other hand, besides stimulating glucose uptake, has recently been shown to have multiple anti-inflammatory actions (27). In this regard, the insulin-resistant state may not only be one of impaired glucose uptake, but also one of impaired ability to dampen proinflammatory signaling. Thus, the multiple signaling interactions between inflammatory mediators and insulin appear to be the molecular substrate for the association we have described.

Moreover, the importance of adipose tissue in the production of an inflammatory response may explain the major reduction in the inflammation marker–diabetes associations seen after adjustment for obesity indexes found here and in nearly all other studies. That the association remained large and statistically significant in white nonsmokers after full adjustment suggests that it does reflect direct causal links between inflammatory mediators generated by adipose tissue, such as tumor necrosis factor-α, adiponectin (6) and angiotensin II, and diabetes. However, it remains possible that the markers we investigated are not causally linked to diabetes development, that obesity causes diabetes predominantly through pathways not involving inflammatory mediators, and that the associations that remain after full adjustment are the result of residual confounding due to obesity and hyperglycemia. On the other hand, it should be noted that inflammation markers demonstrate greater within-individual variation than BMI and WHR (28). As such, modeling of the inflammation marker–diabetes associations when adjusted for obesity indexes may not adequately reflect the importance of obesity-related inflammatory processes. Finally, as reported previously by the ARIC Study, several inflammation markers also predict weight gain (29). Obesity, if itself caused in part by inflammatory processes, may be one pathway by which these processes cause diabetes, even if obesity causes diabetes via noninflammatory pathophysiologic mechanisms. As such, addition of obesity indexes in models would result in over adjustment.

Our finding that the association is limited to nonsmokers is consistent with a previous report that described in Japanese workers a lesser association of an elevated white cell count with incident diabetes or impaired fasting glucose among smokers (10). In the Japanese study, however, the interaction was not statistically tested.

Smoking generates systemic inflammation, which is related to resulting chronic pulmonary inflammation and to the proinflammatory molecules in cigarette smoke (30,31). In agreement with this, smokers in our study had notably higher values of our composite inflammation score. However, smoking appears to activate proinflammatory macroregulatory molecules differentially, with one study showing a blunted activation of JNK (30), which has recently been suggested to be important in weight gain and obesity-related diabetes (22). Additionally, nicotine, through the nicotinic receptor, has recently been shown to have anti-inflammatory effects (32–34). If adipocytes have nicotinic receptors similar to those recently shown to exist on macrophages, then smoking, though generating an overall proinflammatory state, could selectively inhibit the effects of inflammation on adipocyte metabolism and adipocytokine production, a mechanism that might explain the heterogeneity found.

The recent report of a positive association between CRP and incident diabetes in Mexican women but not in men (5) might, in fact, be due to the modifying effects of smoking and obesity. In that report, 48% of men smoked versus only 20% of women. Women had a mean BMI of 28.6 kg/m2, while men had a BMI of only 26.8 kg/m2.

Our observation that inflammation markers were not associated with diabetes in African Americans is consistent with the reported absence of a white cell count–incident diabetes association in African-American participants in the National Health and Nutrition Examination Survey (NHANES) I cohort (9). The association of diabetes with other inflammation markers, to our knowledge, has not been previously investigated in African Americans. African Americans had a nonsignificantly greater inflammation score than whites. They also have lower white cell counts than whites (35,36), suggesting that the character of the systemic inflammatory burden may differ according to ethnicity. African Americans also have a notably different composition of metabolic syndrome elements, with more hypertension and diabetes but less dyslipidemia (37). They were found to be somewhat less insulin sensitive than Hispanic and non-Hispanic whites in the IRAS. IRAS also found the association between insulin sensitivity and carotid intimal media thickness to differ by ethnicity—a positive association being seen in whites and a tendency
toward a negative one being present in African Americans (38). Along the same lines, the association between insulin sensitivity and blood pressure has been shown to be weaker in African Americans (39). Despite the lack of an inflammation–incident diabetes association, African Americans have a greater prevalence and incidence of diabetes than whites. The basis for all of these differences remains unexplained, and our finding of a possible difference in the causality of diabetes between whites and African Americans requires further investigation.

Whatever the explanation for the variability described in the inflammation marker–incident diabetes across population subgroups, the heterogeneity described is large, suggesting that not all sources of a low-grade systemic inflammatory state increase risk for diabetes.

Potential limitations to our study merit comment. Although acute-phase proteins appear to be stable on long-term storage, it is possible that such storage has led to the degradation of one or more of our markers. Additionally, as our analyses were based on fasting samples, we may not have fully captured the effects of inflammation in the postprandial period (27). If so, our findings may underestimate the strength of the true associations. Selection bias, due to either a participant not returning for follow-up or not having sample available for measurement, could conceivably have influenced our results. However, we have little a priori reason to believe that the association between inflammatory elements and incident diabetes should be stronger or weaker among those lost to follow-up or without available sample. Also, reverse causality should be considered, as recent studies have shown that hyperglycemia, by producing oxidative stress, is itself proinflammatory (40). Although it is possible that a greater inflammatory score merely reflects greater insulin resistance and resultant greater postprandial glycemia at baseline, and thus a greater predisposition to diabetes, such an explanation cannot account for the heterogeneity in the inflammation and diabetes association we report. A final limitation is that epidemiologic studies are in general restricted in their ability to assess independent effects of interrelated variables, such as obesity, inflammation, glucose, and insulin resistance, especially when they present different measurement errors.

In conclusion, these findings provide further evidence that a low-grade systemic inflammation precedes and predicts the development of diabetes in adults, at least in white nonsmokers. Stronger associations in the obese, unrelated to pancreatic autoimmunity, suggest that the outcome in question is indeed type 2 diabetes. The findings support the hypothesis that diabetes is an inflammatory as well as a metabolic disease process. Additional heterogeneity in associations suggests that not all sources of low-grade inflammation will equally increase diabetes risk.

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