Leukocyte Count, Erythrocyte Sedimentation Rate, and Diabetes Incidence in a National Sample of US Adults

Earl S. Ford

Emerging data suggest that inflammation may play a role in the etiology of diabetes mellitus. Because few prospective studies have addressed this issue, the author examined the relation between leukocyte count and erythrocyte sedimentation rate and diabetes incidence using data from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (from 1971–1975 to 1992–1993). Of 8,352 participants included in the analysis, 878 developed incident diabetes during the approximately 20-year follow-up. After adjustment for age, smoking status, systolic blood pressure, cholesterol concentration, use of antihypertensive medication, recreational exercise, nonrecreational activity, alcohol use, and body mass index, the hazard ratios from proportional hazards for participants with a leukocyte count of ≥9.1 × 10^9/liter compared with participants with a leukocyte count of ≤5.7 × 10^9/liter were 1.33 (95% confidence interval (CI): 0.81, 2.19) for men and 1.68 (95% CI: 1.21, 2.34) for women. The adjusted hazard ratios for participants with an erythrocyte sedimentation rate of ≥26 mm/hour compared with participants with an erythrocyte sedimentation rate of ≤5 mm/hour were 1.85 (95% CI: 0.97, 3.54) for men and 0.83 (95% CI: 0.47, 1.44) for women. These results provide limited support to the hypothesis that inflammation is an etiologic factor for diabetes. Am J Epidemiol 2002;155:57–64.

The incidence and prevalence of diabetes mellitus in the United States continue to escalate largely in response to the continuously increasing prevalence of obesity. About 16 million people in the United States are estimated to have diabetes, and the number is expected to grow to 22 million by the year 2025 (1, 2). The human and economic burden generated by this disease is enormous and growing. In 1997, the economic costs were estimated to be about 100 billion dollars (3).

The pathogenesis of type 2 diabetes mellitus is becoming better understood. Obesity, the major modifiable risk factor for diabetes, was known to be strongly associated with insulin resistance, which strongly predisposed to developing diabetes. Until recently, the mechanisms linking obesity to insulin resistance were not understood. Because of advances in molecular biology, the genetic factors and cellular processes responsible for this transition are coming into focus. Research is now revealing the critical role that adipocytes play in the development of insulin resistance by producing various cytokines and hormones (4, 5).

The possibility that excess weight is associated with a state of low-grade inflammation (6, 7) has heightened interest in the role of inflammation in the pathophysiology of diabetes mellitus (8). Some epidemiologic data, mostly from cross-sectional studies, have shown that diabetes and its precursor states are associated with increased concentrations of several inflammatory markers (6, 8, 9–19). Only one prospective study has explored the relations between leukocyte count or leukocyte populations and diabetes incidence (20). Whether leukocytes are involved in the pathogenesis of type 2 diabetes is unknown. Nevertheless, in prospective studies, leukocyte count has consistently been shown to be a risk factor for all-cause mortality (21) and coronary heart disease (22). In addition, results of fewer studies have suggested that white blood cell count may also be directly associated with an increased risk for cancer (23, 24), cerebrovascular disease (25), and hypertension (26).

To explore the relations between leukocyte count and erythrocyte sedimentation rate (a nonspecific marker for inflammation) and incident diabetes, I used data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS).

MATERIALS AND METHODS

From 1971 through 1975, a representative sample of the US civilian population participated in the First National Health and Nutrition Examination Survey (NHANES I). The original sample was selected by using a complex sampling design so that results would be representative of the noninstitutionalized civilian population. Details of the
of the NHEFS have been published elsewhere (27–33). Participants aged 25–74 years (n = 14,407) in the NHANES I were subsequently followed up through 1992–1993 and thus became part of the NHEFS.

During the course of the follow-up study, up to four attempts were made to contact participants or their surrogates in person and, during later follow-ups, by telephone as well: in 1982–1984, 1986 (only participants aged ≥55 years), 1987, and 1992–1993. Permission was requested to obtain hospital records. Deaths were identified through searches of the National Death Index, enrollee files of the Health Care Financing Administration, and other tracing mechanisms. A participant was considered deceased only if a death certificate had been received or a proxy interview had been completed to verify the death. Death certificates have been obtained for 97 percent of participants who died through 1993.

Participants had incident diabetes if 1) they confirmed that they had ever been told by a doctor that they had diabetes during any of the four follow-up contacts; or 2) a hospitalization record listed the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification, code 250 on any one of 10 diagnoses on the hospital discharge sheet; or 3) the death certificate included the ICD-9 code 250. Participants who reported that they had diabetes were asked the year of disease onset. The midpoint of that year was designated as the date of onset. For participants who did not report a year of onset, I assigned the midpoint between the last date of known contact and the date of the most recent interview. The date of onset was chosen as the date the condition was first reported or recorded in institutional records or death certificates.

Participants who reported at baseline that they had diabetes were considered prevalent cases, as were participants who during later follow-up contacts reported a date of onset that occurred in the year of their baseline interview or earlier, and they were excluded from the analyses.

White blood cell counts were measured in duplicate on a Coulter FN cell counter (Beckman Coulter, Inc., Fullerton, California) (33). The erythrocyte sedimentation rate was measured by using an adaptation of the Wintrobe method (30).

Baseline covariates included age, race or ethnicity (African American, White), education (years), cigarette smoking (never, former, current), systolic blood pressure (mmHg), use of antihypertensive medication (yes/no), serum cholesterol concentration (mg/dl), body mass index (kg/m²), alcohol consumption (0, 1–2, ≥3 drinks per day), recreational exercise (much, moderate, little or no exercise), and nonrecreational exercise (very active, moderately active, quite inactive). For smoking, I used a variable constructed in part from responses obtained during the baseline interview and in part from the first follow-up interview (34, 35). Two questions were used to create the categories of smoking: “Have you smoked at least 100 cigarettes during your entire life?” and “Do you smoke cigarettes now?” Cholesterol was measured by using a modification of the Abell-Kendall method.

Two-sample comparisons of categorical and continuous variables were made by using chi-squared tests and t tests, respectively. With the use of direct standardization, baseline characteristics and incidence rates were standardized to the age distribution from the 1980 US Census. Person-time was calculated for each participant from the time of entry into the study until one of the following conditions occurred: 1) the participant developed diabetes; 2) the participant died or left the study; or 3) follow-up was completed in 1993. The independent association between leukocyte count and erythrocyte sedimentation rate at baseline and diabetes mellitus incidence was examined by using proportional hazard models. In these models, leukocyte counts and erythrocyte sedimentation rate were entered as approximate quintiles. To account for the complex sampling design, SUDAAN software (36) was used in all analyses except for the evaluation of proportionality assumptions that were done with SAS software (37). Analyses showed that the hazards were proportional.

RESULT

Of the 14,407 participants of the NHEFS, 9,814 had a value for white blood cell count and erythrocyte sedimentation rate. After participants who were last to follow-up were excluded, 9,436 remained. The author excluded participants with a race or ethnicity other than White or African American (n = 172), as well as participants with incomplete information to establish diabetes incidence, participants with diabetes prevalence, pregnant women, and participants with missing data for covariates. These exclusions reduced the analytical sample to 8,352 participants, of whom 878 developed diabetes during the course of the study.

Participants who developed diabetes were older than participants who remained free of the disease (table 1). After adjustment for age, the data showed that participants who developed diabetes were less likely to be White, had fewer years of education, had higher systolic blood pressure, were more likely to be taking antihypertensive medication, had a higher serum cholesterol concentration, were heavier, were more likely to be sedentary, and had a higher erythrocyte sedimentation rate and leukocyte count than participants who remained free of diabetes.

The unadjusted incidence rates and corresponding hazard ratios increased as the erythrocyte sedimentation rate increased (table 2). After adjustment for age, sex, smoking status, systolic blood pressure, cholesterol concentration, use of antihypertensive medication, recreational exercise, nonrecreational activity, alcohol use, and body mass index, the association between erythrocyte sedimentation rate and diabetes incidence was no longer significant. Although it appeared that the association between erythrocyte sedimentation rate and diabetes incidence was stronger among men than women, sex was not a significant effect modifier of this association (p = 0.304). Race was also not a significant effect modifier (p = 0.236).

White blood cell count was significantly associated with diabetes incidence in unadjusted, age-adjusted, and multiple-adjusted analyses (table 3). The incidence rate was lowest for participants in the quintile with a white blood cell count of 5.8–6.7 × 10^9/liter. In addition to calculating hazard
TABLE 1. Age-adjusted means or percentages (standard error) of selected characteristics at baseline examination among adults aged 25–74 years, by diabetes status, National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, from 1971–1975 to 1992–1993

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants with incident diabetes mellitus (n = 878)</th>
<th>Participants without incident diabetes mellitus (n = 7,474)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.6 (0.5)</td>
<td>46.2 (0.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Men (%)</td>
<td>45.8 (2.6)</td>
<td>45.9 (0.7)</td>
<td>0.976</td>
</tr>
<tr>
<td>White (%)</td>
<td>81.4 (2.6)</td>
<td>90.7 (0.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.7 (0.2)</td>
<td>11.6 (0.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>38.9 (2.9)</td>
<td>40.7 (0.9)</td>
<td>0.526</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>139.1 (1.3)</td>
<td>130.3 (0.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Antihypertensive medication (%)</td>
<td>21.7 (2.5)</td>
<td>11.3 (0.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cholesterol concentration (mg/dl)</td>
<td>223.3 (2.4)</td>
<td>218.7 (0.9)</td>
<td>0.048</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8 (0.3)</td>
<td>25.0 (0.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alcohol intake (drinks/day)</td>
<td>0.5 (0.1)</td>
<td>0.6 (0.0)</td>
<td>0.114</td>
</tr>
<tr>
<td>Recreational exercise (% little or no exercise)</td>
<td>52.2 (2.9)</td>
<td>42.2 (1.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Nonrecreational activity (% quite inactive)</td>
<td>10.8 (1.5)</td>
<td>9.5 (0.6)</td>
<td>0.404</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hour)</td>
<td>16.2 (0.8)</td>
<td>13.8 (0.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White blood cell count (1,000/ml)</td>
<td>7.9 (0.1)</td>
<td>7.5 (0.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

DISCUSSION

In this study of US adults, a baseline determination of leukocyte count was significantly associated with diabetes incidence over a period of approximately 20 years. Participants’ risk of developing diabetes increased progressively as their leukocyte count increased, suggesting a dose-response relation. Thus, diabetes mellitus joins other conditions—such as coronary heart disease, stroke, hypertension, and cancer—for which leukocyte count appears to be associated with an increased risk (38). These results are consistent with the theory that inflammation has a role in the etiology of diabetes. However, the erythrocyte sedimentation rate was not significantly associated with diabetes mellitus incidence after data were adjusted for various possible confounders.

The results from the NHEFS are consistent with those previously published from the Atherosclerosis Risk in Communities (ARIC) Study (20). In that study of 12,330 men and women aged 45–64 years who were followed for an average of 7 years, 1,335 participants developed diabetes. After adjustment for age, sex, center, ethnic origin, baseline glucose concentration, family history of diabetes, physical activity, smoking, body mass index, and waist/hip ratio, participants with a white blood cell count of >6.9 × 10^9/liter had an odds ratio of 1.5 (95 percent CI: 1.3, 1.8) compared with participants with a white blood cell count of <5.7 × 10^9/liter. In comparison, I found a hazard ratio of 1.50 (95 percent CI: 1.12, 1.99) for participants with a white blood cell count of >9.0 × 10^9/liter compared with participants with a white blood cell count of <5.8 × 10^9/liter using the NHEFS data. A recent report from the West of Scotland Coronary Prevention Study showed that the risk of developing diabetes was lower among participants who were assigned to using pravastatin therapy than among participants not assigned to such therapy (39). The antiinflammatory properties of statins may have accounted for these results. In a cross-sectional study of 4,096 men aged 31–45 years, leukocyte counts showed a small but significant correlation with fasting glucose concentrations (40). In another study of 90 men aged 38 years, the white blood cell count was significantly associated with components of the metabolic syndrome, including 2-hour plasma glucose concentrations (41).

The mechanisms through which an increased leukocyte count might increase a person’s risk of diabetes remain to be

<table>
<thead>
<tr>
<th>Erythrocyte sedimentation rate (mm/hour)</th>
<th>No. of cases</th>
<th>No. of person-years</th>
<th>Unadjusted incidence/100,000 person-years</th>
<th>Age-adjusted incidence/100,000 person-years</th>
<th>Hazard ratio (95% confidence interval)</th>
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<tbody>
<tr>
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<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Total sample (878 people with diabetes/8,352 in sample)</td>
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</tr>
<tr>
<td>1–5</td>
<td>126</td>
<td>26,354</td>
<td>419.0</td>
<td>483.0</td>
<td>1.00</td>
</tr>
<tr>
<td>6–10</td>
<td>158</td>
<td>28,184</td>
<td>481.6</td>
<td>529.2</td>
<td>1.13 (0.90, 1.43)</td>
</tr>
<tr>
<td>11–16</td>
<td>175</td>
<td>30,739</td>
<td>499.5</td>
<td>501.2</td>
<td>1.16 (0.89, 1.50)</td>
</tr>
<tr>
<td>17–25</td>
<td>211</td>
<td>27,555</td>
<td>699.5</td>
<td>663.2</td>
<td>1.65 (1.21, 2.26)</td>
</tr>
<tr>
<td>≥26</td>
<td>208</td>
<td>20,695</td>
<td>942.8</td>
<td>870.5</td>
<td>2.23 (1.62, 3.07)</td>
</tr>
<tr>
<td>p for overall test‡</td>
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<td>&lt;0.001</td>
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<td>1.02 (1.02, 1.03)</td>
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<tr>
<td>Men (537 with diabetes/3,312 in sample)</td>
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<td></td>
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<tr>
<td>1–5</td>
<td>89</td>
<td>17,849</td>
<td>422.0</td>
<td>492.4</td>
<td>1.00</td>
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<tr>
<td>6–10</td>
<td>90</td>
<td>12,232</td>
<td>581.5</td>
<td>630.1</td>
<td>1.38 (1.02, 1.87)</td>
</tr>
<tr>
<td>11–16</td>
<td>72</td>
<td>8,507</td>
<td>697.0</td>
<td>676.3</td>
<td>1.61 (1.16, 2.25)</td>
</tr>
<tr>
<td>17–25</td>
<td>63</td>
<td>6,263</td>
<td>939.2</td>
<td>821.3</td>
<td>2.32 (1.48, 3.64)</td>
</tr>
<tr>
<td>≥26</td>
<td>43</td>
<td>3,597</td>
<td>1,538.6</td>
<td>1,349.6</td>
<td>3.91 (2.17, 7.03)</td>
</tr>
<tr>
<td>p for overall test</td>
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<td>&lt;0.001</td>
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<tr>
<td>Continuous</td>
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<td>1.04 (1.03, 1.05)</td>
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<tr>
<td>Women (521 with diabetes/5,040 in sample)</td>
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<tr>
<td>1–5</td>
<td>37</td>
<td>8,505</td>
<td>409.6</td>
<td>459.2</td>
<td>1.00</td>
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<tr>
<td>6–10</td>
<td>68</td>
<td>15,951</td>
<td>371.1</td>
<td>408.6</td>
<td>0.88 (0.49, 1.58)</td>
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<td>11–16</td>
<td>103</td>
<td>22,232</td>
<td>394.3</td>
<td>399.0</td>
<td>0.93 (0.53, 1.63)</td>
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<tr>
<td>17–25</td>
<td>148</td>
<td>21,292</td>
<td>613.8</td>
<td>603.2</td>
<td>1.45 (0.81, 2.60)</td>
</tr>
<tr>
<td>≥26</td>
<td>165</td>
<td>17,097</td>
<td>818.8</td>
<td>768.3</td>
<td>1.94 (1.09, 3.44)</td>
</tr>
<tr>
<td>p for overall test</td>
<td></td>
<td></td>
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<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Continuous</td>
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<td>1.03 (1.02, 1.04)</td>
</tr>
</tbody>
</table>

* Weighted estimate.
† Adjusted for age, sex (except sex-specific models), smoking status, systolic blood pressure, cholesterol concentration, use of antihypertensive medication, recreational exercise, nonrecreational activity, alcohol use, and body mass index.
‡ Wald chi-squared test.

elucidated. In contrast to atherosclerotic lesions of the coronary arteries where increased monocytic cellularity can be demonstrated on histopathologic examination, no inflammatory infiltrate of the pancreas among people with type 2 diabetes has been shown. Thus, it would appear unlikely that leukocytes might contribute directly to harming the β cells of the pancreas that are responsible for the production and secretion of insulin by local release of various factors. Perhaps the raised leukocyte count reflects the effects of a low-grade inflammation initiated by obesity or other mechanisms. Because cytokines can raise a person’s leukocyte count, leukocyte count may act as a surrogate marker for such cytokines.

Although the erythrocyte sedimentation rate showed a fairly strong association with diabetes incidence among men, adjustment for various confounders seriously attenuated the magnitude of this association. The hazard ratio suggested that men with an erythrocyte sedimentation rate in the top quartile may have been at higher risk of diabetes than men with an erythrocyte sedimentation rate in the lowest quartile, but because the confidence interval failed to exclude unity, this hazard ratio does not provide strong support for the hypothesis that inflammation may be important in the etiology of diabetes. The erythrocyte sedimentation rate has been widely used as a nonspecific indicator of inflammation to help diagnose conditions and follow disease activity. Its utility has often been compared with that of other acute phase reactants including C-reactive protein, particularly in the settings of infections and rheumatic conditions. No clear consensus about the superiority of any one of these measurements of inflammation has emerged. Many of these comparisons were performed at a time when lower sensitivity C-reactive protein assays were commonly used. Comparisons between the erythrocyte sedimentation rate
and C-reactive protein or other acute phase reactants in predicting cardiovascular disease mortality or incidence have apparently not been conducted. In previous analyses of NHEFS data, the erythrocyte sedimentation rate was shown to predict the risk of coronary heart disease and stroke incidence among a subset of adults (42, 43).

Mounting evidence implicates inflammation in the pathogenesis of type 2 diabetes. Researchers conducting cross-sectional studies have noted direct associations between C-reactive protein and glucose concentrations, glycosylated hemoglobin concentrations, metabolic syndrome, and diabetes status (6, 9–19). Furthermore, inverse associations have been reported for C-reactive protein and measures of insulin resistance (6, 17, 18). In addition, elevated concentrations of other markers of inflammation, such as orosomucoid and sialic acid, have been associated with an increased risk of diabetes (20).

Whether inflammatory markers themselves have a role in producing insulin resistance and diabetes remains speculative. It is striking that many markers of inflammation have been associated with insulin resistance or diabetes, raising questions about the specificity of the associations. Furthermore, evidence that acute phase reactants directly affect cellular processes that lead to insulin resistance and glucose intolerance is scant. An additional difficulty in attributing a causal role to acute phase reactants is that other disease processes can lead to elevations in the concentrations of these substances. Generally, it is now agreed that atherosclerosis involves a significant inflammatory component. The vast majority of people with diabetes will die of some form of cardiovascular disease. In addition, people with diabetes are at increased risk of developing infections that can also raise concentrations of proinflammatory cytokines and acute phase reactants. People destined to

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<table>
<thead>
<tr>
<th>White blood cell count (1,000/ml)</th>
<th>No. of cases</th>
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<th>Age-adjusted incidence/100,000 person-years</th>
<th>Hazard ratio (95% confidence interval)</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1–5.7</td>
<td>160</td>
<td>28,955</td>
<td>484.9</td>
<td>469.4</td>
<td>1.00</td>
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<tr>
<td>5.8–6.7</td>
<td>153</td>
<td>27,386</td>
<td>442.6</td>
<td>431.2</td>
<td>0.92 (0.68, 1.24)</td>
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<tr>
<td>6.8–7.7</td>
<td>174</td>
<td>26,755</td>
<td>612.4</td>
<td>598.9</td>
<td>1.28 (1.00, 1.62)</td>
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<td>7.8–9.0</td>
<td>198</td>
<td>27,422</td>
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<td>193</td>
<td>23,008</td>
<td>743.0</td>
<td>766.7</td>
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<td>&lt;0.001</td>
<td>0.005</td>
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<td>1.06 (1.03, 1.09)</td>
<td>1.05 (1.02, 1.08)</td>
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<td></td>
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<tr>
<td>Men (357 with diabetes/3,312 in sample)</td>
<td>62</td>
<td>9,819</td>
<td>527.9</td>
<td>515.7</td>
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<td>9,689</td>
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<td>5.8–6.7</td>
<td>80</td>
<td>9,732</td>
<td>802.7</td>
<td>817.6</td>
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</tr>
<tr>
<td>7.8–9.0</td>
<td>71</td>
<td>8,570</td>
<td>666.4</td>
<td>735.8</td>
<td>1.04 (0.97, 1.06)</td>
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<td>0.096</td>
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<td>1.03 (0.99, 1.07)</td>
<td>1.03 (0.97, 1.08)</td>
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<td></td>
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<tr>
<td>Women (521 with diabetes/5,040 in sample)</td>
<td>98</td>
<td>19,135</td>
<td>455.0</td>
<td>435.9</td>
<td>0.87 (0.59, 1.28)</td>
</tr>
<tr>
<td>2.1–5.7</td>
<td>92</td>
<td>17,697</td>
<td>395.2</td>
<td>390.3</td>
<td>1.04 (0.75, 1.44)</td>
</tr>
<tr>
<td>5.8–6.7</td>
<td>94</td>
<td>17,023</td>
<td>469.4</td>
<td>456.9</td>
<td>1.22 (0.87, 1.72)</td>
</tr>
<tr>
<td>6.8–7.7</td>
<td>115</td>
<td>16,785</td>
<td>550.6</td>
<td>567.2</td>
<td>1.82 (1.27, 2.60)</td>
</tr>
<tr>
<td>7.8–9.0</td>
<td>122</td>
<td>14,438</td>
<td>810.9</td>
<td>802.1</td>
<td>0.99 (0.66, 1.49)</td>
</tr>
<tr>
<td>p for overall test</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.09 (1.06, 1.13)</td>
<td>1.09 (1.06, 1.13)</td>
<td>1.08 (1.05, 1.12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Weighted estimate.
† Adjusted for age, sex (except sex-specific models), smoking status, systolic blood pressure, cholesterol concentration, use of antihypertensive medication, recreational exercise, nonrecreational activity, alcohol use, and body mass index.
‡ Wald chi-squared test.
develop diabetes may also be at increased risk of developing such infections. Ruling out both clinical and subclinical disease in epidemiologic studies of the associations between acute phase reactants and glucose intolerance may be difficult. Finally, determining which confounders should be controlled for in these types of analyses is not clear, nor can residual confounding be ruled out. Most studies control for body mass index and perhaps some measure of body fat distribution. However, it is unclear whether these measures can completely adjust for obesity in all its complexity. On the other hand, researchers recently reported that fibrinogen concentration and white blood cell count predicted weight gain (44). Therefore, controlling for body mass index could constitute an overadjustment. When I reran the multiple-adjusted model for white blood cell count for all participants in table 3 after removing body mass index from the model, the hazard ratios were 1.04 (95 percent CI: 0.77, 1.40), 1.47 (95 percent CI: 1.13, 1.93), 1.32 (95 percent CI: 0.96, 1.81), and 1.86 (95 percent CI: 1.38, 2.52) for quintiles 2 through 5, respectively. Finally, proinflammatory cytokines that result in the production of acute phase reactants are more likely to participate in the pathophysiology of glucose intolerance than the acute phase reactants themselves.

Several lines of research are providing insights into the role of inflammation in the pathophysiology of diabetes. Various insults, including free radicals and cytokines (such as tumor necrosis factor-α and interleukin-1β), can disturb normal endothelial functioning. This disturbance in turn can impair insulin-mediated vasodilatation, resulting in delays in transendothelial insulin transport, reduced glucose disposal, and eventually insulin resistance (45, 46). Furthermore, the inflammatory process produces reactive oxygen species that injure pancreatic β cells, which are characterized by poor intracellular antioxidant defenses and are susceptible to oxidative damage (47). Free radicals have been shown to disrupt insulin action and total body glucose disposal (48, 49). Cytokines such as tumor necrosis factor-α may cause insulin resistance by impairing insulin signaling and indirectly by stimulating free fatty acid production, which may also increase insulin resistance. Furthermore, tumor necrosis factor-α, interleukin-1, interleukin-6, and free fatty acids may affect β-cell function (50, 51).

Several limitations of this study should be acknowledged. Diabetes incidence was established from self-reports, hospitalization discharges, and death certificates. These sources provide less rigorous definitions of diabetes than the results of oral glucose tolerance tests or measurements of fasting glucose concentrations. Some misclassification inevitably resulted. If this misclassification was nondifferential, the likely effect was an underestimate of some of the associations. Nevertheless, endpoints based on these data sources are commonly used, and known risk factors for diabetes such as excess weight are strongly associated with diabetes defined by using these data sources. In addition, participants with evidence of inflammation may be more likely to be seen by health care providers and may be more likely to be diagnosed with diabetes than participants without evidence of inflammation, thus possibly producing the associations observed in this study. Although I cannot entirely rule out this possibility, several considerations bolster the findings of this study. First, the results from the NHEFS are very consistent with those from the Atherosclerosis Risk in Communities Study in which the authors based their definition of incident diabetes mellitus on harder criteria (20). Second, during the long follow-up period of this study (about 20 years), it is very likely that the vast majority of participants were seen by a physician one or more times, given that large numbers of Americans visit a physician each year. Because chemistry panels that include a glucose determination are routinely performed on patients, many participants who developed diabetes were probably identified. Third, to gauge the degree of possible ascertainment bias, I examined the cross-sectional data from the Third National Health and Nutrition Examination Survey to see if the proportion of all participants with diabetes—both diagnosed cases (from self-report) and undiagnosed cases (using fasting glucose concentrations’ criteria of ≥126 mg/dl)—who reported having diabetes varied across the quintiles of white blood cell count as defined for the NHEFS analysis. These proportions were 0.592, 0.699, 0.602, 0.673, and 0.648 for quintiles 1 through 5 of white blood cell count, respectively (p = 0.756). An additional limitation was that participants with type 1 diabetes could not be distinguished from those with type 2 diabetes. However, the overwhelming majority of participants who develop newly diagnosed diabetes after the age of 30 years are more likely to have type 2 diabetes.

In conclusion, the NHEFS data show that leukocyte count is significantly and positively related to diabetes incidence in a dose-response fashion. The data were less conclusive about an association between the erythrocyte sedimentation rate and diabetes incidence. Thus, the results from this study using leukocyte count and erythrocyte sedimentation rate, which are perhaps less specific indicators of inflammation, provide limited support to emerging data that suggest that inflammation may impact the pathogenesis of diabetes. Because only a few prospective studies have examined the role of inflammation in the development of diabetes, more research in this area is warranted. Studies that include both cytokines and hormones implicated in insulin resistance as well as various acute phase reactants will be necessary to sort out their independent effects and to provide insights into biologic mechanisms. Because it is unclear whether many of the acute phase reactants truly participate in the pathogenesis of diabetes, additional research into the possible biologic mechanisms of these substances is needed. Despite these uncertainties, this emerging and promising field of investigation may provide novel insights into the disease mechanisms for diabetes and possibly into new approaches for the prevention and treatment of this disease and its complications.

REFERENCES


21. Grimm RH, Neaton JD, Ludwig W. Prognostic importance of
17. Yudkin JS, Stehouwer CD, Emeis JJ, et al. C-reactive protein in
12. Mendall MA, Patel P, Ballam L, et al. C reactive protein and
10. Juhan-Vague I, Thompson SG, Jespersen J. Involvement of the
9. McMillan DE. Increased levels of acute-phase serum proteins
8. Pickup JC, Mattock MB, Chusney GD, et al. NIDDM as a dis-
7. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
6. Ford ES. Body mass index, diabetes, and C-reactive protein
5. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin
4. Hotamisligil GS. Molecular mechanisms of insulin resistance and
3. American Diabetes Association. Economic consequences of dia-

38. Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte
count: its relationship to plasma insulin and other cardiovascular
factors and ischemic vascular diseases. Thromb Res 1996:82:
245–55.

sensitive marker of inflammation, predicts future risk of coro-
15. Tracy RP, Psaty BM, Macy E, et al. Lifetime smoking exposure
affects the association of C-reactive protein with cardiovascular
disease risk factors and subclinical disease in healthy elderly

protein and coronary heart disease in the MRFIT nested case-

count, fibrinogen and C-reactive protein with vascular risk fac-
tors and ischemic vascular diseases. Thromb Res 1996;82:
245–55.

12. Mendall MA, Patel P, Ballam L, et al. C reactive protein and
its relation to cardiovascular risk factors: a population based

11. O'Riordain MG, Ross JA, Fearon KC, et al. Insulin and coun-
trolling from adipose tissue? Arterioscler Thromb Vasc Biol 1999;
19:237–42.

10. Sandler AB, Sandler RS, Pettersson P, et al. The impact of
C-reactive protein on cardiovascular disease: a meta-analysis of
population-based studies. JAMA 1997;278:1477–82.

9. McMillan DE. Increased levels of acute-phase serum proteins

8. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
reactive protein levels in overweight and obese adults. JAMA

7. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
reactive protein levels in overweight and obese adults. JAMA

6. Ford ES. Body mass index, diabetes, and C-reactive protein

5. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin
and the role of the adipocyte. Int J Obes Relat Metab DISord

4. Hotamisligil GS. Molecular mechanisms of insulin resistance and
the role of the adipocyte. Int J Obes Relat Metab DISord

3. American Diabetes Association. Economic consequences of dia-
betes mellitus in the U.S. in 1997. Diabetes Care 1998;21:
296–309.

2. Hotamisligil GS. Molecular mechanisms of insulin resistance and
the role of the adipocyte. Int J Obes Relat Metab DISord

1. Leukocyte Count and Diabetes Incidence
63


23. Friedman GD, Fireman BH. The leukocyte count and cancer

and the role of the adipocyte. Int J Obes Relat Metab DISord

21. Grimm RH, Neaton JD, Ludwig W. Prognostic importance of
C-reactive protein, albumin, or leukocyte count with coronary
heart disease: meta-analyses of prospective studies. JAMA

20. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of
inflammation and predication of diabetes mellitus in adults
(Atherosclerosis Risk in Communities Study): a cohort study.

reactive protein and features of the metabolic syndrome—a

18. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
reactive protein levels in overweight and obese adults. JAMA

17. Yudkin JS, Stehouwer CD, Emeis JJ, et al. C-reactive protein in

sensitive marker of inflammation, predicts future risk of coro-
nary heart disease in initially healthy middle-aged men: results
from the MONICA Augsburg Cohort Study, 1984 to

15. Tracy RP, Psaty BM, Macy E, et al. Lifetime smoking exposure
affects the association of C-reactive protein with cardiovascular
disease risk factors and subclinical disease in healthy elderly

protein and coronary heart disease in the MRFIT nested case-

count, fibrinogen and C-reactive protein with vascular risk fac-
tors and ischemic vascular diseases. Thromb Res 1996;82:
245–55.

12. Mendall MA, Patel P, Ballam L, et al. C reactive protein and
its relation to cardiovascular risk factors: a population based

11. O'Riordain MG, Ross JA, Fearon KC, et al. Insulin and coun-
trolling from adipose tissue? Arterioscler Thromb Vasc Biol 1999;
19:237–42.

10. Sandler AB, Sandler RS, Pettersson P, et al. The impact of
C-reactive protein on cardiovascular disease: a meta-analysis of
population-based studies. JAMA 1997;278:1477–82.

9. McMillan DE. Increased levels of acute-phase serum proteins

8. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
reactive protein levels in overweight and obese adults. JAMA

7. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-
reactive protein levels in overweight and obese adults. JAMA

6. Ford ES. Body mass index, diabetes, and C-reactive protein

5. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin
and the role of the adipocyte. Int J Obes Relat Metab DISord

4. Hotamisligil GS. Molecular mechanisms of insulin resistance and
the role of the adipocyte. Int J Obes Relat Metab DISord

3. American Diabetes Association. Economic consequences of dia-
betes mellitus in the U.S. in 1997. Diabetes Care 1998;21:
296–309.

2. Hotamisligil GS. Molecular mechanisms of insulin resistance and
the role of the adipocyte. Int J Obes Relat Metab DISord

1. Leukocyte Count and Diabetes Incidence
63


23. Friedman GD, Fireman BH. The leukocyte count and cancer