Insulin-Resistant Prediabetic Subjects Have More Atherogenic Risk Factors Than Insulin-Sensitive Prediabetic Subjects

Implications for Preventing Coronary Heart Disease During the Prediabetic State

Steven M. Haffner, MD; Leena Mykkänen, MD; Andreas Festa, MD; James P. Burke, PhD; Michael P. Stern, MD

Background—Subjects who convert to type 2 diabetes mellitus have increased cardiovascular risk factors relative to nonconverters. However, it is not known whether these atherogenic changes in the prediabetic state are predominantly due to insulin resistance, decreased insulin secretion, or both.

Methods and Results—We examined this issue in the 7-year follow-up of the San Antonio Heart Study, in which 195 of 1734 subjects converted to type 2 diabetes. At baseline, converters had significantly higher body mass index, waist circumference, triglyceride concentration, and blood pressure and lower HDL cholesterol than nonconverters. Atherogenic changes in converters were markedly attenuated (and no longer significant) after adjustment for the homeostasis model assessment of insulin resistance (HOMA IR, a surrogate for insulin resistance); in contrast, the differences in risk factors between converters and nonconverters increased after adjustment for the ratio of early insulin increment to early glucose increment (ΔI_30-0/ΔG_30-0) during an oral glucose tolerance test (a surrogate for insulin secretion). We also compared converters who had a predominant insulin resistance (high HOMA IR and high ΔI_30-0/ΔG_30-0) (n=56) and converters who had a predominant decrease in insulin secretion (low HOMA IR and low ΔI_30-0/ΔG_30-0) (n=31) with nonconverters (n=1539). Only the converters who were insulin resistant had higher blood pressure and triglyceride levels and lower HDL cholesterol levels than nonconverters.

Conclusions—Our data suggest that atherogenic changes in the prediabetic state are mainly seen in insulin-resistant subjects and that strategies to prevent type 2 diabetes might focus on insulin-sensitizing interventions rather than interventions that increase insulin secretion because of potential effects on cardiovascular risk. (Circulation. 2000;101:975-980.)

Key Words: insulin ■ diabetes mellitus ■ lipids ■ cholesterol ■ blood pressure

Type 2 diabetes mellitus is associated with a marked increase in coronary heart disease (CHD). The relationship between glycemia and CHD in type 2 diabetes has been controversial, with some studies showing strong associations, some weak associations, and others no associations. The recently published United Kingdom Prospective Diabetes Study (UKPDS) found a greater benefit of glycemic control on microvascular events than for CHD or stroke. One explanation for the relatively weak effect of glycemia on CHD in type 2 diabetes might be the existence of a highly atherogenic state before the onset of diabetes. Increased risk factors for CHD before the onset of type 2 diabetes have been shown in several populations, including Israelis, elderly American subjects, elderly Finnish subjects, Mexican American subjects, and Pima Indians. The causes of increased atherogenicity of the prediabetic state are not fully understood. Both insulin resistance (measured directly or through surrogates such as fasting insulin and decreased insulin secretion) predict the development of type 2 diabetes. It is not known whether the increased atherogenicity of the prediabetic state is primarily due to increased insulin resistance or decreased insulin secretion, although increased resistance may be likely given the amount of information on the insulin-resistance syndrome.

In this report, we examine whether insulin resistance or decreased insulin secretion is responsible for the atherogenic prediabetic state. In particular, we were interested in whether cardiovascular risk factors were similar in prediabetic subjects who had a predominant insulin-secretory defect (normal
insulin sensitivity but low insulin-secretory response) as opposed to subjects with a predominant insulin-resistance defect (insulin resistant but with good insulin-secretory response). This issue is important because recently, a number of projects to prevent type 2 diabetes have been undertaken with methods that either improve insulin sensitivity (Diabetes Prevention Project [DPP: metformin, intensive lifestyle24] and STOP-NIDDM [acarbose]25) or increase insulin secretion (NANSY [sulfonylurea: Amylase]; Arne Melander, Sweden, oral communication, 1999). If atherogenic changes in the prediabetic state are limited to subjects with insulin resistance, the use of insulin-sensitizing agents to prevent diabetes could have a beneficial effect on CHD. We used data from the San Antonio Heart Study, in which we have previously shown that both high fasting insulin (a surrogate for insulin resistance) and a decreased ratio of insulin increment (over the first 30 minutes) to glucose increment (over the first 30 minutes) during an oral glucose tolerance test \( \frac{\Delta I_{30-0}/G_{30-0}}{} \) (a surrogate for insulin secretion) predict the development of type 2 diabetes in Mexican Americans.20

### Methods

The San Antonio Heart Study is a population-based study of diabetes and cardiovascular disease in Mexican American and non-Hispanic whites. From 1984 to 1988, we randomly selected households from low-income (barrio), middle-income (transitional), and high-income (suburban) census tracts in San Antonio, Tex.26 All men and nonpregnant women aged 25 to 64 years who resided in the randomly sampled households were eligible to participate. Mexican Americans were defined as individuals whose ancestry derived from a Mexican national origin. Detailed descriptions of this study have been published previously.26 This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave informed consent. Beginning in October 1991, we began a 7-year follow-up of the cohort.20 The results in this report are based on risk factors for the development of type 2 diabetes. Subjects with diabetes at the baseline examination were excluded from this report.

At the baseline and follow-up visits, blood specimens were obtained after a 12- to 14-hour fast for determination of plasma glucose, serum insulin, and serum lipids and lipoproteins. Methods for determination of lipids and lipoproteins and glucose have been described previously.20 We measured serum insulin with a solid-phase radioimmunoassay (Diagnostic Products Corporation) that shows a relatively high degree of cross-reactivity with proinsulin (≈70% to 100%).26 A 75-g oral glucose load (Orangedex; Custom Laboratories) was administered, and blood specimens were obtained 30 minutes, 1 hour, and 2 hours later for plasma glucose and serum insulin concentrations. At the follow-up examination, post–glucose-load specimens were obtained only at the 2-hour time point. Diabetes was diagnosed according to World Health Organization (WHO) criteria.27 Subjects who did not meet WHO plasma glucose criteria but who were undergoing treatment with oral antidiabetic agents or insulin were considered to have diabetes. In this report, we use the homeostasis model of insulin resistance (HOMA IR) as a measure of insulin resistance28–30 and \( \frac{\Delta I_{30-0}/G_{30-0}}{} \) as a measure of insulin secretion (early secretory response to an oral glucose load). The formula for the HOMA IR model28 follows:

\[
\text{HOMA IR} = \frac{\text{Fasting insulin (mU/mL)} \times \text{fasting glucose (mmol/L)}}{22.5}
\]

The correlation of HOMA IR and fasting insulin in nondiabetic subjects is 0.98.

Anthropometric measurements (height, weight, and waist and hip circumferences) were made after participants had removed their shoes and upper garments and donned an examination gown. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Waist circumference was chosen as a measure of central adiposity.

The systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit by use of a random-zero sphygmomanometer (Hawksley-Gelman). Three readings were recorded for each individual, and the average of the second and third readings was defined as the patient’s blood pressure.

Statistical analyses included ANCOVA performed with SAS software. Two-way ANCOVA was done initially with conversion to diabetes and ethnicity (Mexican American versus non-Hispanic whites as the grouping variable). The \( P \) value for these interaction terms (ethnicity times conversion status) were all >0.100. Because there was no evidence of different effect of conversion status by ethnicity on variables of interest (ie, triglycerides or blood pressure), we pooled the ethnic groups with control for ethnicity to increase statistical power and to simplify the analysis. One-way ANCOVA was done with conversion to diabetes as the main effect (Tables 1 and 2). Additional analysis was done with 2-way ANCOVA among the converters to diabetes by dividing subjects by their insulin-resistance or insulin-secretion status at baseline (HOMA IR above and below median of 3.0 and insulin secretion \( \frac{\Delta I_{30-0}/G_{30-0}}{} \)) and above and below median of 155.6 pmol/L (Table 3). The median was based on the overall nondiabetic population at baseline. Finally, 1-way ANCOVAs (with pairwise contrasts) were done with conversion to diabetes as the dependent variable to compare subjects with predomi-

### Results

Table 1 shows the baseline characteristics of subjects by conversion to diabetes, adjusted for age, sex, and ethnicity. Fasting insulin and HOMA IR were higher and \( \frac{\Delta I_{30-0}/G_{30-0}}{} \) was lower in converters to diabetes than in subjects who remained nondiabetic. Subjects who converted to diabetes had greater obesity and an unfavorable body fat distribution, higher blood pressure, higher prevalence of hypertension, higher glucose levels, higher triglyceride levels, and lower HDL cholesterol than subjects who did not convert to diabetes. Total and LDL cholesterol levels and smoking status were similar in converters and nonconverters.

As shown in Table 2 (model A), after further adjustment for fasting glucose and waist circumference, converters continued to have higher blood pressure and higher triglyceride levels and lower HDL cholesterol levels than subjects who did not convert to diabetes. Table 2 shows the effects of additional adjustment for HOMA IR (a surrogate for insulin resistance) (model B) versus the effect of adjustment for \( \frac{\Delta I_{30-0}/G_{30-0}}{} \) (model C), a surrogate for insulin secretion. Adjustment for HOMA IR attenuated the differences between converters and nonconverters, making them no longer statistically significant. In contrast, after adjustment for insulin secretion \( \frac{\Delta I_{30-0}/G_{30-0}}{} \), the differences between converters and nonconverters to type 2 diabetes remained statistically significant.

We next categorized the subjects simultaneously by insulin resistance (above and below the median for HOMA IR in the overall nondiabetic population at baseline) and insulin secretion (above and below the median for \( \frac{\Delta I_{30-0}/G_{30-0}}{} \)).
incidence of type 2 diabetes by insulin resistance and secretion categories is shown in Figure 1. As expected, subjects with the highest rate of developing type 2 diabetes had both insulin resistance and decreased insulin secretion (31.8% in 7 years), and the lowest rate was in subjects who were insulin sensitive with good secretory capacity (1.0%). Subjects with insulin resistance but good insulin secretion had a higher conversion rate than subjects with low insulin secretion who were insulin sensitive (11.0% versus 6.2%). These results are similar to those presented for a smaller cohort of Mexican Americans only.20

We also characterized the distribution of insulin resistance and secretory effects of converters to diabetes and insulin secretion. Fifty-four percent of converters had both an insulin secretory defect and were insulin resistant compared with 15.9% of subjects who had low insulin secretion but were insulin sensitive (predominantly insulin sensitive). Insulin resistance had a BMI 3 to 4 kg/m² higher than subjects who did not convert to diabetes or who converted to diabetes but had a predominant insulin-secretory defect. Adjustment for differences in BMI somewhat attenuated the differences but had a predominant insulin-secretory defect. Among converters to diabetes, the only subjects with adverse cardiovascular risk factors (high systolic blood pressure and triglyceride levels and low HDL cholesterol levels) were converters to diabetes with high IR and insulin-resistant subjects.

Subjects who converted to diabetes but had predominant insulin resistance had a BMI 3 to 4 kg/m² higher than subjects who did not convert to diabetes or who converted to diabetes but had a predominant insulin-secretory defect. Adjustment for differences in BMI somewhat attenuated the differences in lipoproteins or blood pressure (≈30%), but converters to diabetes who had predominant insulin resistance continued to have significantly more atherogenic risk factors than the other 2 groups (P<0.01).

**Discussion**

We have confirmed that prediabetic subjects have increased cardiovascular risk factors at baseline relative to subjects who do not convert to type 2 diabetes. These results extend previous results in earlier reports in a variety of ethnic groups,9–13 including reports on smaller groups of Mexican Americans in the San Antonio Heart Study.12 The increased atherogenicity of the prediabetic state was due only in part to differences in overall adiposity and upper-body adiposity between the converters and nonconverters to type 2 diabetes (Table 1).
More interesting is whether the atherogenic differences in prediabetic subjects are due to increased insulin resistance, decreased insulin secretion, or both. To address this issue, we used 2 different approaches: that of statistical adjustment (Tables 1 and 2) and that of stratification (Table 3 and Figure 2). After adjustment for HOMA IR, the differences between converters and nonconverters were attenuated and were no longer statistically significant. In contrast, after adjustment for $\Delta G_{30-0}$ (a surrogate for decreased secretory response that has been shown to be a significant predictor of type 2 diabetes in this cohort), the differences between converters and nonconverters actually widened (Table 2).

Subjects who converted to diabetes but were insulin resistant had significantly higher triglyceride levels, systolic blood pressure, and diastolic blood pressure and lower HDL cholesterol levels than subjects who converted to diabetes but who were insulin sensitive. The 2 groups of converters to type 2 diabetes (predominantly insulin-resistant versus insulin-sensitive converters) had similar values for both fasting and 2-hour glucose levels, but the insulin-resistant converters were more obese (Table 3). After additional adjustment for BMI (data not shown), insulin-resistant converters to type 2 diabetes still had worse cardiovascular risk factors than insulin-sensitive converters. Interestingly, insulin-sensitive converters to type 2 diabetes had triglyceride and HDL cholesterol levels and systolic blood pressure similar to those of subjects who remained nondiabetic at baseline.

We have thus identified different subgroups of converters to type 2 diabetes with markedly different patterns of cardiovascular risk factors. The implication is that the subjects who were insulin resistant and converted to diabetes would have more cardiovascular disease than the insulin-sensitive subjects who converted to diabetes.

We should point out that the differences in lipids (triglyceride 0.9 mmol and HDL cholesterol 0.24 mmol) and systolic blood pressure (6.5 mm Hg) (Table 3) are actually larger than the differences between diabetic (n=303) and nondiabetic (n=2564) subjects in the San Antonio Heart Study (for diabetic versus nondiabetic subjects, respectively: triglyceride 2.3 versus 1.6 mmol/L, a 0.7 mmol/L difference; HDL

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**TABLE 2. Clinical Characteristics of Subjects at Baseline According to Conversion Status at Follow-Up, Adjusted for Either Insulin Resistance or Insulin Sensitivity**

<table>
<thead>
<tr>
<th>Conversion Status at Follow-Up</th>
<th>Nondiabetic (n=1539)</th>
<th>Type 2 Diabetes (n=195)</th>
<th>Difference (DM – Non-DM)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Adjusted for age, sex, ethnicity, fasting glucose, and waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.25±0.01</td>
<td>1.14±0.02</td>
<td>−0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.23±0.02</td>
<td>3.09±0.07</td>
<td>−0.14</td>
<td>0.459</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.53±0.03</td>
<td>2.02±0.07</td>
<td>0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>117.8±0.35</td>
<td>120.7±1.0</td>
<td>2.9</td>
<td>0.016</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71.5±0.2</td>
<td>73.2±0.7</td>
<td>2.2</td>
<td>0.042</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>74±2</td>
<td>108±6</td>
<td>34.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>2.8±0.1</td>
<td>3.9±0.2</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\Delta G_{30-0}$, pmol/mmol</td>
<td>227±11</td>
<td>119±30</td>
<td>−108</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

B. Adjusted for age, sex, ethnicity, fasting glucose, waist circumference, and HOMA IR (surrogate for insulin resistance)

| HDL cholesterol, mmol/L | 1.21±0.01 | 1.18±0.02 | −0.03 | 0.352 |
| LDL cholesterol, mmol/L | 3.24±0.01 | 3.09±0.07 | −0.15 | 0.552 |
| Triglyceride, mmol/L | 1.69±0.03 | 1.82±0.08 | 0.13 | 0.101 |
| SBP, mm Hg | 119.9±2.6 | 122.1±0 | 2.2 | 0.271 |
| DBP, mm Hg | 72.2±0.7 | 72.2±0.23 | 0.0 | 0.900 |

C. Adjusted for age, sex, ethnicity, fasting glucose, waist circumference, and $\Delta G_{30-0}$ (surrogate for insulin secretion)

| HDL cholesterol, mmol/L | 1.26±0.01 | 1.11±0.02 | −0.15 | <0.001 |
| LDL cholesterol, mmol/L | 3.25±0.01 | 3.07±0.07 | −0.18 | 0.373 |
| Triglyceride, mmol/L | 1.44±0.03 | 2.10±0.08 | 0.66 | <0.001 |
| SBP, mm Hg | 117.3±0.4 | 121.7±1 | 4.4 | 0.008 |
| DBP, mm Hg | 71.0±0.2 | 73.4±0.7 | 2.4 | 0.024 |

Values are mean±SEM. DM indicates diabetes mellitus; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

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Figure 1. Seven-year incidence of type 2 diabetes by baseline status for insulin resistance (HOMA IR surrogate for insulin resistance) and insulin secretion ($\Delta G_{30-0}$/$\Delta G_{30-0}$ surrogate for insulin secretion).
TABLE 3. Clinical Characteristics of Subjects at Baseline Who Converted to Type 2 Diabetes by Whether They Had Predominantly Insulin Resistance, Decreased Insulin Secretion, or a Mixed Picture (Adjusted for Age, Sex, and Ethnicity)

<table>
<thead>
<tr>
<th>HOMA IR (&quot;Insulin Resistant&quot;)</th>
<th>Low HOMA IR (&quot;Insulin Sensitive&quot;)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>High (&quot;good&quot;)</td>
<td>Low (&quot;bad&quot;)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>236±15</td>
<td>128±11</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>6.5±2.6</td>
<td>6.0±1.8</td>
</tr>
<tr>
<td>ΔG30-0/ΔG30-0, pmol/mmol</td>
<td>281±12</td>
<td>99±9</td>
</tr>
<tr>
<td>Waist circumference, mm</td>
<td>1011±23</td>
<td>901±17</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.3±0.7</td>
<td>30.7±0.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.97±0.04</td>
<td>1.07±0.03</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.96±0.13</td>
<td>3.26±.10</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.80±0.48</td>
<td>2.43±0.15</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>128.8±2.4</td>
<td>126.2±1.8</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.5±1.3</td>
<td>76.5±1.0</td>
</tr>
<tr>
<td>Fasting glucose, mmol</td>
<td>5.38±0.08</td>
<td>5.31±0.06</td>
</tr>
<tr>
<td>2-h Glucose, mmol</td>
<td>7.85±0.24</td>
<td>7.81±0.17</td>
</tr>
<tr>
<td>%IGT</td>
<td>54.0%</td>
<td>54.6%</td>
</tr>
</tbody>
</table>

Values are mean ± SEM unless otherwise indicated. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and IGT, impaired glucose tolerance.

*P value by 2-way ANCOVA.

Our results may have important implications for the prevention of diabetes. Currently, a number of clinical trials on insulin-sensitizing agents are under way (DPP [metformin, intensive lifestyle24] and STOPNIDDM [acarbose]25). Similarly, there are prevention trials involving insulin secretagogues (NANSY [sulfonylurea {Amaryl}]). If our results are confirmed, they should encourage further studies comparing fasting insulin versus insulin secretion status in prediabetic subjects. Insulin-sensitive converters to diabetes have an atherogenic pattern of cardiovascular risk factors, and conversion status.

Figure 2. Levels of cardiovascular risk factors by HOMA IR (fasting insulin), insulin secretion (∆G30-0/∆G30-0), and conversion status.

Haffner et al. Prediabetic Subjects and Atherogenic Risk.
References


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