Relation of Impaired Fasting and Postload Glucose With Incident Type 2 Diabetes in a Dutch Population

The Hoorn Study

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Worldwide, the prevalence of type 2 diabetes is very high and increasing. The World Health Organization (WHO) predicts that between 1995 and 2025, the worldwide prevalence of diabetes among persons aged 20 years and older will increase from 4.0% to 5.4%.1 Diabetes is associated with a high risk for microvascular and macrovascular complications and with a high risk of premature death.2,4

For prevention purposes, there is great interest in the identification of persons at high risk for developing diabetes. Therefore, several follow-up studies have been performed in nonwhite populations with a high prevalence of diabetes5-7 and among persons with impaired glucose tolerance (IGT).6,10 Edelstein et al11 reported cumulative incidences ranging from 23% to 62% in 6 prospective studies among persons with IGT, within 2 to 27 years of follow-up. The incidence was higher among the Hispanic, Mexican-American, Pima, and Nau-
cose levels.\textsuperscript{17} still taking into account the postload glucose criteria differ from the ADA criteria by the WHO in 1999. The WHO-1999 lower cutoff point for FPG was adopted this affects the incidence of diabetes. This

The Hoorn Study, begun in 1989, is a population-based cohort study on glucose intolerance in a general Dutch elderly population. The study population and design have been described in detail previously.\textsuperscript{18} In summary, a random sample (n=3553) of all inhabitants of Hoorn aged 50 to 75 years was invited to take part in the study. A total of 2540 subjects (71\%) agreed to participate. After exclusion of 56 nonwhite participants, the study cohort consisted of 2484 men and women. The baseline examination took place between October 1989 and February 1992.

Between January 1996 and December 1998, a follow-up examination was carried out. Of the initial cohort, 150 persons had died and 108 had moved out of Hoorn before 1996. One hundred forty other persons were not invited because of logistic reasons. Of the remaining 2086 persons who were invited for the follow-up examination, 1513 (72.5\%) participated. In the present study all analyses have been done line according to the WHO-1985, ADA, and WHO-1999 diagnostic criteria. We also determined which other variables were predictive of the development of diabetes.

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Diastolic blood pressure was 160 mm Hg or greater, their diastolic blood pressure was 95 mm Hg or greater, or if they were using antihypertensive medication. Information on smoking habits (yes or no) and participation in sports (hours per week) was obtained by questionnaire.

Statistical Methods
All statistical analyses were done with SPSS 9.0. All P values were based on 2-sided tests, and the cutoff for statistical significance was .05.

The cumulative incidence of diabetes was calculated as the number of participants who developed diabetes during the follow-up divided by the total number of those at risk at baseline. We compared the 6-year cumulative incidence of diabetes between the WHO-1985, the ADA, and the WHO-1999 diagnostic criteria. Furthermore, we compared the cumulative incidences for combinations of normal, impaired fasting, and impaired postload glucose levels.

The follow-up duration was calculated as the time between the baseline and the follow-up measurements, and the incidence densities were calculated. Because the mean follow-up duration was not equal in the categories of glucose intolerance, logistic regression adjusting for follow-up duration was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The ORs were also adjusted for age and sex. The Hosmer-Lemeshow goodness-of-fit test was used to assess the overall fit of the logistic regression model.

The OR is the ratio of the odds of 2 categories and can be interpreted as an approximation of the relative risk. In this study, odds represent the chance for conversion to diabetes relative to the chance for nonconversion to diabetes in 1 particular category. The ORs will overestimate the relative risk when the disease under study is not rare.

To investigate which other variables were predictive of the development of diabetes, the variables WHR (×100), BMI, hypertension, smoking, and participation in sports were added 1 by 1 into a logistic regression model including also FPG, 2hPG, age, sex, and follow-up duration as independent variables. Finally, all statistically significant variables were included together into 1 logistic regression model.

RESULTS
The study population consisted of 610 men and 732 women with a mean age of 60.3 (SD, 6.9) years at baseline, who were followed up for 6.4 years (range, 4.4-8.1 years).

As a consequence of the definitions used, the cumulative incidence of diabetes was highest according to the WHO-1999 criteria: 9.9% compared with 6.1% and 8.3% according to the WHO-1985 and the ADA criteria, respectively. Of the 1231 participants with NGT at baseline, 46 (3.7%) had diabetes at follow-up according to the WHO-1985 criteria. For participants with IGT the cumulative incidence was 32.4% (WHO-1985 criteria). According to the ADA criteria, the cumulative incidence was 5.0% for participants with NFG and 38.0% for those with IFG (TABLE 1).

The cumulative incidence (WHO-1999 criteria) among participants with both impaired fasting and impaired postload glucose levels was 64.5%, compared with 4.5% for those with both normal fasting and normal postload glucose levels. Among participants with isolated IFG or IGT, the cumulative incidence of diabetes was similar (33.0% and 33.8%, respectively). However, the mean follow-up durations were not equal in these categories. The ORs adjusted for follow-up duration, age, and sex were 10.0 and 10.9 for isolated IFG and IGT, respectively. The OR for participants with both IFG and IGT relative to those with normal glucose levels was very high (39.5 [95% CI, 17.0-92.1]) (TABLE 2).

When the analyses were stratified for men and women, we observed a slightly higher cumulative incidence of diabetes in men than in women (10.5% vs 9.4%, respectively; WHO-1999 criteria). For participants with the combined presence of IFG and IGT the cumulative incidence was more pronounced in women (75.0%) than in men (53.3%).

In addition to fasting and postload glucose levels, which were the 2 most important predictors for progression to diabetes (both P < .001), the WHR also was highly predictive of incident diabetes (P = .002). Of less importance, and not statistically significant, were smoking, hypertension, participation in sports, and BMI. Including the statistically significant variables into 1 model, the OR expressed per 1-SD difference was 2.32 (95% CI, 1.85-2.90) for FPG, 1.97 (95% CI, 1.59-2.44) for 2hPG, and 1.57 (95% CI, 1.19-2.08) for the WHR (TABLE 3).

COMMENT
In this prospective cohort study of a white population, 64.5% of the participants who had both impaired fasting

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and impaired postload glucose levels at baseline progressed to diabetes (WHO-1999 criteria) during the 6-year follow-up. Of those with normal fasting and postload glucose levels at baseline, 4.5% had diabetes at the follow-up examination. To our knowledge, this is the first large prospective study among whites that reports on the cumulative incidence of type 2 diabetes according to WHO-1985, ADA, and WHO-1999 diagnostic criteria.

The baseline cohort (n = 2484) of the Hoorn Study was a random sample of the population of the municipality of Hoorn, aged 50 to 75 years. The present analyses have been done in 1342 participants who did not have diabetes according to any of the diagnostic criteria at baseline and who did not have missing values for glucose. Of the 2086 persons who were invited for the follow-up examination, 1513 participated and 573 did not. As is frequently observed in population studies, the participants were more healthy. The participants were younger (60.6 vs 63.2 years), less hypertensive (28.2% vs 34.8%), had a lower WHR (0.89 vs 0.90), and a more favorable lipid profile at baseline. Furthermore, they had lower mean baseline FPG levels (101.8 mg/dL [5.65 mmol/L] vs 105.5 mg/dL [5.85 mmol/L]), lower 2hPG levels (106.5 mg/dL [5.91 mmol/L] vs 112.2 mg/dL [6.23 mmol/L]), and lower glycosylated hemoglobin values (5.4% vs 5.6%). Therefore, we may have underestimated the true cumulative incidence of diabetes in the general population.

Because of ongoing follow-up studies, persons with IGT were first invited for the follow-up measurements. This resulted in an unequal distribution over the categories for the mean follow-up duration, with persons with the highest risks for progression to diabetes having the shortest follow-up duration. In a logistic regression model we therefore adjusted for follow-up duration.

The glucose levels were determined only once at baseline and at follow-up. Because of the known high intra-individual variation in glucose levels, especially for postload glucose, some misclassification might have occurred when participants were categorized into glucose tolerance categories. However, we previously reported that the reproducibility of the classification in glucose tolerance categories by WHO-1985 and ADA for 1109 persons with duplicate OGTTs within 6 weeks was very similar, with κ values of 0.59 and 0.61, respectively, which represent fair-to-good reproducibility.

The incidence of diabetes was highest according to the WHO-1999 combined criteria and the lowest incidence was observed if using the WHO-1985 criteria, which is due to the higher cutoff level for FPG. However, the true incidence according to the WHO-1985 was slightly underestimated, because participants with FPG levels between 126 mg/dL (7.0 mmol/L) and 140 mg/dL (7.8 mmol/L) at baseline were excluded in the analyses. If these participants (n = 23) were included, the cumulative incidence of diabetes according to WHO-1985 criteria was 6.9% instead of 6.1%. For participants with IGT and NGT the incidences then were 35.5% and 4.1%, respectively. When only the ADA diagnostic criteria should have been used, the analyses could have been done in 1391 participants instead of 1342. Then the cumulative incidence of diabetes was 5.5% for participants with NFG and 40.8% for those with IFG, which is quite similar to the values in Table 1.

Previous studies on the incidence of diabetes were mainly performed in persons with IGT only, or in nonwhite populations with a high risk for diabetes, using the WHO-1985 diagnostic criteria. In South African persons, the incidence of diabetes was 50.4% within 4 years and for Pima Indians the cumulative incidence of diabetes was 62% within 7 years. In Kinmen, a series of islands located in the Pacific Ocean, the cumulative incidence was 8.8% per year. We previously reported on the 2-year cumulative incidence of diabetes in a subsample of participants with IGT in the Hoorn Study. The cumulative incidence of diabetes was 28.5% when using the mean of duplicate OGTTs for the classification in glucose tolerance categories.

Less is known about the cumulative incidence of diabetes of persons with

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**Table 2. Cumulative Incidence of Diabetes (WHO-1999 Criteria) for Combinations of Impaired Fasting and Impaired Postload Glucose Levels**

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>Cutoff Values, FPG/2hPG, mg/dL</th>
<th>Cumulative Incidence, No. (%)</th>
<th>Mean Follow-up Duration†</th>
<th>Incidence Density (No./1000 Person-years) OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1125</td>
<td>&lt;110/140</td>
<td>51 (4.5)</td>
<td>6.47</td>
<td>7.0</td>
</tr>
<tr>
<td>IFG and NGT</td>
<td>106</td>
<td>110-126/&lt;140</td>
<td>35 (33.0)</td>
<td>6.42</td>
<td>51.4</td>
</tr>
<tr>
<td>NFG and IGT</td>
<td>80</td>
<td>&lt;110/140-200</td>
<td>27 (33.8)</td>
<td>5.83</td>
<td>57.9</td>
</tr>
<tr>
<td>IFG and IGT</td>
<td>31</td>
<td>110-126/140-200</td>
<td>20 (64.5)</td>
<td>5.75</td>
<td>112.2</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval. For expansion of other terms, see Table 1 footnote. To convert mg/dL to mmol/L, multiply mg/dL by 0.05551.

†Years between baseline and follow-up measurements.

‡Calculated by logistic regression adjusted for follow-up duration, age, and sex.

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**Table 3. Variables Predictive of the Development of Diabetes During 6 Years of Follow-up, Adjusted for Age, Sex, and Follow-up Duration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD (n = 1342)</th>
<th>OR (95% CI), per SD Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG, mg/dL</td>
<td>9.36</td>
<td>2.32 (1.85-2.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2hPG, mg/dL</td>
<td>29.33</td>
<td>1.97 (1.59-2.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WHR &gt; 100</td>
<td>8.46</td>
<td>1.57 (1.92-2.08)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; FPG, fasting plasma glucose; 2hPG, 2-hour postload glucose; and WHR, waist-hip ratio.
IFG. In the present study, we observed a 6-year incidence of 38%. Dinnen et al also observed a cumulative incidence of 39% within 9 years of follow-up among Olmsted County residents aged 40 years or older with baseline IFG. In a prospective study in Mauritius among persons aged 25 to 74 years, 28.9% of the participants with baseline IFG progressed to diabetes in 5 years, compared with 24.4% with IGT. In a study in Italy among 1245 whites who were followed up for 11.5 years, participants with both IFG and IGT at baseline had an OR of 10.3 for developing diabetes relative to those with both NFG and NGT. The cumulative incidence of diabetes among participants with IGT only was higher than the cumulative incidence for subjects with IFG only (32.5% and 9.1%, respectively). These results are therefore only partly in line with the results of the present study: we observed a 14-fold higher risk for diabetes in subjects with both IFG and IGT, while the risks of the IFG-only and IGT-only categories were similar. However, the participants in the Italian study were younger (40-59 years) and the number of those who progressed to diabetes was in some categories quite small.

Impaired fasting glucose and IGT represent different physiologic abnormalities. The primary cause for fasting hyperglycemia is the elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia, while IGT is characterized by defects in both insulin secretion and insulin sensitivity.

Therefore, as demonstrated herein, when there is a combined presence of these disorders the risk for future diabetes is very high. Furthermore, we observed that the WHR, not the BMI, was an important predictor for progression to diabetes. Edelstein et al also observed in 4 prospective studies that the WHR was consistently associated with the development of diabetes. The association between BMI and incident diabetes differed between the studies reported. Therefore, the body fat distribution may be a better predictor for progression to diabetes than the BMI.

In this study, the highest cumulative incidence of diabetes was observed for participants with both IFG and IGT at baseline. Therefore, we conclude that the cumulative incidence of diabetes among white persons aged 50 to 75 years is strongly related to both impaired fasting and impaired postload glucose levels at baseline.

Author Contributions: Study concept and design: de Vegt, Dekker, Jager, Nijpels. Analysis and interpretation of data: de Vegt, Dekker, Kostense. Drafting of the manuscript: de Vegt, Dekker, Kostense. Critical revision of the manuscript for important intellectual content: de Vegt, Dekker, Jager, Kostense, Stehouwer, Nijpels, Bouter, Heine. Statistical expertise: Kostense. Obtained funding: Dekker, Stehouwer, Nijpels, Bouter, Heine. Study supervision: Dekker, Stehouwer, Nijpels, Bouter, Heine.

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