Combined Use of Fasting Plasma Glucose and HbA1c Predicts the Progression to Diabetes in Chinese Subjects

GARY T.C. KO, FRCPI
JULIANA C.N. CHAN, FRCPI
LYNN W.W. TSANG, MPHIL
CLIVE S. COCKRAM, FRCPI

OBJECTIVE — We have previously suggested using the paired values of fasting plasma glucose (FPG) and HbA1c to identify potential diabetic subjects. In this article, we followed up on 208 nondiabetic subjects and examined their rates of progression to diabetes. We analyzed their likelihood of becoming diabetic according to their baseline FPG and HbA1c concentrations.

RESEARCH DESIGN AND METHODS — Between 1988 and 1995, 2,877 Chinese subjects with risk factors for diabetes underwent screening. Of these, 2,250 had FPG <7.8 mmol/l and 2-h plasma glucose (PG) <11.1 mmol/l. Of these 2,250 subjects, 265 were randomly recruited for an annual oral glucose tolerance test (OGTT) until they progressed to develop diabetes. Of those 265 subjects, 37 had baseline FPG ≥7.0 mmol/l and were excluded from the present analysis. Hence, the progression of glucose tolerance in 208 subjects who were nondiabetic according to the new American Diabetes Association diagnostic criteria (FPG <7.0 mmol/l and 2-h PG <11.1 mmol/l) was examined.

RESULTS — Of the 208 nondiabetic subjects, 26 (12.5%) were men and 182 (87.5%) were women. After a mean follow-up of 1.60 ± 1.16 years (range 1–7, median 1), 44 (21.2%) progressed to develop diabetes and 164 (78.8%) remained nondiabetic. Those who were diabetic at the end of the study had a high likelihood ratio (LR) of 9.3 to have baseline FPG ≥6.1 mmol/l and baseline HbA1c ≥6.1%. This was compared with a low LR of 0.6–1.1 in diabetic subjects who had either FPG <6.1 mmol/l or HbA1c <6.1% or both at baseline. The crude rate of progression to diabetes was more than five times higher (44.1 vs. 8.1%) in those whose baseline FPG was ≥6.1 mmol/l and baseline HbA1c was ≥6.1% compared with those whose baseline FPG was <6.1 mmol/l and baseline HbA1c was <6.1%.

CONCLUSIONS — For Chinese subjects with risk factors for glucose intolerance, the use of paired FPG and HbA1c values helped to identify potential diabetic subjects. Those with an FPG ≥6.1 mmol/l and HbA1c ≥6.1% had a rate of progression to diabetes more than five times higher than those with an FPG <6.1 mmol/l and an HbA1c <6.1% after a mean follow-up of 1.6 years. Those with an FPG ≥6.1 but <7.0 mmol/l, especially if their HbA1c was ≥6.1%, should undergo an OGTT to confirm diabetes. Subjects with an FPG <6.1 mmol/l and/or an HbA1c <6.1% should have regular screening using the paired values of FPG and HbA1c.

Diabetes Care 23:1770–1773, 2000

Because the performance of an oral glucose tolerance test (OGTT) is time consuming, laborious, and poorly reproducible (1–3), the American Diabetes Association (ADA) recently recommended moving away from the OGTT to using fasting plasma glucose (FPG) as a diagnostic criterion (4). Furthermore, the diagnostic FPG value of 7.8 mmol/l as recommended by the World Health Organization (WHO) in 1985 has often been criticized as being too high in many racial groups (5–8). In Hong Kong Chinese, the FPG value corresponding to the 2-h plasma glucose (PG) of 11.1 mmol/l was 5.7 mmol/l (8). For these reasons, the ADA has recommended an FPG diagnostic criterion of ≥7.0 mmol/l for diabetes instead of 7.8 mmol/l (4).

Although the use of FPG is simpler and more reproducible (9,10), the omission of the 2-h PG will miss a proportion of diabetic subjects who have normal FPG but elevated 2-h PG (≥11.1 mmol/l) (11). We have suggested using the paired values of FPG and HbA1c to identify potential diabetic subjects (12). Only those with high FPG (6.1–6.9 mmol/l) and high HbA1c (≥6.1%) required an OGTT to confirm diabetes. With use of this approach, >80% of OGTTs could be saved (12). In this article, we followed up on 208 nondiabetic subjects and examined their rates of progression to diabetes. We analyzed their likelihood of becoming diabetic according to their baseline FPG and HbA1c concentrations.

RESEARCH DESIGN AND METHODS

Patients and methods
The Diabetes and Endocrine Center of the Prince of Wales Hospital encourages subjects with risk factors to undergo an OGTT to screen for diabetes. The risk factors for screening included family history of diabetes, history of gestational diabetes, history of impaired glucose tolerance (IGT), or obesity (with BMI ≥25 kg/m²). Between 1988 and 1995, 2,877 subjects underwent screening. Of these, 2,250 had FPG <7.8 mmol/l and 2-h PG <11.1 mmol/l. Of these 2,250 subjects, 265 were randomly (every 1 in 10, consecutively) recruited for a regular yearly OGTT until they had progressed to develop diabetes. Of the 265 subjects, 57 had baseline FPG ≥7.0 mmol/l and were excluded from the present analysis. Hence, the progression of glucose tolerance in 208...
Table 1—Clinical characteristics of 208 nondiabetic Chinese subjects with risk factors for glucose intolerance at baseline and end of study

<table>
<thead>
<tr>
<th>Baseline</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.0 ± 7.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 4.0</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118.7 ± 16.8</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74.7 ± 10.0</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.36 ± 0.72</td>
</tr>
<tr>
<td>2-h PG (mmol/l)</td>
<td>7.55 ± 1.97</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.78 ± 0.75</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise stated. *P < 0.001; †P < 0.01.

Subjects who were nondiabetic according to the new ADA diagnostic criteria (FPG <7.0 mmol/l and 2-h PG <11.1 mmol/l) was examined (4).

On the study day, the subjects attended in a fasting state without taking any medication. Their demographic data, medical history, family history of diabetes, and smoking habit were recorded. Height and weight (measured to the nearest 0.1 kg) were measured with the subject wearing light clothing and without shoes. BMI was calculated as the weight (kilograms) divided by the square of the height (meters). After the subject was sitting for at least 5 min, blood pressure (BP) was measured in his or her right arm by a standard mercury sphygmomanometer. The Korotkoff sound V was taken as the diastolic BP. The mean value of two readings 1 min apart was used. All subjects underwent a 75-g OGTT for diagnosis of diabetes and IGT using the ADA criteria (4). Smoking was not allowed during the test. HbA1c and fasting and 2-h PG concentrations were measured during the OGTT. Diabetes was diagnosed if FPG was ≥7.1 mmol/l. IGT was diagnosed if FPG was <7.0 mmol/l and 2-h PG was ≥7.8 but <11.1 mmol/l. Subjects with FPG <7.0 mmol/l and 2-h PG <7.8 mmol/l had normal glucose tolerance.

PG was measured by a glucose oxidase method (Diagnostic Chemicals reagent kit). Both the intra- and interassay coefficients of variation (CVs) for glucose were 2% at 6.6 mmol/l and <0.5% at values >8.5 mmol/l. HbA1c was measured by an automated ion-exchange chromatographic method (Bio-Rad, Hercules, CA [manufacturer’s reference range 5.1–6.4%]). The intra- and interassay CVs for HbA1c were ≤3.1% at values <8.5%.

Statistical analysis

Statistical analysis was performed using the SPSS (version 6.0) software on an IBM-compatible computer. All results are expressed as means ± SD. The likelihood ratio (LR) (13) was calculated to estimate the odds of having glucose intolerance using the ADA criteria in subjects categorized according to the screening values of FPG (<6.1 mmol/l) and HbA1c (<6%). Kaplan-Meier analysis was performed to study the progression to diabetes in subjects with various FPG and HbA1c concentrations. A P value <0.05 (two-tailed) was considered to be significant.

RESULTS — Of the 208 nondiabetic subjects, 26 (12.5%) were men and 182 (87.5%) were women. Their baseline characteristics are summarized in Table 1. After a mean follow-up of 1.60 ± 1.16 years (range 1–7, median 1), 44 (21.2%) progressed to develop diabetes and 164 (78.8%) remained nondiabetic (90 [43.4%] had a normal OGTT and 74 [35.6%] had IGT).

The 208 subjects were categorized into four groups based on their baseline FPG (≥6.1 or <6.1 mmol/l) and HbA1c (≥6.1 or <6.1%) concentrations. These values were selected on the basis of our previous analyses (12,14) using FPG of 6.1 mmol/l (the cutoff for impaired fasting glucose) and HbA1c of 6.1% (the optimal value corresponding to 2-h PG ≥11.1 mmol/l using receiver operating characteristic analysis in our previous study) as the cutoff. The paired values of FPG ≥6.1 mmol/l and HbA1c ≥6.1% had a high LR of 17.2 to occur in diabetic subjects as compared with nondiabetic subjects (14).

Their outcomes based on the results of the OGTT are summarized in Table 2. Those who were diabetic at the end of the study had a high LR of 9.3 to have baseline FPG ≥6.1 mmol/l and baseline HbA1c ≥6.1%. This finding was compared with a low LR of 0.6–1.1 in diabetic subjects who had either FPG <6.1 mmol/l or HbA1c <6.1% or both at baseline. The crude rate of progression to diabetes was more than five times higher (44.1 vs. 8.1%) in those whose baseline FPG was ≥6.1 mmol/l and baseline HbA1c was ≥6.1% compared with those whose baseline FPG was <6.1 mmol/l and baseline HbA1c was <6.1%. The corresponding 50% “survival time” was 2.27 years (1.38–3.17) and 5.85 years in those whose baseline FPG was <6.1 mmol/l and baseline HbA1c was <6.1%.

Table 2—Outcomes of the glycemic status of 208 subjects categorized according to baseline FPG and HbA1c concentrations

<table>
<thead>
<tr>
<th>Baseline FPG (mmol/l)</th>
<th>n (%)</th>
<th>OGTT*</th>
<th>Follow-up (years)</th>
<th>Crude rate of progression to diabetes (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6.1</td>
<td>≥6.1</td>
<td>21 (10.1)</td>
<td>Normal</td>
<td>1.32 ± 1.20</td>
</tr>
<tr>
<td>≥6.1</td>
<td>&lt;6.1</td>
<td>18 (8.7)</td>
<td>IGT</td>
<td>1.28 ± 0.57</td>
</tr>
<tr>
<td>&lt;6.1</td>
<td>≥6.1</td>
<td>36 (17.3)</td>
<td>Diabetes</td>
<td>1.42 ± 0.73</td>
</tr>
<tr>
<td>&lt;6.1</td>
<td>&lt;6.1</td>
<td>133 (63.9)</td>
<td>LR</td>
<td>1.68 ± 1.30</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>208</td>
<td></td>
<td>1.60 ± 1.16</td>
</tr>
</tbody>
</table>

*According to the 1997 ADA criteria: Normal, FPG <7.0 mmol/l and 2-h PG <7.8 mmol/l; IGT, FPG <7.0 mmol/l and 2-h PG ≥7.8 and <11.1 mmol/l; Diabetes, FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l.
Fasting plasma glucose and HbA1c predict diabetes

CONCLUSIONS — The new ADA diagnostic criterion using FPG is much simpler in application in the community (4). However, if the 2-h PG is omitted, fewer people will be diagnosed with diabetes. Harris et al. (15) reported that in the U.S. population, of the 6.4% undiagnosed diabetic subjects according to the 1985 WHO criteria, 4.0% were diagnosed on the basis of the 2-h PG (i.e., FPG < 7.8 mmol/l and 2-h PG ≥ 11.1 mmol/l), 2.2% had both FPG ≥ 7.8 mmol/l and 2-h PG ≥ 11.1 mmol/l, and only 0.2% were diagnosed on the basis of FPG (i.e., FPG ≥ 7.8 mmol/l and 2-h PG < 11.1 mmol/l). If a lower cutoff value of 7.0 mmol/l was used, a high proportion (3.0% of the total 6.4%) of diabetic subjects would still be missed (i.e., FPG < 7.0 mmol/l and 2-h PG ≥ 11.1 mmol/l). Similarly, in Hong Kong Chinese, our population-based epidemiological study showed that 70–80% of our diabetic subjects were diagnosed on the basis of the 2-h PG (i.e., FPG < 7.8 mmol/l and 2-h PG ≥ 11.1 mmol/l) (7). In selected Chinese subjects with known risk factors for glucose intolerance who underwent screening by OGTT, 40% had FPG < 7.0 mmol/l and 2-h PG ≥ 11.1 mmol/l, whereas 60% had FPG < 7.8 mmol/l and 2-h PG ≥ 11.1 mmol/l (12). Hence, despite the use of the new diagnostic criteria, 40% of diabetic subjects would still have been missed if only FPG was used. In fact, in Chinese, < 10% of diabetic subjects were diagnosed solely on the basis of FPG (i.e., FPG ≥ 7.0 mmol/l and 2-h PG < 11.1 mmol/l) (12).

In light of the data presented above, the WHO has therefore continued to recommend the use of the OGTT in subjects who have impaired fasting glycemia (FPG 6.1–6.9 mmol/l) to exclude diabetes or IGT (16). The key question is how to screen for these high-risk subjects for confirmatory OGTT. The screening test needs to be simple, reproducible, and easily available as well as sensitive and specific. Combining the sensitivity of FPG and the specificity of HbA1c, we have reported the predictive value of this paired value for the diagnosis of diabetic subjects. With use of the 2-h postglucose loading PG ≥ 11.1 mmol/l (as the reference test) (12,14), the paired values of FPG ≥ 6.1 mmol/l and HbA1c ≥ 6.1% had a 13- to 17-fold increased likelihood to occur in diabetic subjects (depending on whether the 1985 WHO or 1997 ADA criteria were used) than nondiabetic subjects. This finding was compared with a likelihood of only 0.16 for subjects with FPG < 6.1 mmol/l and HbA1c < 6.1% (14). When such an approach is used, only those with FPG > 6.1 mmol/l but < 7.8 mmol/l (or FPG ≥ 6.1 but < 7.0 mmol/l if the 1997 ADA criteria were used) and an HbA1c ≥ 6.1% required an OGTT to confirm diabetes, thereby saving 88–93% of all OGTTs (14).

The present study involved subjects at high risk for diabetes. Hence, a relatively high proportion of 21.2% progressed to develop diabetes after a mean follow-up of 1.6 years. This finding gave a crude rate of progression to diabetes of 13.3% per year. Accordingly, we have previously shown that 11.5% of Hong Kong Chinese with IGT progress to diabetes each year (17). This conversion rate is one of the highest reported among different ethnic populations, although it is still lower than the rate of 15.7% per year reported by Pan et al. (18) in the Da Qing Study, which involved the Chinese population in northern China.

In Caucasians with or without risk factors for diabetes, it is not clear whether the use of paired values of FPG and HbA1c can predict progression to diabetes as accurately as in the present study. However, we have previously shown that this screening approach also performs well in Hong Kong Chinese without risk factors for diabetes who were recruited in a population-based study (19). On the other hand, a recent study in the U.S. by Davidson et al. (20) reported that ~60% of subjects being diagnosed as diabetic based on FPG alone had normal HbA1c levels. They suggested that diabetes should not be diagnosed in those with FPG concentrations < 7.8 mmol/l, unless excess glycosylation (HbA1c above a certain cutoff) is evident (20). Wiener and Roberts (21) also reported a significant number of individual discrepancies (false positives and negatives) in using FPG (≥ 7 mmol/l) alone to diagnose diabetes, and they suggested that more diagnostic confidence could be placed in a positive HbA1c (> 6.2%).

In this study, we have shown that nondiabetic Chinese subjects with risk factors for glucose intolerance who had FPG ≥ 6.1 mmol/l and HbA1c ≥ 6.1% had a crude rate of progression to diabetes of 44.1% per year. This result was 5.4 times higher in comparison to those with FPG < 6.1 mmol/l and HbA1c < 6.1% who had a crude rate of progression of 8.1% per year. These high conversion rates might be related to the high-risk characteristics of these subjects (17). These findings complement our previous reports regarding the use of high
FPG and high HbA1c in predicting progression to diabetes. In this respect, a recent report has also shown that an HbA1c value of 2 SD above the normal mean was also highly predictive of diabetes (22).

In conclusion, for subjects with risk factors for glucose intolerance, the use of paired values of FPG and HbA1c helped to identify potential diabetic subjects. Those with FPG ≥6.1 mmol/l and HbA1c ≥6.1% had a rate of progression to diabetes more than five times higher than those with FPG <6.1 mmol/l and HbA1c <6.1% after a mean follow-up of 1.6 years. In agreement with the 1998 WHO recommendation, those with an FPG ≥6.1 mmol/l but <7.0 mmol/l, especially if their HbA1c is ≥6.1%, should undergo an OGTT to confirm diabetes. Other subjects at risk for diabetes (such as those who are >45 years of age) with an FPG <6.1 mmol/l and/or an HbA1c ≥6.1% should have regular screening. Whether the use of a paired value of FPG and HbA1c, as a screening method will be superior to others needs further prospective study.

References
17. Ko GTC, Li JKY, Cheung AYK, Yeung VTF, Chow CC, Tsang LWW, Cockram CS, Chan JCN: Two-hour post-glucose loading plasma glucose is the main determinant for the progression from impaired glucose tolerance to diabetes in Hong Kong Chinese. Diabetes Care 22:2096–2099, 1999