

Combined Use of Fasting Plasma Glucose and HbA_{1c} Predicts the Progression to Diabetes in Chinese Subjects

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OBJECTIVE — We have previously suggested using the paired values of fasting plasma glucose (FPG) and HbA_{1c} 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 HbA_{1c} 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, 57 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 HbA_{1c} ≥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 HbA_{1c} <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 HbA_{1c} was ≥6.1% compared with those whose baseline FPG was <6.1 mmol/l and baseline HbA_{1c} was <6.1%.

CONCLUSIONS — For Chinese subjects with risk factors for glucose intolerance, the use of paired FPG and HbA_{1c} values helped to identify potential diabetic subjects. Those with an FPG ≥6.1 mmol/l and HbA_{1c} ≥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 HbA_{1c} <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 HbA_{1c} was ≥6.1%, should undergo an OGTT to confirm diabetes. Subjects with an FPG <6.1 mmol/l and/or an HbA_{1c} <6.1% should have regular screening using the paired values of FPG and HbA_{1c}.

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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 fast-

ing 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 HbA_{1c} to identify potential diabetic subjects (12). Only those with high FPG (6.1–6.9 mmol/l) and high HbA_{1c} (≥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 HbA_{1c} 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

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Abbreviations: ADA, American Diabetes Association; BP, blood pressure; CV, coefficient of variation; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; LR, likelihood ratio; OGTT, oral glucose tolerance test; PG, plasma glucose; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical characteristics of 208 nondiabetic Chinese subjects with risk factors for glucose intolerance at baseline and end of study

	Baseline	End of study
Age (years)	35.0 ± 7.7	36.6 ± 7.6*
BMI (kg/m ²)	24.8 ± 4.0	26.2 ± 19.1
Systolic BP (mmHg)	118.7 ± 16.8	121.8 ± 15.5
Diastolic BP (mmHg)	74.7 ± 10.0	77.6 ± 10.0
FPG (mmol/l)	5.36 ± 0.72	5.70 ± 1.62†
2-h PG (mmol/l)	7.55 ± 1.97	8.45 ± 3.2*
HbA _{1c} (%)	5.78 ± 0.75	5.98 ± 0.92*
Smoking (%)	5.3	—

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 the same research nurse using a standard mercury sphygmomanometer. The Korotkoff sound V was taken as the diastolic BP. The mean value of two readings measured 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. HbA_{1c} and fasting and 2-h PG concentrations were measured during the OGTT. Diabetes was diagnosed if FPG was ≥7.0 mmol/l or 2-h PG

was ≥11.1 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. HbA_{1c} 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 HbA_{1c} 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 criterion in subjects categorized according to the screening values of FPG (<6 mmol/l) and HbA_{1c} (<6%). Kaplan-Meier analysis was performed to study the progression to diabetes in subjects with various FPG and HbA_{1c} concen-

trations. 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 HbA_{1c} (≥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 HbA_{1c} 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 HbA_{1c} ≥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 HbA_{1c} ≥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 HbA_{1c} <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 HbA_{1c} was ≥6.1% compared with those whose baseline FPG was <6.1 mmol/l and baseline HbA_{1c} was <6.1%. The corresponding 50% “survival time” was 2.27 years (1.38–3.17) and 5.85 years

Table 2—Outcomes of the glycemic status of 208 subjects categorized according to baseline FPG and HbA_{1c} concentrations

Baseline FPG (mmol/l)	Baseline HbA _{1c} (%)	n (%)	OGTT*			LR	Follow-up (years)	Crude rate of progression to diabetes (%/year)
			Normal	IGT	Diabetes			
≥6.1	≥6.1	21 (10.1)	2	4	15	9.32	1.32 ± 1.20	44.1
≥6.1	<6.1	18 (8.7)	6	8	4	1.06	1.28 ± 0.57	17.4
<6.1	≥6.1	36 (17.3)	17	12	7	0.90	1.42 ± 0.73	13.7
<6.1	<6.1	133 (63.9)	65	50	18	0.58	1.68 ± 1.30	8.1
Total		208	90	74	44		1.60 ± 1.16	13.2

*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.

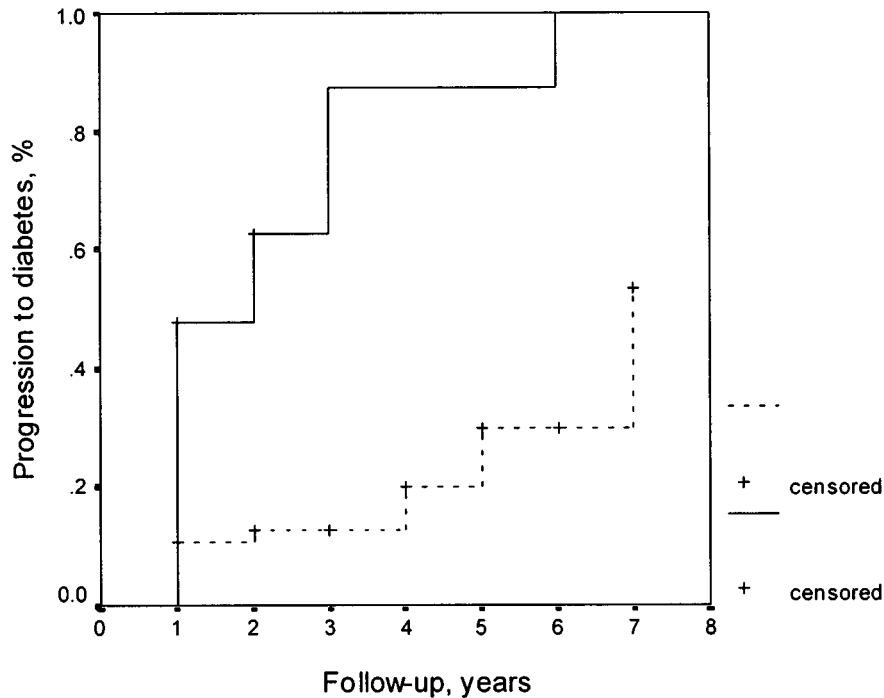


Figure 1—Progression to diabetes in subjects with FPG ≥ 6.1 mmol/l and HbA_{1c} $\geq 6.1\%$ versus FPG < 6.1 mmol/l and HbA_{1c} $< 6.1\%$ with Kaplan-Meier analysis. —, FPG ≥ 6.1 mmol/l and HbA_{1c} $\geq 6.1\%$; ---, FPG < 6.1 mmol/l and HbA_{1c} $< 6.1\%$. Log-rank test: $P < 0.001$.

(5.21–6.49), respectively (log-rank test: $P < 0.001$) (Fig. 1).

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 HbA_{1c}, 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 HbA_{1c} $\geq 6.1\%$ 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 HbA_{1c} $< 6.1\%$ (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 HbA_{1c} $\geq 6.1\%$ 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 HbA_{1c} 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 HbA_{1c} levels. They suggested that diabetes should not be diagnosed in those with FPG concentrations < 7.8 mmol/l, unless excess glycosylation (HbA_{1c} 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 HbA_{1c} ($> 6.2\%$).

In this study, we have shown that nondiabetic Chinese subjects with risk factors for glucose intolerance who had FPG ≥ 6.1 mmol/l and HbA_{1c} $\geq 6.1\%$ 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 HbA_{1c} $< 6.1\%$ 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 HbA_{1c} in predicting progression to diabetes. In this respect, a recent report has also shown that an HbA_{1c} 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 HbA_{1c} helped to identify potential diabetic subjects. Those with FPG ≥ 6.1 mmol/l and HbA_{1c} $\geq 6.1\%$ had a rate of progression to diabetes more than five times higher than those with FPG < 6.1 mmol/l and HbA_{1c} $< 6.1\%$ 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 HbA_{1c} is $\geq 6.1\%$, 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 HbA_{1c} $< 6.1\%$ should have regular screening. Whether the use of a paired value of FPG and HbA_{1c} as a screening method will be superior to others needs further prospective study.

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