Combined Use of a Fasting Plasma Glucose Concentration and HbA_{1c} or Fructosamine Predicts the Likelihood of Having Diabetes in High-Risk Subjects

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OBJECTIVE — To assess the validity of using fasting plasma glucose (FPG) concentrations in conjunction with HbA_{1c} or fructosamine for the screening of diabetes in high-risk individuals.

RESEARCH DESIGN AND METHODS — In this study, 2,877 Hong Kong Chinese (565 [19.6%] men; 2,312 [80.4%] women) with various risk factors for glucose intolerance underwent a 75-g oral glucose tolerance test (OGTT) for screening of diabetes. The risk factors included a family history positive for diabetes, a history of gestational diabetes or impaired glucose tolerance, and obesity.

RESULTS — Using World Health Organization (WHO) criteria, 1,593 (55.4%) had normal glucose tolerance, 657 (22.8%) had impaired glucose tolerance, and 627 (21.8%) had diabetes. When the 1997 American Diabetes Association (ADA) criteria were applied, 394 (13.7%) had diabetes with an FPG ≥7.0 mmol/l. Using multiple receiver operating characteristic curve analysis, the paired values of an FPG of 5.6 mmol/l and a HbA_{1c} of 5.5% gave an optimal sensitivity of 83.8% and specificity of 83.6% to predict a 2-h plasma glucose (PG) ≥11.1 mmol/l. Likewise, the paired values of an FPG of 5.4 mmol/l and a fructosamine level of 235 μmol/l (n = 2,408) gave an optimal sensitivity of 81.5% and specificity of 83.2%. An FPG ≥5.6 mmol/l and an HbA_{1c} ≥5.5% was 5.4-fold more likely to occur in diabetic subjects (based on the WHO criteria) compared with nondiabetic subjects. For paired parameters less than these values, the likelihood ratio of this occurring in diabetic subjects was only 0.11. Similarly, an FPG ≥5.4 mmol/l and a fructosamine ≥235 μmol/l was fivefold more likely to occur in diabetic subjects than in nondiabetic subjects, with both parameters less than these values having a likelihood ratio of 0.04. Using these paired values as initial screening tests, only subjects who had an FPG ≥5.6 mmol/l and <7.8 mmol/l and an HbA_{1c} ≥5.5% (n = 642) required an OGTT to confirm diabetes, thereby saving 77.7% [(2,877 − 642)/2,877] of the OGTTs performed. Similarly, only subjects who had an FPG ≥5.4 mmol/l and <7.8 mmol/l and a fructosamine ≥235 μmol/l (n = 526) required OGTT to confirm diabetes, meaning that 78.2% [(2,408 − 526)/2,408] of the OGTTs could have been saved. Based on the 1997 ADA criterion of an FPG cutoff value of 7.0 mmol/l, the corresponding numbers of OGTTs to be saved were 82.6% and 85.5%, respectively.

CONCLUSIONS — The paired values of FPG and HbA_{1c} or FPG and fructosamine helped to identify potentially diabetic subjects, the diagnosis of which could be further confirmed by the 75-g OGTT. Using this approach, ~80% of OGTTs could have been saved, depending on the diagnostic cutoff value of FPG.

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Abbreviations: ADA, American Diabetes Association; CV, coefficient of variation; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose; ROC, receiver operating characteristic curve; WHO, World Health Organization.

The 75-g oral glucose tolerance test (OGTT) using World Health Organization (WHO) criteria is considered to be the gold standard in the diagnosis of glucose intolerance (1). However, this test is labor-intensive, causes inconvenience to the patient, and often has poorly reproducible results (2,3). A single blood test is therefore desired in the diagnosis of diabetes. The diagnostic 2-h plasma glucose (PG) concentration of 11.1 mmol/l was based on the development of microangiopathic complications (4,5). However, the validity of this value is often limited by the uncertainty over the postprandial period. Although the fasting plasma glucose (FPG) is a more reproducible test, increasing data suggest that the diagnostic value of 7.8 mmol/l has low sensitivity (6–8). Our group (9,10) and others (11,12) have shown that the predicted FPG corresponding to the 2-h PG of 11.1 mmol/l lies at ~6 mmol/l. Recently, the American Diabetes Association (ADA) recommended an FPG diagnostic criterion of ≥7.0 mmol/l for diabetes (8). However, the validity of using this lower FPG cutoff value in diagnosing diabetes remains to be established.

HbA_{1c} and plasma protein (fructosamine) are useful indexes that reflect chronic glycemia. These values correlate with mean PG concentrations in the preceding 2–3 months and 2–3 weeks, respectively (13–17). Although these indexes are useful in monitoring glycemic control in diabetic patients, their use as a screening test for diabetes remains inconclusive (18–22). We examined the results of 2,877 OGTTs and assessed whether the use of HbA_{1c} or fructosamine (available in 2,408 subjects) improved the validity of FPG as a screening test for diabetes.

RESEARCH DESIGN AND METHODS

Patients and methods

The results of a 75-g OGTT performed in 2,877 Hong Kong Chinese subjects were

Table 1—*Clinical characteristics and glycemic indexes of the 2,877 Chinese subjects*

Variable	Total	Men	Women	*P* value
n	2,877	565	2,312	
Age (years)	36.6 ± 0.2	42.1 ± 0.5	35.2 ± 0.2	<0.001
BMI (kg/m²)	24.8 ± 0.1	25.1 ± 0.2	24.7 ± 0.1	0.173
Systolic blood pressure (mmHg)	118.7 ± 0.6	129.4 ± 1.8	116.9 ± 0.6	<0.001
Diastolic blood pressure (mmHg)	75.9 ± 0.3	81.3 ± 1.1	75.0 ± 0.4	<0.001
Fasting PG (mmol/l)	5.69 ± 0.03	5.89 ± 0.08	5.64 ± 0.04	0.004
2-h PG (mmol/l)	8.52 ± 0.08	9.04 ± 0.21	8.40 ± 0.09	0.004
HbA_{1c} (%)	5.92 ± 0.02	6.30 ± 0.05	5.83 ± 0.02	<0.001
Fructosamine (μmol/l)	250.5 ± 1.0 (*n* = 2,408)	265.1 ± 2.7 (*n* = 469)	247.0 ± 1.1 (*n* = 1,939)	<0.001

Data are means ± SEM. *P* value represents men vs. women.

examined. These subjects had known risk factors for glucose intolerance and were referred to the Diabetes and Endocrine Center of the Prince of Wales Hospital for diabetes screening. The risk factors for glucose intolerance included a family history of diabetes, a history of gestational diabetes, obesity, and a history of impaired glucose tolerance. The test was performed after 3 days of normal carbohydrate intake and physical activity and after an 8-h fast. No smoking was allowed during the test. FPG and 2-h PG were measured together with HbA_{1c} and fructosamine. Both the WHO and ADA criteria were used for the diagnosis of glucose intolerance (1,8).

Plasma glucose was measured by a glucose oxidase method (reagent kit; Diagnostic Chemicals, Los Angeles, CA). 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 inter- and intra-assay CVs for HbA_{1c} were ≤3.1% at values <8.5%. Fructosamine was measured using a commercial reagent kit (Roche, Basel, Switzerland) with a centrifugal analyzer (Cobas Bio; Hoffman-La Roche, Basel. Switzerland). The interassay CV was 8.4% at the low plasma fructosamine concentration (mean ± SD, 153 ± 12.9 μmol/l) and 4.2% at the high plasma fructosamine concentration (313 ± 13.0 μmol/l). The intra-assay CV was <5%. In Hong Kong Chinese subjects with normal OGTT using WHO criteria, the range for FPG was 2.6–7.4 mmol/l (mean ± SD, 4.8 ± 0.5 mmol/l); for HbA_{1c}, 2.9–6.9% (mean ± SD, 4.7 ± 0.6%); and for fructosamine, 123–316 μmol/l (mean ± SD, 224.8 ± 36.2 μmol/l) (23).

Statistical analysis

Statistical analysis was performed using the SPSS (version 6.0) software on an IBM-compatible computer. All results, unless otherwise noted, are expressed as means ± SEM. The optimal sensitivity and specificity of using FPG, HbA_{1c}, and fructosamine to predict a 2-h PG ≥11.1 mmol/l were examined by receiver operating characteristic curve (ROC) analysis. Age-adjusted partial correlation coefficients were used to test the associations between variables. A *P* value <0.05 (two-tailed) was considered to be significant. The likelihood ratio (24) was calculated to estimate the odds of having glucose intolerance using WHO criteria in subjects categorized according to the screening values of FPG, HbA_{1c}, and fructosamine.

RESULTS — The characteristics of the 2,877 subjects are summarized in Table 1. There were 565 men (19.6%) and 2,312 women (80.4%). The men were older and had higher systolic and diastolic blood pressure, FPG and 2-h PG concentrations, HbA_{1c}, and fructosamine than women. There was a close correlation among FPG, HbA_{1c}, and fructosamine (Table 2).

According to the WHO criterion, 627 (21.8%) subjects (181 male and 446 female) had diabetes with an FPG ≥7.8 mmol/l and/or a 2-h PG ≥11.1 mmol/l. Of these 627 subjects, 605 (96.5%) had a 2-h PG ≥11.1 mmol/l and 22 (3.5%; 8 [4.4%] male and 14 [3.1%] female) had an FPG ≥7.8 mmol/l and 2-h PG <11.1 mmol/l. Of the 605 subjects with 2-h PG ≥11.1 mmol/l, 384 (63.5%) had an FPG <7.8 mmol/l and 221 (36.5%) had an FPG ≥7.8 mmol/l (Table 3).

Using the new ADA diagnostic criteria, 394 (13.7%) subjects (112 male and 282 female) had diabetes, with an FPG ≥7.0 mmol/l. Of these 394 subjects, 337 (85.5%) had a 2-h PG ≥11.1 mmol/l and 57 (14.5%) had a 2-h PG < 11.1 mmol/l. Of the 605 subjects with a 2-h PG ≥11.1 mmol/l, 337 (55.7%) had an FPG ≥7.0 mmol/l and 268 (44.3%) had an FPG <7.0 mmol/l (Table 3).

Using a 2-h PG ≥11.1 mmol/l as the reference test, the ROC analysis was used to define the screening values for post–glucose loading hyperglycemia. An FPG of 5.8 mmol/l gave an optimal sensitivity of 85.1% and a specificity of 84.4%, an HbA_{1c} of 6.1% gave an optimal sensitivity of 77.5% and a specificity of 78.8%, and a plasma fructosamine concentration (*n* = 2,408; 469 male and 1,939 female) of 255 μmol/l gave an optimal sensitivity of 75.2% and a specificity of 76.9%. This was compared with a sensitivity of 36.5% with an FPG of 7.8 mmol/l. Using multiple ROC analysis, an FPG of 5.6 mmol/l and an HbA_{1c} of 5.5% gave an optimal sensitivity of 83.8% and specificity of 83.6% to predict a 2-h PG ≥11.1 mmol/l.

The subjects were further divided into four groups using these paired values (FPG = 5.6 mmol/l, HbA_{1c} = 5.5%), as shown in Table 4. Individuals with glucose intolerance as defined by the WHO criteria had increased likelihood of having a high FPG (≥5.6 mmol/l) together with a high HbA_{1c} (≥5.5%). Individuals with glucose intolerance had the lowest likelihood ratio for an FPG <5.6 mmol/l and an HbA_{1c} <5.5%.

Similarly, an FPG of 5.4 mmol/l and a fructosamine of 235 μmol/l gave an optimal sensitivity of 81.5% and specificity of

Table 2—*Age-adjusted partial correlations between FPG and 2-h PG, HbA_{1c}, and fructosamine*

	2-h PG	HBA_{1c}	Fructosamine
FPG	0.736 (<0.001)	0.640 (<0.001)	0.458 (<0.001)
2-h PG	—	0.511 (<0.001)	0.455 (<0.001)
HbA_{1c}	—	—	0.335 (<0.001)

Data are *r* (*P*).

Table 3—*Categorization of glycemic status using FPG and 2-h PG in the 2,877 subjects based on WHO or 1997 ADA diagnostic criteria*

FPG (mmol/l)	2-h PG (mmol/l)	Number of subjects (%)	WHO criteria	ADA (1997) criteria
<7	<11.1	2,215 (77.0)	Nondiabetic	Nondiabetic
	≥11.1	268 (9.3)	Diabetic	Diabetic
≥7.0 and < 7.8	<11.1	35 (1.2)	Nondiabetic	Diabetic
	≥11.1	116 (4.0)	Diabetic	Diabetic
≥7.8 mmol/l	<11.1	22 (0.8)	Diabetic	Diabetic
	≥11.1	221 (7.7)	Diabetic	Diabetic

83.2% to predict post–glucose loading hyperglycemia. The subjects were divided into four groups using these paired values, as shown in Table 5. Individuals with glucose intolerance had the highest likelihood ratio for having a high FPG (≥5.4 mmol/l) together with a high fructosamine (≥235 μmol/l). The lowest likelihood ratio was observed in subjects with low values of these parameters.

Based on these results, only subjects who had an FPG ≥5.6 and <7.8 mmol/l and an HbA_{1c} ≥5.5% (n = 642) required OGTT to confirm diabetes, thereby potentially saving 77.7% [(2,877 − 642)/2,877] of the OGTTs performed. Similar figures were found for male (72.2%) and female (79.1%) subjects. Similarly, only those who had an FPG ≥5.4 and <7.8 mmol/l and a fructosamine ≥235 μmol/l (n = 526) required an OGTT to confirm diabetes, meaning that 78.2% [(2,408 − 526)/2,408] of the OGTTs could be saved. The corresponding figures in male and female subjects were 76.6% and 83.8%, respectively.

If we adopted the new ADA criteria using an FPG ≥7.0 mmol/l to diagnose diabetes, only subjects who had an FPG ≥5.6 mmol/l and <7.0 mmol/l and an HbA_{1c} ≥5.5% (n = 500) required OGTT to confirm diabetes, thereby potentially saving 82.6% [(2877–500)/2877] of the OGTTs performed (79.5% in male subjects and 83.4% in female subjects). Similarly, only those who had an FPG ≥5.4 mmol/l and <7.0 mmol/l and fructosamine ≥235 μmol/l (n = 349) required an OGTT to confirm diabetes, meaning that 85.5% [(2408–349)/2408] of the OGTTs could be saved (81.0% in male subjects and 86.6% in female subjects).

CONCLUSIONS — In 1990, the prevalence of diabetes in Hong Kong was reported to be 4.5% using WHO criteria (25). A 1996 study showed a prevalence of 10% in Hong Kong Chinese (26). In the present analysis, the high prevalence of glucose intolerance (21.8%) was due to the high-risk nature of the subjects, the majority of whom had a family history positive for diabetes or a history of glucose intolerance. With regard to the female preponderance, gestational diabetes was considered an indication for diabetes screening in our hospital. Despite this high prevalence of glucose intolerance, in agreement with our previous study (9), the majority of subjects were diagnosed using the 2-h PG values.

The diagnostic 2-h OGTT PG value of 11.1 mmol/l was based on the development of microangiopathic complications (5) and was chosen as the reference test in our analysis. Because the performance of an OGTT is time-consuming and laborious, the ADA has recently recommended moving away from an OGTT to using the FPG as a diagnostic procedure. The 2-h OGTT value is still considered a valid diagnostic criterion, but the use of OGTTs is not recommended on a routine basis. Furthermore, the diagnostic FPG value of 7.8 mmol/l recommended by WHO has often been criticized as being too high in many racial groups (6–10). In Hong Kong Chinese, the FPG value corresponding to the 2-h PG of 11.1 mmol/l was 5.7 mmol/l (10). Among the nondiabetic subjects (2-h PG <11.1 mmol/l), those with an FPG of 5.7–7.8 mmol/l were more obese; had higher blood pressure, glycemic, and lipid indexes; and had higher urinary albumin concentrations than those with an FPG <5.7 mmol/l (9).

In the present analysis using a different data set, we found close correlations between PG, HbA_{1c}, and fructosamine. In agreement with our previous studies, an FPG of 5.8 mmol/l gave an optimal sensitivity of 85.1% and specificity of 84.4% in predicting a 2-h PG ≥11.1 mmol/l. Despite using a lower FPG cutoff value of 7.0 mmol/l, as recommended by the ADA, <60% of our subjects with 2-h PG ≥11.1 mmol/l would have been diagnosed. Hence a significant proportion of our diabetic subjects would have been missed if only FPG was used as the diagnostic criterion. Despite these limitations, the use of an FPG to estimate the prevalence of diabetes in population surveys will greatly increase the practicality of the study. However, this approach may be less desirable in clinical settings when high-risk subjects are screened with therapeutic implications. In these high-risk subjects, ideally both the FPG and 2-h PG should be available. To minimize the use of OGTTs without compromising the likelihood of diagnosing diabetes, we examined the possibility of using FPG and a glycemic index obtained from a single blood test to screen out subjects with low likelihood for diabetes and also select those with high likelihood of having diabetes for a confirmatory OGTT. Although combining tests so that both must exceed a cutoff level may result in increased specificity but decreased sensitivity, the use of a single test with a high cutoff value can have

Table 4—*The 2,877 subjects categorized according to paired values of FPG of 5.6 mmol/l and HbA_{1c} of 5.5% and the likelihood of having glucose intolerance (diabetes and impaired glucose tolerance) as defined by WHO criteria*

FPG (mmol/l)	HbA_{1c} (%)	Number of subjects	75-g OGTT			Likelihood ratio	
			Normal	IGT	Diabetes	Abnormal	Diabetes
≥5.6	≥5.5	880	132	221	527	7.03	5.36
≥5.6	<5.5	143	64	52	27	1.53	0.84
<5.6	≥5.5	965	683	234	48	0.51	0.19
<5.6	<5.5	889	714	150	25	0.30	0.10
	Total	2,877	1,593 (55.4%)	657 (22.8%)	627 (21.8%)		

IGT, impaired glucose tolerance; abnormal, likelihood ratio for abnormal glucose tolerance (diabetes and IGT); diabetes, likelihood ratio for diabetes.

Table 5—*The 2,408 subjects categorized according to paired values of FPG of 5.4 mmol/l and fructosamine of 235 μmol/l and the likelihood of having glucose intolerance (diabetes and impaired glucose tolerance) as defined by WHO criteria*

FPG (mmol/l)	Fructosamine (μmol/l)	Number of subjects	75-g OGTT			Likelihood ratio	
			Normal	IGT	Diabetes	Abnormal	Diabetes
≥5.4	≥235	695	154	164	377	5.82	4.98
≥5.4	<235	254	142	69	43	1.31	0.86
<5.4	≥235	684	546	102	36	0.42	0.23
<5.4	<235	775	660	108	7	0.29	0.04
	Total	2,408	1,502 (62.4%)	443 (18.4%)	463 (19.2%)		

IGT, impaired glucose tolerance; abnormal, likelihood ratio for abnormal glucose tolerance (diabetes and IGT); diabetes, likelihood ratio for diabetes.

an even worse sensitivity without improving specificity.

HbA_{1c} accounts for ~40% of the total blood hemoglobin (27) and has been found to be increased in diabetic patients (28). Similarly, fructosamine, a glycosylated plasma protein ketoamine, also reflects chronic hyperglycemia (29). These two indexes correlate with mean PG concentrations in the preceding 2–3 months and 2–3 weeks, respectively, in diabetic patients (13–17). Although these indexes are useful in the monitoring of glycemic control and adjustment of antidiabetic therapy, their use as a diagnostic test remains controversial. The sensitivity of HbA_{1c} in predicting glucose intolerance varies from 20 to 80% (18,19,22,30,31). In one study, although an HbA_{1c} >3 SDs of the mean was shown to be highly specific for diabetes, the sensitivity was only 48% (20). Others have shown that an HbA_{1c} >6% has a specificity of >90% to detect diabetes, but the sensitivity varied from 30 to 85% (32). In a meta-analysis using more than 8,000 HbA_{1c} and OGTT results, a cutoff value at the mean HbA_{1c} + 4 SDs gave a predictive value of 97% in diagnosing diabetes with 100% specificity, but only 36% sensitivity (33). With this low sensitivity, HbA_{1c} measurement cannot be recommended as the sole replacement for the OGTT (34). Similarly, the use of fructosamine as a screening test for diabetes has also been shown to have poor sensitivity and specificity (21,22,35).

In this study, we used a 2-h PG ≥11.1 mmol/l, the threshold value for development of microangiopathic complications (5), as the reference test in the ROC analysis. Using multiple ROC analyses, the paired values of an FPG of 5.6 mmol/l and an HbA_{1c} of 5.5% or an FPG of 5.4 mmol/l and fructosamine of 235 μmol/l provided the optimal sensitivity and specificity, both exceeding 80%, to predict post–glucose loading hyperglycemia. Using these paired values, we were able to show that an FPG ≥5.6 mmol/l together with an HbA_{1c} ≥5.5% was fivefold more likely to occur in diabetic than in nondiabetic subjects. This was compared with a likelihood of only 0.10 for diabetic subjects having an FPG <5.6 mmol/l together with an HbA_{1c} <5.5%. Similarly, the likelihood of having an FPG ≥5.4 mmol/l and fructosamine ≥235 μmol/l was approximately fivefold higher in diabetic than in nondiabetic subjects. The likelihood of an FPG <5.4 mmol/l and fructosamine <235 μmol/l occurring in diabetic subjects was only 0.04. Between the two glycemic indexes, fructosamine is less sensitive than HbA_{1c} in predicting chronic hyperglycemia. Furthermore, the interpretation of fructosamine may be influenced by low plasma albumin concentration and increased albuminuria (36). Nevertheless, the fructosamine assay has the advantages of being more readily automated, less labor-intensive, quicker, and cheaper than an assay for HbA_{1c} (37–39).

Although subjects with FPG and HbA_{1c} (or fructosamine) above the cutoff values had an increased likelihood of having diabetes, some only had impaired glucose tolerance, based on the WHO criteria. Both IGT and diabetes are associated with increased cardiovascular risks (40). However, diabetic subjects have the additional risk of developing microangiopathic complications (5), which calls for a more comprehensive assessment and treatment formulation. Hence, until a better test becomes available, it is prudent to confirm the diagnosis of diabetes by performing a 75-g OGTT in these individuals. In asymptomatic subjects in whom glucose intolerance is suspected, especially among those with risk factors for diabetes, such as a history of gestational diabetes, these paired values may be used as initial screening tests. If OGTTs are performed only in subjects with elevated values, over 77% of the OGTTs could have been saved. If an FPG cutoff value of 7.0 mmol/l was adopted (as suggested by the ADA), up to 85% of OGTT could be saved, since subjects with an FPG of 7.0–7.8 mmol/l only require a repeat FPG to confirm diabetes. Admittedly, a few diabetic individuals who have low screening values may be initially missed. However, in view of their risk factors for glucose intolerance, periodic screening is often recommended in these subjects, so that the diabetic individuals will eventually be identified. Finally, prospective studies are clearly needed to correlate these cutoff values and clinical events as well as their cost-effectiveness.

In summary, using multiple ROC analysis, the paired values of an FPG of 5.6 mmol/l and an HbA_{1c} of 5.5% as well as that of an FPG of 5.4 mmol/l and fructosamine of 235 μmol/l gave optimal sensitivity and specificity of over 80% to predict post–glucose loading hyperglycemia. Subjects who had these cutoff values or above were more likely to have diabetes than those with lower values. These paired values would help to identify potential diabetic subjects, the diagnosis of which could be further confirmed by the 75-g OGTT. Depending on the FPG cutoff value, ~80% of OGTTs could have been saved using this approach.

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