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ORIGINAL ARTICLE

Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance

Yaomin Hu · Wei Liu · Yawen Chen · Ming Zhang · Lihua Wang · Huan Zhou · Peihong Wu · Xiangyu Teng · Ying Dong · Jia wen Zhou · Hua Xu · Jun Zheng · Shengxian Li · Tao Tao · Yumei Hu · Yun Jia

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Abstract The aim of this study is to assess the validity of combined use of fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c) as screening tests for diabetes and impaired glucose tolerance (IGT) in high-risk subjects. A total of 2,298 subjects were included. All subjects underwent a 75-g oral glucose tolerance test (OGTT) and HbA1c measurement. Receiver operating characteristic curve (ROC curve) analysis was used to examine the sensitivity and specificity of FPG and HbA1c for detecting diabetes and IGT, which was defined according to the 1999 World Health Organization (WHO) criteria. (1) Based on the ROC curve, the optimal cut point of FPG related to diabetes diagnosed by OGTT was 6.1 mmol/l that was associated with a sensitivity and specificity of 81.5 and 81.0%, respectively; The optimal cut point of HbA1c related to diabetes diagnosed by OGTT was 6.1%, which was associated with a sensitivity and specificity of 81.0 and 81.0%, respectively; The screening model using FPG $\geq$ 6.1 mmol/l or HbA1c $\geq$ 6.1% had sensitivity of 96.5% for detecting undiagnosed diabetes; the screening model using FPG $\geq$ 6.1 mmol/l and HbA1c $\geq$ 6.1% had specificity of 96.3% for detecting undiagnosed diabetes. (2) Based on the ROC curve, the optimal cut point of FPG related to IGT diagnosed by OGTT was 5.6 mmol/l that was associated with a sensitivity and specificity of 64.1 and 65.4%, respectively; The optimal cut point of HbA1c related to IGT diagnosed by OGTT was 5.6%, which was associated with a sensitivity and specificity of 66.2 and 51.0%, respectively; The screening model using FPG $\geq$ 5.6 mmol/l or HbA1c $\geq$ 5.6% had sensitivity of 87.9% for detecting undiagnosed IGT; The screening model using FPG $\geq$ 5.6 mmol/l and HbA1c $\geq$ 5.6% had specificity of 82.4% for detecting undiagnosed IGT. Compared with FPG or HbA1c alone, the simultaneous measurement of FPG and HbA1c (FPG and/or HbA1C) might be a more sensitive and specific screening tool for identifying high-risk individuals with diabetes and IGT at an early stage.

Keywords Oral glucose tolerance test · Glycated hemoglobin A1c · Diabetes · Impaired glucose tolerance · Screening

Introduction

The oral glucose tolerance test (OGTT) using World Health Organization (WHO) criteria are considered to be the gold standard in the diagnosis of diabetes [1]. However, this test is time-consuming and laborious, 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. Although the use of fasting plasma glucose (FPG) is simpler and more reproducible [4, 5], the omission of the 2-h PG will miss a proportion of diabetic subjects who have normal FPG but elevated 2-h PG [6].

Glycated hemoglobin (HbA1c), which does not require special preparation, reflects the average plasma glucose and is accepted as the gold standard for assessing glycemic control in subjects with diabetes. Compared with the OGTT, HbA1c measurement is quicker and more convenient. HbA1c can be measured at any time of the day

Y. Hu · W. Liu (✉) · Y. Chen · M. Zhang · L. Wang · H. Zhou · P. Wu · X. Teng · Y. Dong · J. w. Zhou · H. Xu · J. Zheng · S. Li · T. Tao · Y. Hu · Y. Jia
Department of Endocrinology, Renji Hospital, Shanghai Jiaotong University, 200127 Shanghai, China
e-mail: amin1031@hotmail.com

regardless of the duration of fasting or the content of the previous meal. In recent years, the validity of HbA1c as a screening tool for diabetes has also been examined. Though some reports have suggested that HbA1c may not be a suitable screening test [7, 8]. Most of studies have suggested the opposite [9–12]. And these studies have been conducted in different countries and different ethnic populations. In different ethnic populations, there is no consensus on a suitable cutoff point for HbA1c in the detection of diabetes. And also till now, there is still no study on the validity of HbA1c as a screening tool for diabetes from China mainland population.

Impaired glucose tolerance (IGT), which is characterized by a blood glucose level between 7.8 and 11.1 mmol/l 2 h after a 75-g oral glucose load, can be diagnosed, by definition, only with the OGTT. IGT is associated with a higher risk of diabetes and cardiovascular disease. FPG is not useful in the screening of IGT. HbA1c is also not sufficiently sensitivity to be used as a screening method for IGT, although a combination of HbA1C and FPG has been used for identification of subjects with IGT in a clinical trial of prevention of type 2 diabetes [13].

Therefore, the purpose of this study is to assess the validity of a measurement of HbA1c as a screening test for undiagnosed diabetes from a population of Chinese Han nationality in Shanghai. Especially, we determined whether the combined use of FPG and HbA1c as screening tests enhanced the detection of diabetes and IGT in individuals at high risk for diabetes.

Research design and methods

Subjects

By retrieving data from medical examination center database (from December 2000 to December 2008) of Renji Hospital, and 3,100 Chinese Han nationality subjects over 18 years of age who had known risk factors for diabetes were invited for diabetes screening. And we received 2,298 subjects [mean age = 52.4 years (SD 13.3), sex ratio M/F 956:1342) who had at least one of known risk factors for diabetes and were referred to the Diabetes and Endocrine Department of Shanghai Renji Hospital for diabetes screening. The risk factors for diabetes included a family history of diabetes, a history of gestational diabetes, obesity (BMI $\geq$ 25 kg/m^2 or WHR $\geq$ 0.9 for male and WHR $\geq$ 0.85 for female), and a history of impaired glucose tolerance. All these subjects were Shanghai population. Pregnant women, patients with previously diagnosed diabetes, and patients receiving hypoglycemic treatment were excluded from the study.

Written, informed consent was obtained from subjects who agreed to participate in the study and the study had the approval of our local ethics committee.

Laboratory measurements

The test was performed after 3 days of normal carbohydrate intake and physical activity and venous blood samples were drawn after an overnight fast of at least 10 h. OGTT was performed with 75-g glucose and FPG and 2-h PG were measured together with HbA1c. 1999 WHO criteria were used [8]:

Normal glucose tolerance (NGT): FPG $<$ 6.1 mmol/l and 2-h PG $<$ 7.8 mmol/l;
Diabetes: FPG $\geqq$ 7.0 mmol/l or 2-h PG $\geqq$ 11.1 mmol/l;
Impaired glucose tolerance (IGT): FPG $<$ 7.0 mmol/l and 2-h PG $\geqq$ 7.8 mmol/l but $<$11.1 mmol/l;
Impaired fasting glucose (IFG): FPG $\geqq$ 6.1 mmol/l but $<$7.0 mmol/l and 2-h PG $<$ 7.8 mmol/l.

Plasma glucose was measured by a glucose oxidase method (reagent kit; Diagnostic Chemicals, Los Angeles, CA). HbA1c was measured by the high-performance liquid chromatography (HPLC) method with a BIO-RAD analyzer (Bio-Rad Variant II; Bio-Rad Laboratories, Hercules, CA, USA) which has been certified by the National Glycohemoglobin Standardization Program. The inter- and intra-assay CVs for HbA1c were 0.6 and 2.8%. And the normal range is 4.4–6.0%.

Statistical analysis

Data are presented as mean $\pm$ SEM. Categorical variables were compared by Chi-square analysis. Differences between continuous variables were evaluated by Student's *t* test. Receiver operating characteristic curve (ROC curve) analysis was used to examine the sensitivity and specificity of FPG and HbA1c for screening diabetes and IGT, which was defined according to the 1999 World Health Organization criteria. Subjects with undiagnosed diabetes were excluded in the calculation of sensitivity, specificity, and positive and negative likelihood ratios for IGT. Sensitivity is percentage of individuals with undiagnosed diabetes or IGT who had a positive screening test; specificity is percentage of individuals without undiagnosed diabetes or IGT who had a negative screening test. For each cut point, positive and negative likelihood ratios (LR) were calculated. The positive LR is the ratio of sensitivity to 1-specificity, and the negative LR is the ratio of 1-sensitivity to specificity. The LR was calculated to estimate the odds of having diabetes or IGT using OGTT criteria in subjects categorized according to the screening

values of FPG and HbA1c. P value <0.05 was considered significant. Data were evaluated using SPSS version 11.5 (SPSS, Chicago, IL).

Results

1. Based on 1999 WHO criteria, 2,298 subjects are divided into five groups. The characteristics of these five groups are summarized in Table 1. 830 had normal glucose tolerance(NGT), 110 had impaired fasting glucose(IFG), 380 had IGT, 183 had IGT and IFG,795 had diabetes. The prevalence of newly diagnosed diabetes was 34.6% ($n = 795$). The current criterion of FPG (≥7.0 mmol/l) for diabetes screening was used, 45.5% of diabetic subjects remained unidentified.
2. Figure 1a shows the ROC plot representing the sensitivity and specificity of HbA1c and FPG in detecting undiagnosed diabetes. Based on the ROC curve, the optimal cut point of FPG for detecting new diabetes diagnosed by OGTT was 6.1 mmol/l that was associated with a sensitivity and specificity of 81.5 and 81.0%, respectively (AUC 0.899, 95% CI 0.885–0.914); The optimal cut point of HbA1c for detecting new diabetes diagnosed by OGTT was 6.1%, which was associated with a sensitivity and specificity of 81.0 and 81.0%, respectively (AUC 0.899, 95% CI 0.885–0.914).

Table 2 shows the sensitivity and specificity of several different models of criteria for detecting undiagnosed diabetes. The model with only FPG ≥ 7.0 mmol/l had a low sensitivity (54.5%), although the specificity was 100%. Lowering the diagnostic threshold of FPG from 7.0 to 6.1 mmol/l resulted in a rise in sensitivity to 81.5%, but the specificity decreased to 80.5%. The model using HbA1c of 6.1% showed a similar sensitivity and specificity to that using FPG of 6.1 mmol/l. If either FPG was ≥6.1 mmol/l or HbA1c was ≥6.1%, then the sensitivity was 96.5% and also associated with a highest positive LR of 17.84; the combined model using both HbA1c ≥ 6.1% and FPG ≥ 6.1 mmol/l showed a high specificity (96.3%) and also associated with a lowest negative LR of 0.05.

3. Figure 1b shows the ROC plot representing the sensitivity and specificity of HbA1c and FPG in detecting undiagnosed IGT. Based on the ROC curve, the optimal cut point of FPG related to IGT diagnosed by OGTT was 5.6 mmol/l that was associated with a

Table 1 Clinical and laboratory data of 2,298 subjects

Group	Subject	Age (years)	Male/female	FPG (mmol/l)	2-h PG (mmol/l)	HbA1c (%)
NGT	830	48.72 ± 14.90	304/526	5.18 ± 0.50	6.08 ± 1.08	5.52 ± 0.42
IFG	110	55.53 ± 9.65*	43/67	6.34 ± 0.23*	6.51 ± 0.85*	5.83 ± 0.53*
IGT	380	52.76 ± 13.48*	149/231	5.45 ± 0.39*#	8.93 ± 0.92*#	5.87 ± 2.45
IFG + IGT	183	57.09 ± 10.90*,△	78/105	6.41 ± 0.23*,△	9.29 ± 0.93*,#,△	6.04 ± 0.71*
DM	795	54.70 ± 11.34*	382/413	7.34 ± 1.77*#,△,☆	14.53 ± 3.56*,#,△,☆	7.01 ± 1.22*,#,△,☆

Note: Compared with NGT * $P < 0.05$; compared with IFG # $P < 0.05$; compared with IGT △ $P < 0.05$; compared with IFG + IGT ☆ $P < 0.05$

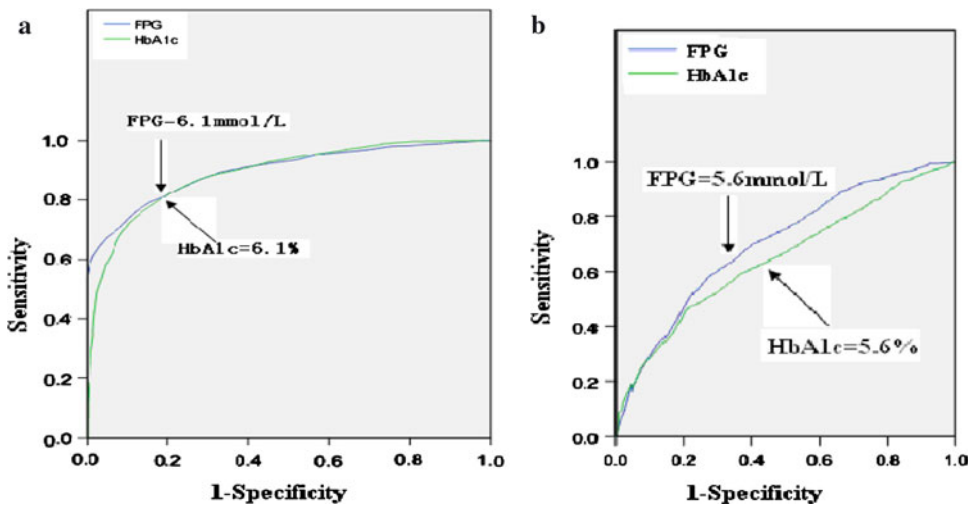

Fig. 1 ROC curve used to examine the sensitivity and specificity of FPG and HbA1c for screening diabetes (**a**) and for screening IGT (**b**)

Table 2 Sensitivities and specificities of different screening models for detecting diabetes

Screening model	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio	Negative likelihood ratio
FPG ≥ 5.6 mmol/l	92.5 (91.4, 93.6)	54.3 (52.3, 56.3)	2.02	0.14
FPG ≥ 7.0 mmol/l	54.5 (52.5, 56.5)	100 (100, 100)	∞	0.46
FPG ≥ 6.1 mmol/l	81.5 (79.9, 83.1)	80.5 (78.9, 82.1)	4.18	0.23
HbA1c ≥ 6.1%	81.0 (79.4, 82.6)	81.0 (79.4, 82.6)	4.26	0.23
FPG ≥ 6.1 mmol/l and HbA1c ≥ 6.1%	66.0 (64.1, 67.9)	96.3 (95.5, 97.1)	17.84	0.35
FPG ≥ 6.1 mmol/l or HbA1c ≥ 6.1%	96.5 (95.7, 97.3)	65.2 (63.3, 67.1)	2.77	0.05

Note: 95% CI: 95% confidence interval

Table 3 Sensitivities and specificities of different screening models for detecting IGT

Screening model	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio	Negative likelihood ratio
FPG ≥ 5.6 mmol/l	64.1 (61.7, 66.5)	65.4 (63.0, 67.8)	1.85	0.55
FPG ≥ 6.1 mmol/l	32.4 (30.0, 34.8)	88.3 (86.7, 89.9)	2.77	0.77
HbA1c ≥ 5.6%	66.2 (63.8, 68.6)	51.0 (48.5, 53.5)	1.35	0.66
FPG ≥ 5.6 mmol/l and HbA1c ≥ 5.6%	42.4 (39.9, 44.9)	82.4 (80.5, 84.3)	2.41	0.70
FPG ≥ 5.6 mmol/l or HbA1c ≥ 5.6%	87.9 (86.3, 89.5)	33.4 (31.0, 35.8)	1.32	0.36

sensitivity and specificity of 64.1 and 65.4%, respectively (AUC 0.701, 95% CI 0.674–0.728); The optimal cut point of HbA1c related to IGT diagnosed by OGTT was 5.6%, which was associated with a sensitivity and specificity of 66.2 and 51.0%, respectively (AUC 0.647, 95% CI 0.618–0.676). Table 3 shows the sensitivity and specificity of several different models of criteria for detecting IGT. The screening model using FPG ≥ 5.6 mmol/l or HbA1c ≥ 5.6% had sensitivity of 87.9% and associated with a high positive LR of 2.41 for detecting undiagnosed IGT. The screening model using FPG ≥ 5.6 mmol/l and HbA1c ≥ 5.6% had specificity of 87.9% and associated with a lowest negative LR of 0.36 for detecting undiagnosed IGT.

Discussion

Based on the WHO criteria, OGTT is the diagnostic standard for diabetes, but it is difficult to apply in large populations for screening purposes. For this reason, the American Diabetes Association (ADA) has proposed to use fasting plasma glucose for diagnosis, lowering diagnostic thresholds from 7.8 to 7.0 mmol/l [14]. Several observations showed that FPG alone does not have sufficient sensitivity to screen for diabetes [15–17]. In this study, based on the current guideline of FPG ≥ 7.0 mmol/l for diabetes screening, only 54.5% of diabetic subjects were detected. And from the ROC curve, the cutoff point of FPG corresponding to diabetes diagnosed by OGTT was 6.1 mmol/l, with sensitivity of 81.5% and specificity of 80.5%. This indicated that there was a large gap between FPG and OGTT criteria for diagnosing diabetes. Therefore, a significant proportion of diabetic subjects would have been missed if only FPG was used as the screening test for diabetes.

Although HbA1c is not currently recommended for the screening or diagnosis of diabetes [7, 8], there are several studies which advocate HbA1c as a screening test for undiagnosed diabetes [18–23]. This study demonstrated that HbA1c had the similar sensitive and specific for detecting undiagnosed diabetes as defined by a FPG ≥ 7.0 mmol/l in high-risk individuals with early diabetes. And our study also showed that the combined use of HbA1c and FPG made up for the lack of sensitivity in FPG alone. If both criteria were satisfied, the specificity was relatively high (96.3%), so these subjects would be regarded as having diabetes. If either FPG was ≥6.1 mmol/l or HbA1c was ≥6.1%, then the sensitivity was 96.5%. And this approach would overcome the large gap between FPG and 2-h PG criteria for diagnosing diabetes. In our study, the cutoff values of FPG ≥ 6.1 mmol/l and HbA1c ≥ 6.1% selected were similar to those proposed by other studies [23, 24]. But compared with these studies, there is a different sensitivity and specificity with the same cutoff values of FPG and HbA1c in our study. First, ethnic differences among these studies are an important reason,

which may be related to genetic differences in the concentration of haemoglobin, the rates of glycation and the lifespan or amount of red blood cell. Second, the inclusion criteria and laboratory measurements in these studies were varies. Our study included Chinese subjects who had known risk factors for diabetes, while some of studies from Bennett et al. [23] review included random samples from the general population. And the laboratory measurements of FPG and HbA1c are also different.

Till now, there is no study report on the validity of HbA1c as a screening tool for diabetes from China mainland population. But Ko GTC has reported similar study in Hong Kong Chinese. And the cut points of FPG and HbA1c for diabetes are different between these two studies. In Hong Kong Chinese study, the cut point of FPG is 5.6 mmol/l and HbA1c is 5.5%, while in our study, the cut point of FPG is 6.1 mmol/l and HbA1c is 6.1%. The reason maybe is the different criteria which have been applied. In Hong Kong study, 1985 WHO criteria were used, while in our study, 1999 WHO criteria were applied.

IGT, which is defined by a 2-h post-load glycemia between 7.8 and 11.1 mmol/l, is a risk factor for diabetes [25] and cardiovascular disease [26, 27]. The previous studies showed that determination of FPG or HbA1c is not useful in the screening of IGT [16, 28]. And the combined use of HbA1C and FPG has been proposed for the identification of patients with glucose intolerance to be enrolled in a clinical trial [13]. As these studies, our study also showed that either FPG or HbA1c was not reliable to identify IGT. And the combination of the two parameters, with a threshold of 5.6% for HbA1C and 5.6 mmol/l for FPG, improves the sensitivity and specificity of screening, facilitating the identification of individuals with IGT.

In this study, only Shanghai Han nationality subjects participated and the high-risk group enrolled in this study was not representative of the general population. Therefore, a large scale study in various populations in China should be done.

In conclusion, using ROC analysis, the cutoff values for FPG of 6.1 mmol/l and HbA1c of 6.1% had the similar sensitivity and specificity to predict diabetes, respectively. The combined use of HbA1c and FPG (FPG and/or HbA1C) might be more sensitive and specific screening tool for the early identification of high-risk individuals with early diabetes. On the other hand, both FPG and HbA1C are not suitable for screening for IGT; the combination of the two parameters (FPG and/or HbA1C) improves sensitivity and specificity, and could be used for case finding in clinical research.

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