Performance of Fasting Plasma Glucose and Postprandial Urine Glucose in Screening for Diabetes in Chinese High‑risk Population

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Abstract

Background: The conventional approaches to diabetes screening are potentially limited by poor compliance and laboratory demand. This study aimed to evaluate the performance of fasting plasma glucose (FPG) and postprandial urine glucose (PUG) in screening for diabetes in Chinese high-risk population.

Methods: Nine hundred and nine subjects with high-risk factors of diabetes underwent oral glucose tolerance test after an overnight fast. FPG, hemoglobin A1c, 2-h plasma glucose (2 h–PG), and 2 h–PUG were evaluated. Diabetes and prediabetes were defined by the American Diabetes Association criteria. The area under the receiver operating characteristic (ROC) curve was used to evaluate the diagnostic accuracy of 2 h-PUG, and the optimal cut-off determined to provide the largest Youden index. Spearman correlation was used for relationship analysis. **Results:** Among 909 subjects, 33.4% (304/909) of subjects had prediabetes, and 17.2% (156/909) had diabetes. The 2 h‑PUG was positively related to FPG and 2 h-PG ($r = 0.428$ and 0.551, respectively, both $P \le 0.001$). For estimation of 2 h-PG ≥ 7.8 mmol/L and $2 h-PG \ge 11.1$ mmol/L using $2 h-PUG$, the area under the ROC curve were 0.772 (95% confidence interval [*CI*]: 0.738–0.806) and 0.885 (95% *CI*: 0.850–0.921), respectively. The corresponding optimal cut-offs for 2 h-PUG were 5.6 mmol/L and 7.5 mmol/L, respectively. Compared with FPG alone, FPG combined with 2 h-PUG had a higher sensitivity for detecting glucose abnormalities (84.1% vs. 73.7%, *P* < 0.001) and diabetes (82.7% vs. 48.1%, *P* < 0.001).

Conclusion: FPG combined with 2 h-PUG substantially improves the sensitivity in detecting prediabetes and diabetes relative to FPG alone, and may represent an efficient layperson‑oriented diabetes screening method.

Key words: Diabetes Screening; Fasting Plasma Glucose; Glycosuria; Prediabetes; Population-based Study; Type 2 Diabetes

Introduction

The prevalence of diabetes mellitus(DM) and prediabetes is rapidly increasing worldwide, especially in the developing countries.[1,2] As a result, both the increase in medical costs and the decrease in the quality of life are becoming formidable challenges.[3] The early diagnosis is of fundamental importance to the management of diabetes and prevention of diabetes‑related complications. Nevertheless, the majority of patients with type 2 diabetes are asymptomatic, and over 30% of type 2 diabetic patients have not been diagnosed

until systemic complications occurred.^[4] Therefore, screening for diabetes, in particular among high-risk

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population, is essential for achieving optimal outcomes of diabetes intervention.

To date, the conventional approaches to screening for diabetes include evaluation of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and FPG in combination with 2‑h plasma glucose (2 h‑PG) after a 75 g oral glucose tolerance test $(OGTT)$.^[5-7] However, FPG alone has not been sensitive enough in detecting postprandial glycemic excursions,[8] while HbA1c has not been recommended for diabetes screening in China because of several issues. For example, diabetes diagnosis based on HbA1c (i.e., HbA1c \geq 6.5%) was reported to result in a significant underestimation of the prevalence of diabetes in both community and hospital based diabetes screening patients in China.[9] Furthermore, HbA1c measurement is laboratory‑dependent and relatively expensive, which limit its application in population-based screening, especially in low‑income regions. OGTT has been used as the gold standard test for the diagnosis of diabetes, which involves venipuncture for blood sampling during fasting and at 2‑h after oral ingestion of 75 g glucose and is reported as the more commonly used approach in China.^[10] However, the compliance of a standard OGTT is often poor, mostly due to the addition of venipuncture and blood sampling at 2‑h after oral glucose. Therefore, alternative methods that are reliable, noninvasive, economical, and convenient are needed for diabetes screening.

The measurement of postprandial urine glucose (PUG) appears to be an attractive option, which reflects the glycemic excursions in excess of the renal glucose threshold. For example, semiquantitative measurement using reagent strips is frequently used to monitor glycosuria and is recommended by the International Diabetes Federation when blood glucose monitoring may not be accessible or affordable.[11] Quantitative measurement of PUG allows more precise assessment on the average elevation of postprandial glucose. Although it is limited by retrospective and indirect interpretation,^[12] we have shown that quantitative monitoring of urine glucose has comparable efficacy to blood glucose on glycemic control.^[13] However, its value in diabetes screening has not been reported. In this study, we evaluated the performance of FPG combined with 2 h-PUG in diabetes screening in Chinese high-risk population, with the measurements of FPG and 2 h‑PG after 75 g oral glucose challenge as reference tests.

Methods

Subjects

A total of 1035 subjects with high-risk factors of diabetes were recruited by advertisement from eight Community Health Service Centres in Nanjing, China, from September 2010 to September 2011 with a nonresponse rate of 12.2%. Eligibility of subjects was assessed through a face‑to‑face interview, according to the 2010 guidelines for prevention and treatment of type 2 diabetes in China. Risk factors for

prediabetes and diabetes include the following: (1) previously reported impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT); (2) being older than 40 years at the entry of the study; (3) body mass index (BMI) ≥ 24 kg/m² and/or the waist circumference ≥ 90 cm in males or ≥ 85 cm in females; (4) having a family history of diabetes in first-degree relatives (i.e., parents or siblings); (5) having an ethnic background of Han; (6) giving birth to a baby weighing more than 4 kg or being diagnosed with gestational diabetes; (7) hypertension (blood pressure \geq 140/90 mmHg) or being treated for high blood pressure; (8) high-density lipoprotein cholesterol below 0.91 mmol/L, or triglyceride above 2.22 mmol/L , or taking lipid-regulating drugs; (9) having a history of cardio‑cerebro‑vascular diseases or being physically inactive (<150 min/week); (10) having a history of transient hyperglycemia induced by steroid; and (11) presence of polycystic ovary syndrome in females. Subjects who presented one or more high-risk factors at the time of interview were considered eligible but were excluded if they met one of the following criteria: (1) unstable health conditions (i.e., unstable angina pectoris, blood pressure >200/100 mmHg, and infections); (2) severe psychiatric disturbance; (3) cancer on radio- and/or chemo-therapy; (4) taking medications which may potentially affect blood and/or urine glucose levels; or (5) suffering from chronic kidney disease, urinal tract infection, or benign prostate hyperplasia.

Study design

Eligible subjects were enrolled into the study after they provided written informed consent. The protocol was approved by the Research Ethics Committee of Zhongda Hospital and was conducted in accordance with the principles of the *Declaration of Helsinki* as revised in 2000.

After at least 10 h of overnight fast, subjects ingested 75 g anhydrous glucose dissolved in water to a volume of 250 ml within 5 min. Fasting venous blood was sampled for the measurements of FPG and HbA1c. At 2‑h after oral glucose, venous, and urine samples were collected for the measurements of 2 h-PG and 2 h-PUG.

The definition of glycemic status was based on the measurements of FPG and 2 h‑PG after OGTT, according to the cut-offs of American Diabetes Association.^[14] Briefly, diagnosis of diabetes is based on FPG \geq 7.0 mmol/L and/or 2 h–PG \geq 11.1 mmol/L. Prediabetes include IGT (i.e., 2 h–PG \geq 7.8 mmol/L and \leq 11.0 mmol/L) and/or IFG (i.e., FPG \geq 5.6 mmol/L and \leq 6.9 mmol/L). Normal glucose tolerance (NGT) is defined based on FPG \leq 5.6 mmol/L and 2 h-PG \leq 7.8 mmol/L. These were used as the references to evaluate the performance of FPG combined with 2 h-PUG in detecting both glucose abnormalities and diabetes.

Laboratory measurements

FPG and 2 h–PG were measured by glucose oxidase method using an automatic chemistry analyzer (Synchron LX-20, Bechman Coulter Inc., California, USA). HbA1c was determined by high-performance liquid chromatography (HPLC, D-10, Bio-Rad Inc., California, USA). Urine glucose concentrations were assayed using a quantitative urine meter (UG-201-H, Tanita Corporation, Tokyo, Japan).^[13] The high-sensitive amperometric glucose sensor allows accurate measurement in the range of 0–111.1 mmol/L with a rapid response time of 6 s.^[15]

Statistical analysis

All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The data are presented as mean ± standard deviation (SD). A *P* < 0.05 was considered statistically significant. A sample size of 460 subjects was calculated to have 81% power (at α = 0.05) to detect a 30% difference in sensitivity between two diagnostic tests,[9] assuming the inter-test discordant proportion of 50% and the prevalence of diseased individual of 10%. The 1035 subjects were recruited to the trial due to overestimation of the nonresponse and dropout rates in the community environment. Because 2 h‑PUG data were not normally distributed, Spearman's correlation was used to assess the relationships between 2 h-PUG and other glycemic variables, including FPG, 2 h‑PG, and HbA1c. Kruskal–Wallis test was first performed to compare the differences among subjects with different glycemic status, followed by Mann–Whitney U‑test for subgroup comparisons between diabetic subjects and subjects with isolated impaired fasting glucose (IIFG), isolated impaired glucose tolerance (IIGT), IFG and IGT, and NGT. To develop a new method that combines FPG and 2 h‑PUG for glycemic screening, Youden indexes with various cut-offs were calculated based on the receiver operating characteristic (ROC) curve analysis.^[16] Cut-off values of 2 h-PUG to predict the 2 h-PG of 7.8 mmol/L and 11.1 mmol/L were determined to provide the largest Youden indexes. McNemar's test was used to compare different ratios. The likelihood ratio (calculated as sensitivity/ $[1 -$ specificity])^[17] was calculated to estimate the odds of having glucose abnormalities and diabetes, based on the screening values of FPG and 2 h-PUG.

Results

General characteristics of study participants

Nine hundred and nine subjects(87.8% of the total number)

completed the study and were included in the analysis. BMI, waist-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and 2 h‑PUG were significantly higher in males than those in females without significant difference in FPG, 2 h-PG, or HbA1c [Table 1].

Glycemic status and categories

According to the predefined criteria, 909 subjects were categorized into five groups: (1) 156 (17.2%) subjects in newly diagnosed diabetes mellitus (NDDM) group; (2) 92 (10.1%) in IIGT group;(3) 138 (15.2%) in IIFG group; (4) 74 (8.1%) in IGT and IFG group; and (5) 449 (49.4%) in NGT group. Subjects with glucose abnormalities were older than those with NGT ($P < 0.05$). In addition, they had significantly higher BMI, WHR, SBP, DBP, and HbA1c than NGT group (all $P < 0.05$). 2 h–PUG was highest in the NDDM group, and higher in the IIGT and IGT and IFG groups than the IIFG and NGT groups (all *P* < 0.05) without significant difference between the IIFG and NGT groups [Table 2].

Correlation of 2 h‑postprandial urine glucose with fasting plasma glucose, 2 h‑plasma glucose, and hemoglobin A1c

The concentrations of 2 h–PUG were positively related to those of FPG ($r = 0.428$, $P \le 0.001$), 2 h-PG ($r = 0.551$, *P* < 0.001), and HbA1c (*r* = 0.467, *P* < 0.001) among 909 subjects. Similar but weaker relationships of 2 h-PUG with FPG, 2 h–PG, and HbA1c $(r = 0.16, 0.20, \text{ and } 0.34, \text{)}$ respectively, all $P < 0.05$) were observed in subjects with NDDM.

Evaluation of fasting plasma glucose combined with 2 h‑postprandial urine glucose in diabetes screening

ROC curves shown in Figure 1 represent the diagnostic accuracy of 2 h‑PUG for the estimation of 2 h–PG \geq 7.8 mmol/L and 2 h–PG \geq 11.1 mmol/L. The areas under the curves were 0.772 (95% confidence interval [*CI*]: 0.738–0.806) and 0.885 (95% *CI*: 0.850– 0.921), respectively, suggesting a good accuracy of 2 h-PUG in predicting 2 h-PG. Youden indexes for both were calculated to determine the optimal cut-off values of 2 h‑PUG. 2 h‑PUG of 5.6 mmol/L gave an optimal sensitivity of 54.4% and specificity of 89.7% to predict

Data are shown as a mean \pm SD. **F* values; *Z values SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose.

Data are shown as mean \pm SD, median (maximum, minimum), or *n* (%). $*P<0.001$, $*P<0.01$, $*P<0.05$, $*P>0.05$, compared with NGT group by LSD. NGT: Normal glucose tolerance, represents 2-h plasma glucose <7.8 mmol/L and FPG <5.6 mmol/L; NDDM: Newly diagnosed diabetes mellitus, represents 2‑h plasma glucose ≥11.1 mmol/L and/or FPG ≥7.0 mmol/L; IIGT: Isolated impaired glucose tolerance, represents 2‑h plasma glucose between 7.8 mmol/L and 11.0 mmol/L only; IIFG: Isolated impaired fasting glucose, represents FPG between 5.6 mmol/L and 6.9 mmol/L only; IGT: Impaired glucose tolerance, represents 2‑h plasma glucose between 7.8 mmol/L and 11.0 mmol/L; IFG: Impaired fasting glucose, represents FPG between 5.6 mmol/L and 6.9 mmol/L; LSD: Least significant difference; SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose.

Figure 1: Receiver operating characteristic curve of 2-h postprandial urine glucose test to detect a 2-h plasma glucose \geq 7.8 mmol/L (a) and a 2 h-plasma glucose \geq 11.1 mmol/L (b).

2 h‑PG of 7.8 mmol/L. 2 h‑PUG of 7.5 mmol/L gave an optimal sensitivity of 76.2% and specificity of 89.4% in the estimation of 2 h-PG of 11.1 mmol/L.

The combined utilization of FPG (\geq 5.6 mmol/L) and 2 h-PUG (\geq 5.6 mmol/L) had a sensitivity of 84.1% (387/460) and a specificity of 86.6% (387/447) for detecting glucose abnormalities. Its sensitivity is significantly higher than that of FPG alone (FPG \geq 5.6 mmol/L; sensitivity: 73.7% [339/460]) (χ^2 = 15.05, *P* < 0.001). By applying these paired values of FPG and 2 h-PUG in glycemia screening, 50.8% (462/909) subjects would be found normal and exempt from entailing a standard 75 g OGTT.

The combined measurements of FPG $(\geq 7.0 \text{ mmol/L})$ and 2 h-PUG (\geq 7.5 mmol/L) also had a better sensitivity (82.7% [129/156]) to identify diabetic patients relative to FPG alone (FBG \geq 7.0 mmol/L; sensitivity: 48.1% [75/156]) (χ^2 = 41.29, *P* < 0.001), with a specificity of 90.4% (681/753).

Subjects with diabetes or abnormal glucose tolerance had increased likelihood of having "abnormal" FPG and 2 h–PUG(i.e., \geq 5.6 mmol/L), and decreased likelihood of having "normal" FPG and 2 h-PUG (i.e., \leq 5.6 mmol/L) [Table 3].

Discussion

In this community-based, cross-sectional study, we showed that in Chinese high-risk population, the prevalences of diabetes and prediabetes approximated 17.2% and 33.4%, both of which were higher than those reported in general Chinese adults.[2,18] The high prevalence of impaired glucose metabolism in this high-risk population suggested that timely screening for diabetes is demanding. We have also demonstrated the diagnostic value of quantitative measurement of 2 h‑PUG in combination with the measurement of FPG. Despite a relatively low specificity, 2 h‑PUG combined with FPG has substantially improved the sensitivity in detecting both glucose abnormalities and diabetes and may represent a promising alternative for diabetes screening.

A large proportion of patients with prediabetes or diabetes are asymptomatic^[19,20] and often have delayed diagnosis.^[4]

Normal represents 2-h plasma glucose <7.8 mmol/L and FPG <5.6 mmol/L; IGT represents 2-h plasma glucose between 7.8 mmol/L and 11.0 mmol/L; Diabetes represents 2‑h plasma glucose ≥11.1 mmol/L and/or FPG ≥7.0 mmol/L; Abnormal represents 2‑h plasma glucose ≥7.8 mmol/L. LR: Sensitivity/ (1−specificity), which is used for assessing the value of performing a diagnostic test. They use the sensitivity and specificity of the test to determine whether a test result usefully changes the probability that a condition exists. FPG: Fasting plasma glucose; 2 h-PUG: 2-h postprandial urine glucose; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test; LR: Likelihood ratio.

The latter is likely to reflect that the present tools for diabetes screening are suboptimal. For example, assessment of diabetes risk scores is economical, but it is largely dependent on self‑report, such that the demographic, behavioral, and medical information are subjective. Therefore, it may be simply used as an initial assessment tool to identify the high-risk individuals. Although a 75 g OGTT can most acutely confirm the diagnosis of diabetes and prediabetes, it has not been recommended as a routine test for diabetes screening due to the unsatisfactory compliance.^[21] Recently, HbA1c being >6.5% has been advocated as a diagnostic criterion of DM while levels ranging from 5.7% to 6.4% are considered risky.[9,22‑24] However, there is evidence that HbA1c‑based diagnosis of diabetes may lead to a significant underestimation in the Chinese population.^[9] In addition, HbA1c measurement is laboratory‑dependent and not inexpensive. In this study, although HbA1c levels were greater than 6.5% in NDDM, but not in these with IFG or IGT, application of HbA1c from 5.7% to 6.4% to predict IGT and/or IFG only yielded a sensitivity of 63.8% and specificity of 53.9% (data not shown). Moreover, HbA1c combined with FPG was still weak in finding patients with IGT. Therefore, HbA1c measurement did not seem to be an optimal method for diabetes screening. As a result, FPG test is frequently recommended. Unfortunately, as previously reported,[25,26] we showed that when FPG test alone was performed, subjects with IIGT and nearly half of the NDDM patients would be undiagnosed.

In this study, we found that FPG combined with 2 h‑PUG resulted in a substantial improvement in the efficacy of glycemic screening, compared to the measurement of FPG alone. Although the diagnostic specificity by these paired values was relatively low, the combined use of FPG and 2 h‑PUG narrowed the suspected subjects who would otherwise require a standard 75 g OGTT for diagnosis. As a result, at least 50% of OGTTs could be saved. In addition, the measurement of 2 h-PUG entails a minimal cost and does not cause any discomfort. Therefore, it is likely to substantially improve the patient compliance. Previously, the measurement of urine glucose in diabetes screening has been largely overlooked, probably because it was limited by semiquantitative, retrospective, and indirect interpretations, although it was reinstated in guidelines, drug benefit programs, and educational programs.[27] In contrast to the

use of traditional urine dipsticks, we were able to precisely quantity 2 h‑PUG in this study by a highly sensitive urine meter.

The occurrence of glycosuria is known to be a result of plasma glucose concentrations in excess of the renal threshold for glucose and is, therefore, indicative of the magnitude of hyperglycemia.[28‑30] In line with this concept, we have demonstrated that 2 h-PUG was related directly with FPG, 2 h-PG, and HbA1c. Furthermore, subjects with glucose intolerance or diabetes had increased the likelihood of abnormally high FPG and 2 h‑PUG and decreased the likelihood of normal FPG and 2 h‑PUG. We have previously shown that self-monitoring of urine glucose in noninsulin-treated type 2 patients has comparable efficacy on glycemic control, and facilitates better compliance than self-monitoring on blood glucose without increasing the risk of hypoglycemia.[13] Interestingly, the relationships between the 2 h‑PUG and the glycemic variables appeared to be weaker in patients with NDDM compared with the whole study population, which may be accounted for by the smaller sample size and the wider range of renal threshold for glucose in subjects with NDDM.[31] Therefore, quantification of urine glucose in conjunction with evaluation of the renal threshold is warranted for further evaluation. Alternatively, it might suggest that 2 h-PUG is more sensitive in reflecting glycemic excursions in prediabetes, which would support the use of 2 h-PUG for diabetes screening.

The limitations of our study should be recognized. First, the study subjects were recruited from limited Community Health Service Centers in one Chinese city, which might cause selective bias. Translation of the epidemiological data into the whole population should be cautious. Second, the definition of the glycemic status was based on the measurement of FPG and 2 h-PG after a 75 g oral glucose challenge while a repeated 2 h‑OGTT for confirmation was not performed, due to the poor compliance. Third, the renal glucose threshold was not evaluated in the study, the variation of which may affect the urine glucose levels and prediction of glycemic status. However, subjects who were considered to potentially have a renal impairment at the interview were excluded. Fourth, we did not collect multiple urine samples after oral glucose administration in this study. Future research is warranted to investigate whether 2‑h

urine sample represents the best timing for the assessment of postprandial glycemic excursions. Finally, PUG may vary with geographical and behavioral differences. Further investigation involving multiple cities is necessary.

In conclusion, our study has demonstrated that as an easy and economical approach, FPG combined with 2 h-PUG has a high sensitivity in detecting glucose abnormalities metabolism, whereby narrowing down the target population and saving unnecessarily performed OGTT. The combined measurements of FPG and 2 h‑PUG may not replace the diagnostic value of a 2 h‑OGTT, but represents a promising alternative for diabetes screening, particularly in low-income regions.

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Conflicts of interest

There are no conflicts of interest.

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