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The utility of fasting glucose for detection of prediabetes

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Abstract

Treatment of prediabetes attenuates progression to type 2 diabetes mellitus. The American Diabetes Association (ADA) previously defined prediabetes as either impaired fasting glucose (IFG) = 6.1 to 6.9 mmol/L (110-125 mg/dL) and/or impaired glucose tolerance (IGT) (2-hour postload glucose of 7.8-11.0 mmol/L [140-199 mg/dL]). For practical reasons, fasting plasma glucose (FPG) is commonly used for diabetes screening. Recently, the ADA lowered the fasting glucose threshold value for IFG from 110 to 100 mg/dL. Our objective was to determine the utility of FPG alone for detecting prediabetes in African Americans. Oral glucose tolerance test (OGTT) data from a cohort of 304 young adult African American men and women were examined. We calculated prediabetes prevalence using the previous ADA criteria and examined the effect of lowering the IFG threshold value for IFG to 100 mg/dL. The prediabetes prevalence in this cohort using the previous ADA criteria was 20.4% (n = 62). Of the 62 cases, 8 had IFG, 45 had IGT, and 9 had IFG together with IGT. Fasting plasma glucose testing alone detected 17 (27.4%) prediabetic cases, whereas a complete OGTT detected 54 (87.1%). Lowering the IFG threshold value to FPG = 100 mg/dL identified 13 of the 45 IGT-only cases. However, this lower IFG threshold increased prediabetes prevalence in the overall cohort from 20.4% to 31.9%. In conclusion, in young adult African Americans, an ethnic group at high risk for developing diabetes, FPG testing alone may be inadequate for diagnosing prediabetes. Until alternative strategies are identified, an OGTT is presently the best method for detecting the prediabetic condition in these high-risk patients.

1. Introduction

The prevalence of diabetes, along with its devastating effects on life expectancy and quality of life, continues to rise in epidemic proportions worldwide [1]. In the United States alone, in 1998, approximately 16 million individuals—6% of the entire population—met the diagnostic criteria for diabetes mellitus (DM). Prediabetes is estimated to affect 11.9 million individuals in the United States [2]. The Diabetes Prevention Program (DPP) demonstrated that prediabetic individuals are at extremely high risk for progression to overt DM [3].

Recent data have also shown that both lifestyle and pharmacologic therapy can alter the progression of prediabetes to overt diabetes [3-6]. The 3 largest studies of prediabetes prevention to date include the Finnish, DPP, and the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trials. In the Finnish Diabetes Prevention Study of more than 500 subjects with impaired glucose tolerance (IGT) [4], the reduction in diabetes incidence in the intervention group was directly related to the degree of improvement in lifestyle (diet and exercise) changes. The DPP conducted in the United States involved more than 3000 subjects [3]. The investigators concluded that both lifestyle intervention and metformin were effective in slowing progression of prediabetes to overt diabetes, although lifestyle changes were more effective. In the 1429-subject STOP-NIDDM trial, subjects randomized to receive acarbose experienced a 36% relative risk reduction in their likelihood of developing type 2 DM compared with subjects taking placebo [5]. Because there is now clear evidence of benefit from clinical intervention in the prediabetic condition, it is important to identify and intervene in prediabetic individuals.

For detection of DM, fasting plasma glucose (FPG) alone is commonly used as a screening test. This practice is based

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on the relative convenience and lower cost of FPG compared with an oral glucose tolerance test (OGTT) [7]. The 1997 American Diabetes Association (ADA) definition of impaired glucose regulation had been impaired fasting glucose (IFG) = 6.1 to 6.9 mmol/L (110-125 mg/dL) and/or IGT, defined as 2-hour postload glucose (2-hour PG) = 7.8 to 11.0 mmol/L (140-199 mg/dL) [7]. In 2003, based on epidemiological data from Pima Indian, Hoorn, San Antonio, and Mauritius cohorts, the Expert Committee of the ADA newly defined prediabetes by lowering the threshold value for IFG from 6.1 mmol/L (110 mg/dL) to 5.5 mmol/L (100 mg/dL) [8].

The purpose of this analysis was to determine the utility of FPG alone for detecting prediabetes in African Americans, an ethnic group at high risk for developing diabetes.

2. Methods

Data were examined from a cohort of young adult African American men and women enrolled in investigations of cardiovascular risk. Subjects with known diabetes were excluded from initial enrollment. Oral glucose tolerance test data from 304 individuals in the cohort were examined. Women who were pregnant, lactating, or up to 6 months postpartum were excluded from analysis. Written informed consent was obtained from each participant at the time of enrollment on an institutionally approved protocol and consent form. Female participants were evaluated during the follicular phase of the menstrual cycle to reduce hormone-induced variability.

2.1. Measurements

Information on health status and current health behaviors was obtained by interview. Height and weight were measured, and body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters.

An OGTT was conducted after a 12-hour overnight fast. A fasting blood sample for plasma glucose was obtained and then 75 g of glucose solution (Glucola; Ames Diagnostics, Elkhart, IN) was ingested. Blood samples were obtained at 30, 60, and 120 minutes after ingestion and were later assayed for glucose concentrations. A second fasting sample was obtained 4 to 12 weeks later, after another 12-hour overnight fast. Subjects were not informed of the results from the first test until they returned for the second test. Collected whole blood was centrifuged immediately after collection, and the plasma samples were frozen at −80°C until the time of assay. Plasma glucose concentration was analyzed with the glucose oxidase technique (YS Model 27; Glucostat, Yellow Springs, OH). The coefficient of variation for the glucose assay was less than 1%.

Table 1
Study sample characteristics

Demographic	Males	Females
No. of subjects	107	197
Age (y)	31.0 ± 3.7	32.6 ± 4.2
Height (m)	1.78 ± 0.075	1.64 ± 0.07
Weight (kg)	87.7 ± 19.8	85.9 ± 24.1
BMI (kg/m^2)	27.8 ± 6.0	31.9 ± 8.7
% Obese	28.7	53.3
Diabetic (n)	3	16

Table 2
Effect of fasting glucose threshold on prediabetes detection (total cohort size N = 304)

FPG criteria for prediabetes (IFG) (mg/dL)	Total no. of prediabetic subjects, n (%)	IFG only (n)	IFG and IGT (n)	IGT only (n)
110-125	62 (20.4)	8	9	45
100-125	97 (31.9)	43	22	32

2.2. Data analysis

Statistical analyses were performed using SAS version 8.0 software (SAS Institute, Cary, NC). Subjects were classified in 3 groups according to glucose tolerance status as defined by the 1997 ADA criteria [7].

- Normal glucose tolerance (NGT): FPG of less than 6.1 mmol/L (110 mg/dL) and 2-hour PG of less than 7.8 mmol/L (140 mg/dL).
- Prediabetic: FPG of 6.1 to 6.9 mmol/L (110-125 mg/dL) and/or IGT (2-hour PG of 7.8-11.0 mmol/L [140-199 mg/dL]).
- Diabetic (DM): FPG of more than 7.0 mmol/L (126 mg/dL) and/or 2-hour PG of 11.1 mmol/L or more (200 mg/dL).

The data were analyzed to determine the number of prediabetes cases detected with FPG alone and the number of prediabetes cases detected using 2-hour PG alone. We then determined whether lowering the threshold value for IFG to 100 mg/dL would increase the detection of prediabetic cases that had been identified by IGT only. The change in overall prevalence of prediabetes with use of the lower threshold for IFG was also calculated.

The reproducibility of FPG was examined by Spearman correlation analysis. The stability of FPG for glycemic status classification was also examined by comparing the glycemic status between the 2 samples.

3. Results

The study cohort is characterized in Table 1. A total of 304 young adult African American men and women (mean age, 31 and 32.6 years, respectively) were included in this investigation. In the study cohort, 28.7% and 53.3% of men and women, respectively, were obese (defined by BMI ≥ 30). Glucose tolerance classification of this cohort according to the 1997 ADA criteria [7] designated 73.4% of our study sample as NGT status, 20.4% as prediabetic, and 6.2% as diabetic. The effect of fasting glucose threshold on prediabetes detection rates is shown in Table 2. With IFG defined between 110 and 126 mg/dL, FPG alone would detect only 17 of the 62 prediabetic cases in this study

Table 3
Stability of glycemic status classification using repeat FPG testing (total N = 280): diabetic subjects excluded

Glycemic status classification	Sample 1 (n)	Sample 2 (n)	Same classification with both tests	% Agreement of sample 2 with sample 1
IFG = FPG 110-125 mg/dL				
Normoglycemic	260	273	254	97.7
IFG	20	7	1	5.0
IFG = FPG 100-125 mg/dL				
Normoglycemic	213	229	186	87.3
IFG	67	51	24	35.8

cohort. Of the 62 cases, 8 had IFG, 45 had IGT, and 9 had IFG together with IGT. Fasting plasma glucose testing alone detected 17 (27.4%) prediabetic cases, whereas a complete OGTT detected 54 (87.1%). Therefore, 45 of the 62 prediabetic cases would be undetected if FPG alone were used to screen for prediabetes.

The data were then reanalyzed to determine if lowering the FPG threshold value for IFG from 110 to 100 mg/dL to define IFG would improve identification of the 45 prediabetic cases that were previously detected with IGT only. Lowering the FPG threshold identified 13 of the 45 previously IGT-only cases. When the lower FPG threshold was applied to the entire study cohort, an additional 35 individuals met the IFG criteria for prediabetes (100-126 mg/dL), increasing the prediabetes prevalence in the cohort from 20.4% to 31.9%.

Two samples obtained and assayed for FPG on separate occasions were obtained from each of the 280 nondiabetic cases in the cohort and compared by correlation analysis to determine the reproducibility of FPG. The Spearman correlation coefficient was 0.36 ($P < .0001$). Although the r value is statistically significant, this correlation coefficient is relatively low. The stability of FPG as a measure of glycemic status classification is shown in Table 3. When IFG is defined by FPG = 110 to 125 mg/dL, 254 of 260 subjects designated as normoglycemic by the first sample remained normoglycemic with the second sample, resulting in 97.7% agreement of the second sample with the first sample for classification of normoglycemic status. In contrast, only 1 of the 20 subjects with IFG on the first sample had a second sample with IFG, resulting in 5.0% agreement in classification of prediabetic status. The second sample from the remaining 19 cases was normoglycemic. When the same analysis is applied with IFG = 100 to 125 mg/dL, the agreement in classification of normoglycemic status (FPG <100 mg/dL) was 87.3%. The agreement in classification of prediabetic status of the second FPG sample with the first was 35.8%.

4. Discussion

In a cohort of young adult African Americans, an ethnic group at high risk for developing diabetes, many prediabetic subjects have IGT without IFG. Lowering the FPG threshold for IFG identifies more prediabetic subjects, but still results in failure to detect most of the IGT-defined prediabetic cases. In addition, using the lower threshold causes the overall prevalence of individuals defined as prediabetic to increase from 20.4% to 31.9%, substantially adding to the number of individuals labeled as having extremely high risk for developing DM. Without performing 2-hour postchallenge testing, approximately one third of prediabetic cases would remain undiagnosed and at risk. Although use of FPG alone is currently favored clinically over 2-hour PG because of the relative cost and inconvenience associated with an OGTT, a substantial proportion of prediabetic subjects will be missed when FPG alone is used to screen African Americans.

Previous studies have examined IFG as a surrogate measure for 2-hour PG [9-12]. A meta-analysis of 29 108 European subjects showed that 31% of diabetic subjects had a nondiabetic fasting glucose but a diabetic 2-hour glucose value, very similar to our findings for prediabetic values in African Americans [9]. More recently, the analysis by Drzewoski and Czupryniak [10] of 1554 elderly Central European subjects at high risk for glucose metabolic disturbances found that only 16.6% of prediabetes or diabetes cases would have been diagnosed using FPG alone vs 41.3% of cases using 2-hour PG testing alone. A study including both younger and older Italian subjects (range, 17-66 years) by Schianca et al [11] reported that FPG alone and 2-hour PG alone would detect 38% and 77% of prediabetic subjects, respectively. Another European study conducted by Lindahl et al [12] showed that only 13% and 19% of men and women, respectively, with IFG fulfilled criteria for IGT. In our African American subjects, 34% of individuals with IFG as currently defined also had IGT. Although these studies were performed using subjects of different ethnicities, they all consistently demonstrate the higher sensitivity of OGTT compared with FPG testing for detecting prediabetes.

Our study cohort consisted exclusively of young adult African Americans, which may limit generalizability of our results to the general population. However, our results are clinically important because African Americans are known to be an ethnic group at high risk for type 2 DM [13]. Little information is available regarding the extent of prediabetes in younger samples of high-risk ethnic groups who could benefit substantially from early preventive intervention.

Although this and other studies have examined the IFG as a surrogate measure for IGT [9-12], it is known that IFG is not equivalent to IGT. The overlap between subjects with IFG and IGT is incomplete enough to suggest that they might represent different metabolic categories of impaired glucose regulation with differences in their pathogenesis. Typically, IFG is found in older individuals and is associated with impaired insulin secretion, whereas IGT is primarily associated with insulin resistance [14]. However, both IFG and IGT are associated with metabolic deterioration and

progression to diabetes over time if untreated. The OGTT includes both a fasting glucose test and a 2-hour postload glucose, therefore, detecting all individuals with IFG and/or IGT. This is clinically more desirable than detecting only those individuals with IFG.

The often cited poor reproducibility of the OGTT compared with FPG is based on its performance in the diagnosis of diabetes and IGT, resulting in overestimation of these conditions [15]. For example, 15% of the 67 Italian subjects with IGT in the study by Riccardi et al [16] reverted to normoglycemia when 2-hour PG was repeated. However, in our cohort of young adult African Americans, FPG testing demonstrated even lower reproducibility for defining prediabetes. Specifically, 95% and 64% of individuals initially classified as prediabetic by FPG (IFG = FPG 110-125 mg/dL and IFG = FPG 100-125 mg/dL definitions, respectively) reverted to normoglycemia with repeat FPG testing (Table 3). The 2 serial FPG values in our cohort were poorly correlated (Spearman correlation = 0.36; $P < .0001$), and classification of prediabetic subjects with serial FPG testing was inconsistent (5% and 35.8% agreement with the 2 IFG definitions; Table 3).

The relatively poor performance of FPG compared with OGTT could be explained by the poor correlation between FPG and measures of insulin sensitivity. In a previous study, we found that FPG in this same study cohort was poorly correlated with insulin sensitivity measured directly with the euglycemic hyperinsulinemic clamp procedure [17]. Of all the indirect indices of insulin sensitivity derived from an OGTT, fasting glucose had the poorest association with direct measures of insulin sensitivity.

Because the etiology of type 2 DM is largely related to insulin resistance, it follows that a poor correlation between FPG and insulin sensitivity (or resistance) would lead to poor performance of FPG in screening and diagnosis of diabetes/prediabetes. These findings are also consistent with the current belief discussed above—that IFG is associated with impaired insulin secretion, whereas IGT is primarily associated with insulin resistance.

Because the OGTT is more expensive and more burdensome to the patient, the FPG is used clinically in diabetes screening. Unlike the OGTT, however, the FPG fails to detect all prediabetes cases. The prediabetic condition itself also confers increased cardiovascular risk [13,18,19]. The existence of cardiovascular injury before the development of overt diabetes confers clinical importance for detecting and intervening at earlier stages in the deterioration of glucose metabolism. Both lifestyle and pharmacologic therapy are effective strategies in preventing the progression of prediabetes to overt DM. Prediabetes treatment reduces the number of individuals at risk for the high morbidity and mortality associated with diabetes.

Our study findings also demonstrate the impact of the recent ADA revision of the lower limit for defining IFG from 110 to 100 mg/dL. We have shown that there is a large increase in the proportion of young adult African American individuals in our cohort who are newly defined as prediabetic by the revised ADA criteria. Besides the personal impact of being labeled with the diagnosis, there is also a large potential societal impact from the increased medical expenditures directed toward preventing diabetes in these individuals. This may not be appropriate, in light of a recently published study of 2763 postmenopausal women with coronary artery disease by Kanaya et al [19]. Subjects with IFG defined with the revised ADA IFG definition (FPG = 100-125 mg/dL) did not have poor cardiovascular outcomes, unlike subjects defined with IFG according to the former ADA definition (FPG = 110-125 mg/dL). Our study results are somewhat limited by the lack of prospective follow-up data demonstrating the clinical implications of our findings. More outcomes studies like the one performed by Kanaya et al are needed to determine the most clinically useful IFG definition.

Ideally, only individuals at highest risk of developing diabetes, and therefore most in need of preventive intervention, should be categorized as prediabetic. Both C-reactive protein and proinsulin have been shown to predict development of diabetes in large cohort studies [20-24]. Future longitudinal studies and correlation analyses of FPG with C-reactive protein and proinsulin levels would be useful in determining the best definition for IFG.

5. Conclusions

Based on these data, the OGTT may have greater utility in screening for prediabetes in African Americans, an ethnic group at high risk for developing diabetes. Applying the revised ADA definition of IFG = 5.5 to 6.9 mmol/L (100-125 mg/dL) improves sensitivity of FPG for detecting prediabetes compared with the previous definition, but also defines more individuals in the population as prediabetic. Other screening strategies that use a combination of more easily obtained laboratory values (such as fasting glucose, HbA_{1c}) along with risk factors (such as hypertension or family history of diabetes) may eventually be developed that will show a high degree of sensitivity and specificity in the detection of prediabetes. Presently, however, the OGTT is the most effective measure for reliably detecting prediabetes in the high-risk ethnic group of African Americans.

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