ARTICLE

Glucose challenge test screening for prediabetes and undiagnosed diabetes

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Abstract

Aims/hypothesis Diabetes prevention and care are limited by lack of screening. We hypothesised that screening could be done with a strategy similar to that used near-universally for gestational diabetes, i.e. a 50 g oral glucose challenge test (GCT) performed at any time of day, regardless of meal status, with one 1 h sample.

Methods At a first visit, participants had random plasma and capillary glucose measured, followed by the GCT with plasma and capillary glucose (GCTplasma and GCTcap, respectively). At a second visit, participants had HbA_{1c} measured and a diagnostic 75 g OGTT.

Results The 1,573 participants had mean age of 48 years, BMI 30.3 kg/m^2 and 58% were women and 58% were black. Diabetes (defined by WHO) was present in 4.6% and prediabetes (defined as impaired glucose tolerance [2 h glucose 7.8–11.1 (140–199 mg/dl) with fasting glucose ≤6.9 (125 mg/dl)] and/or impaired fasting glucose with plasma glucose 6.1–6.9 mmol/l [110–125 mg/dl]) in 18.7%. The GCTplasma provided areas under the receiver-operating-characteristic curves of 0.90, 0.82 and 0.79 for detection of diabetes, diabetes or prediabetes, and prediabetes, respectively, all of which were higher than GCTcap, random and capillary glucose, and HbA_{1c} ($p<0.02$ for all). The perfor-

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mance of GCTplasma was unaffected by time after meals or time of day, and was better in blacks than whites, but otherwise comparable in men and women, and in groups with differing prevalence of glucose intolerance. GCTplasma screening would cost approximately US$84 to identify one person with previously unrecognised diabetes or prediabetes. *Conclusions/interpretation* GCT screening for prediabetes and previously unrecognised diabetes would be accurate, convenient and inexpensive. Widespread use of GCT screening could help improve disease management by permitting early initiation of therapy aimed at preventing or delaying the development of diabetes and its complications.

Keywords Glucose challenge · Natural history · Prediabetes · Preventive management · Screening · Type 2 diabetes

Abbreviations

ADA	American Diabetes Association
AROC	Area under the receiver-operating-characteristic curve
CVD	Cardiovascular disease
Dysglycaemia$_{110}$	Type 2 diabetes or IGT or IFG$_{110}$
FPG	Fasting plasma glucose
GCT	Glucose challenge test
GCTcap	Glucose challenge test: capillary
GCTplasma	Glucose challenge test: plasma
IFG	Impaired fasting glucose
IFG$_{100}$	Impaired fasting glucose with plasma glucose 5.6–6.1 mmol/l (100–109 mg/dl)
IFG$_{110}$	Impaired fasting glucose with plasma glucose 6.1–6.9 mmol/l (110–125 mg/dl)
IGT	Impaired glucose tolerance
NCEP	National Cholesterol Education Program
NHANES-III	National Health and Nutrition Examination Survey III
NPV	Negative predictive value
PPV	Positive predictive value
Prediabetes$_{110}$	IGT or IFG$_{110}$
RCG	Random capillary glucose
RPG	Random plasma glucose

Introduction

Many diabetes patients have poor control of glucose and associated cardiovascular disease (CVD) risk factors [1, 2]. While the causes of inadequate management are complex [3, 4], the problem is due in part to recognition relatively late in the natural history of glucose intolerance [5]. As beta cell function and mass are lost [6, 7], it becomes progressively more difficult to lower glucose levels to normal [8]. In contrast, detection earlier in the natural history at the stage of prediabetes can enable lifestyle change and/or use of pharmacological agents to keep glucose levels near-normal, prevent or delay the development of diabetes, and improve other CVD risk factors [9, 10]. However, the 20% of Americans with prediabetes [11] and 6 million Americans with diabetes [12] are undiagnosed because most Americans are not screened in any systematic way [13].

The most sensitive way to screen is to use OGTTs, but these are inconvenient [14]. Since early glucose intolerance is often pathophysiologically similar to gestational diabetes (high glucose levels after a challenge), it seemed possible that screening could be done using a strategy similar to that used for gestational diabetes, i.e. an oral glucose challenge test (GCT), in which 50 g glucose are given at any time of day, without a prior fast, and glucose levels are measured 1 h later. If the glucose levels exceed a cut-off, patients then have an OGTT. We hypothesised that such a strategy could constitute an effective, convenient, low-cost method of screening in non-pregnant adults.

Methods

Participants Between 1 January 2005 and 31 March 2008 participants aged 18 to 87 years took part in this Screening for Impaired Glucose Tolerance Study (SIGT). Volunteer participants were recruited with posters, flyers, presentations and notices in the media, and included employees of the Grady Health System, Emory HealthCare, and Emory University and Morehouse Schools of Medicine, as well as members of the community. Individuals were eligible if they had no prior diagnosis of diabetes, were not pregnant or nursing, not taking glucocorticoids and were well enough to have worked during the previous week (without requiring actual employment). During recruitment, 4,024 individuals expressed initial interest in the study, 2,111 were scheduled for first visits (selected largely on the basis of need to balance participant sex and race), 1,658 completed first visits, 1,581 completed the protocol and 1,573 had complete GCT and OGTT data (see Electronic supplementary material [ESM] Fig. 1).

Protocol The study was approved by the Emory University Institutional Review Board and was performed in outpatients in the general clinical research centres at Emory University and Grady Memorial Hospitals. At the first visit, which did not require a prior fast and was scheduled during the work day, participants had random plasma glucose

(RPG) and random capillary glucose (RCG) measured (Freestyle; Abbott, North Chicago, IL, USA). Participants then drank 50 g oral glucose (Trutol; NERL Diagnostics, East Providence, RI, USA) within 5 min, with measurement of plasma and capillary glucose after 1 h (GCTplasma and GCTcap, respectively). To avoid confounding via change in behaviour, participants were not given these results. At a second visit (average of 13 days after first visit), a 75 g OGTT was begun before 11.00 hours following an overnight fast, with samples at baseline, 1 and 2 h; blood was also obtained for measurement of plasma lipids and HbA_{1c}.

Measurements Glucose samples were obtained using sodium fluoride/oxalate preservative and plasma frozen at −80°C within 30 min. Chemical analyses were performed in the central clinical laboratory of the Grady Health System using an LX-20 device (Beckman-Coulter, Brea, CA, USA). HbA_{1c} was measured with an assay approved by the National Glycohemoglobin Standardization Program (Beckman Synchron, Fullerton, CA, USA). Sex-adjusted values for HDL-cholesterol (and waist circumference) were expressed relative to cut-offs for the metabolic syndrome defined by National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria.

Estimated costs for screening Projection of costs for screening with GCTplasma assumed follow-up testing with an OGTT if the screening test exceeded a 70% specificity cut-off. We used current Medicare reimbursements of US$6.64 for a gestational diabetes GCT (including 50 g glucose) and $17.99 for the OGTT, assumed 5 min of medical assistant time would be needed ($1.13) for administration of the glucose and expressed costs per case identified, cases being defined as (1) diabetes; (2) prediabetes$_{110}$ (see below).

Analysis Of the 1,581 participants, eight (0.5%) did not have 1 h GCT plasma values; data of the remaining 1,573 participants were used in the primary analyses. Of the 1,573, one did not have an RCG value and two had no triacylglycerol values. Since for analyses involving RCG and triacylglycerol, the number of participants was reduced by less than one-half per cent, no methods of adjustment or imputation of missing data were employed.

Normal glucose tolerance was defined by American Diabetes Association (ADA) criteria (fasting glucose <5.6 mmol/l [100 mg/dl], 2 h glucose <7.8 mmol/l [140 mg/dl]). Impaired fasting glucose (IFG) was defined as IFG with plasma glucose 5.6–6.1 (100–109 mg/dl) (IFG$_{100}$) and IFG with plasma glucose 6.1–6.9 (110–125 mg/dl) (IFG$_{110}$), respectively, both with 2 h glucose <7.8 (140 mg/dl). IGT was defined as 2 h glucose 7.8–11.1

(140–199 mg/dl) with fasting glucose ≤6.9 (125 mg/dl). Diabetes was defined as fasting glucose ≥7.0 mmol/l (126 mg/dl) or 2 h glucose ≥11.1 mmol/l (200 mg/dl). We focused particularly on IGT or IFG$_{110}$ (prediabetes$_{110}$), and on diabetes, IGT or IFG$_{110}$ (dysglycaemia$_{110}$), since these categories are consistent with the WHO definition of prediabetes [15] and such glucose levels confer increased risk of CVD and mortality [16–18]. The prevalence of glucose intolerance in the 1,196 study participants over the age of 40 years in the study population was compared with that in age-matched participants in the National Health and Nutrition Examination Survey III (NHANES III) population (www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm, accessed 15 May 2009), after restricting the latter to black and white participants without previously known diabetes and with OGTTs performed at least 8 h after a meal and before 11.00 hours, with OGTT glucose samples obtained within 115 to 125 min after baseline.

The discriminative effectiveness of screening was evaluated by the area under receiver-operating-characteristic curves (AROCs). Bootstrap methodology was applied to validate the predictive ability of 1 h GCTplasma (bootstrapping involves drawing a large number of random samples, with replacement and with all bootstrapped samples the same size as the original sample; this methodology provides a sampling distribution of the AROC from which validation statistics can be calculated.) In this application, 500 bootstrap replicates were drawn to calculate the over-optimism of sample-calculated AROCs, calibration slopes (a measure of generalisability to other populations) and maximum absolute error in AROCs. Methods were applied to prediction of diabetes, dysglycaemia$_{110}$ and prediabetes$_{110}$. AROCs with different screening tests were compared with the method of DeLong et al. [19]. To assess the performance of GCTplasma in subgroups with different pretest probability of glucose intolerance, we examined subgroups with differences in risk factors such as age. Statistical analyses were conducted using S-Plus, version 7 (Insightful, Seattle, WA, USA) and Stata, version 10 (Stata, College Station, TX, USA).

Results

The 1,573 study participants had an average age of 48 years and BMI 30.3 kg/m^2, and 58% were women and 58% black. Of the 1,573, 4.6% had diabetes, 18.7% prediabetes$_{110}$ and 23.3% dysglycaemia$_{110}$. In the 1,178 study participants aged 40 to 74 years, the proportions with previously unrecognised diabetes and prediabetes$_{110}$ (5.3% and 21.8%) were no greater than those in the 1,807 age-

matched participants in the NHANES III population (11.0% and 27.6%, $p<0.0001$ for both). Extrapolating the study proportions to the US population, approximately 40 million Americans would be expected to have unrecognised diabetes or prediabetes$_{110}$. As shown in Table 1, those with abnormal glucose tolerance were older and heavier; those with IFG only were less likely to be black or women; and those with IGT only were more likely to be women. Although HbA$_{1c}$ levels above the normal range were uncommon except in participants with diabetes (6.9% of participants tested above 6.0%), many of those with diabetes or prediabetes$_{110}$ were at increased risk of CVD because of systolic blood pressure above 130 mmHg (36.9%) or LDL-cholesterol above 5.6 mmol/l (100 mg/dl; 69.4%).

GCTplasma was a strong indicator of unrecognised glucose intolerance (Fig. 1). Thus the AROCs were: 0.79 (95% CI 0.76–0.82) to identify prediabetes$_{110}$; 0.82 (95% CI 0.79–0.84) for dysglycaemia$_{110}$; and 0.90 (95% CI 0.86–0.93) for diabetes ($p<0.001$ for all). Bias-corrected AROCs differed only in the third or fourth decimal place. Calibration slopes for all categories of glucose intolerance were greater than 0.99, indicating excellent generalisability to other populations. Maximum absolute errors (bias) for all AROCs were 0.001 or less. GCTplasma identified IGT (AROC 0.80; 95% CI, 0.77–0.82) better than IFG$_{110}$ (AROC 0.72; 95% CI, 0.67–0.77). In comparisons at different times after meals and times of day (see ESM Table 1), the AROCs for GCTplasma to identify unrecognised diabetes, dysglycaemia$_{110}$ and prediabetes$_{110}$ were unaffected by postprandial time or time of day ($p>0.15$ for all).

The performance of GCTplasma as a screen in subgroups with higher or lower pretest probability of having diabetes, dysglycaemia$_{110}$ or prediabetes$_{110}$ is shown in Table 2. The likelihood of glucose intolerance was significantly increased by well-accepted risk factors for glucose intolerance. Each factor also generally contributed to the probability of having GCTplasma ≥7.8 mmol/l (140 mg/dl), but had little impact on the AROCs for GCTplasma except that AROCs were higher for blacks than whites ($p<0.05$ for all) and AROCs for identification of dysglycaemia$_{110}$ or prediabetes$_{110}$ in participants with triacylglycerol <1.69 mmol/l (150 mg/dl) were higher than in those with triacylglycerol ≥1.69 (150) ($p<0.05$ for both). There were also no general trends with respect to markers of insulin resistance as components of the metabolic syndrome. Thus, the presence of diabetes risk factors was associated with a higher prevalence of glucose intolerance and would increase the positive predictive value of GCTplasma as a screening test, but had little impact on the ability of GCTplasma to detect glucose intolerance.
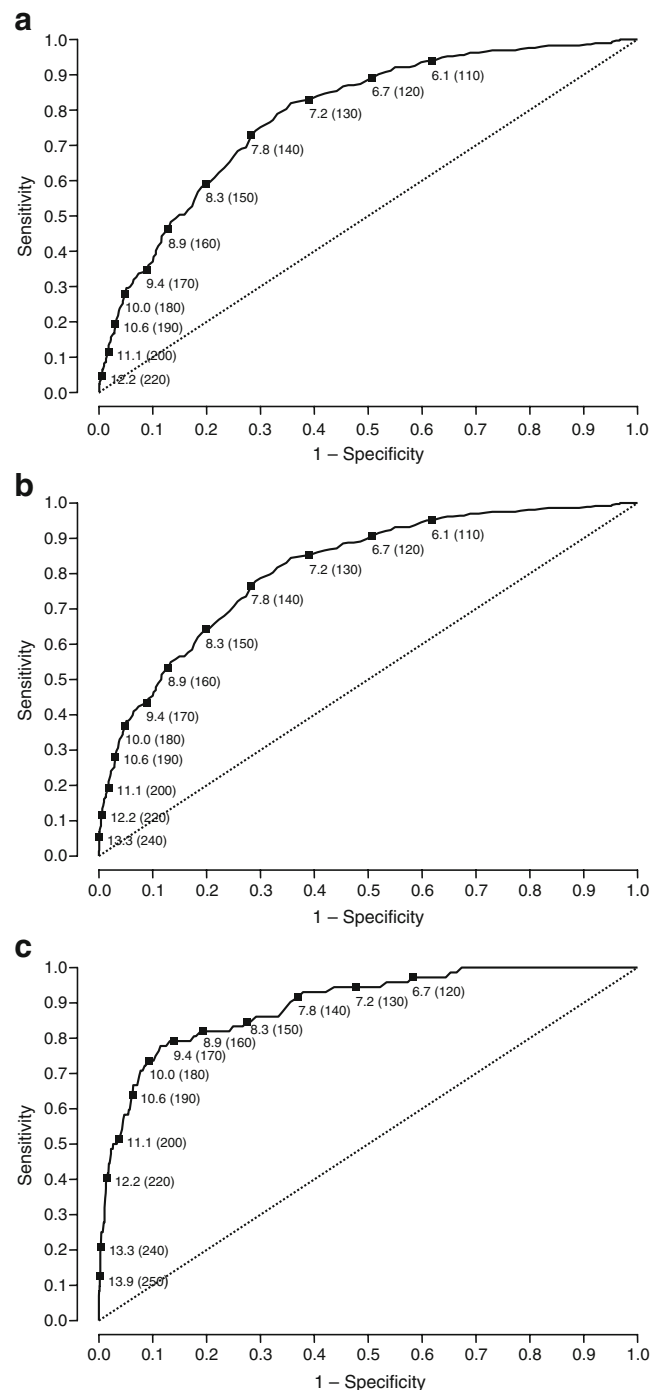

Fig. 1 ROC curves showing performance of GCTplasma in identifying (a) prediabetes$_{110}$ (any IGT or IFG$_{110}$), (b) dysglycaemia$_{110}$ (diabetes or prediabetes$_{110}$) and (c) diabetes. AROC: (a) 0.79 (95% CI 0.76–0.72); (b) 0.82 (95% CI 0.79–0.84); (c) 0.90 (95% CI 0.86–0.93). The values along the curves show different glucose cut-off levels for 50 g glucose challenge test (any time of day, no fast needed) in mmol/l with values in mg/dl in parentheses. The dashed line shows screening test performance equivalent to chance (AUC 0.5)

Table 1 Participant demographics

	All	NGT	IFG$_{100-109}$	IFG$_{110-125}$	IGT only	IGT + IFG$_{100-109}$	IGT + IFG$_{110-125}$	Prediabetes$_{110}$	Dysglycaemia$_{110}$	Diabetes
n	1573	977	230	52	114	76	52	294	366	72
Per cent of all	100	62	15	3	7	5	3	19	23	5
Age (years)	48	45	51	53	52	52	54	52	53	54
BMI (kg/m^2)	30.3	29.2	30.7	32.0	30.5	33.8	35.2	32.5	32.8	34.4
Black (%)	58	58	48	54	61	71	60	62	63	67
Women (%)	58	64	40	40	63	53	50	54	53	49
Fam Hx (%)	46	43	47	46	53	53	60	53	55	63
1hrpGCT (mmol/l)[a]	7.4 (133)	6.7 (120)	7.5 (135)	8.2 (148)	8.6 (155)	9.1 (164)	9.8 (176)	8.9 (160)	9.4 (169)	11.4 (206)
Mean HbA$_{1c}$ (%)	5.4	5.3	5.5	5.5	5.5	5.6	5.8	5.6	5.7	6.2
Median HbA$_{1c}$ (%)	5.4	5.3	5.4	5.5	5.5	5.6	5.8	5.6	5.6	6.2
SBP >130 mmHg (%)	24	19	29	25	36	33	44	35	37	46
LDL>2.59 mmol/l (%)[b]	67	65	71	62	67	79	77	71	69	64

[a] GCT plasma; values in parentheses are in mg/dl

[b] 100 mg/dl

Fam Hx, diabetes in first-degree relative; 1hrpGCT, 1 h GCTplasma; NGT, normal glucose tolerance; SBP, systolic blood pressure

AROC analysis was also used to compare GCTplasma with other tests that would also be convenient for screening, e.g. RPG, GCTcap, RCG and HbA$_{1c}$ (Table 3). When glucose was assessed with challenge vs random tests, the challenge tests were generally superior for GCTplasma compared with RPG and GCTcap vs RCG ($p<0.05$ for all); GCTplasma was also superior to GCTcap ($p<0.001$ for all) and HbA$_{1c}$ ($p<0.001$ for prediabetes$_{110}$ and dysglycaemia$_{110}$; $p=0.018$ for diabetes). We also compared FPG to plasma glucose measured at 1 h during the OGTT, with both tests obtained after similar dietary preparation and 1 h apart. The OGTT 1 h plasma glucose was superior to FPG for detecting dysglycaemia$_{110}$ and prediabetes$_{110}$ ($p<0.001$ for both).

Table 4 shows the effect of different GCTplasma and GCTcap cut-offs on sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The lower cut-offs provide greater sensitivity and NPV, but reduced PPV, since specificity is lower and PPV responds to the underlying presence of the abnormalities in the population. A relatively high-specificity GCTplasma cut-off of 7.8 mmol/l (140 mg/dl) provided good specificity, sensitivity and NPV, with acceptable PPV. Use of a lower cut-off would increase the sensitivity, but a lower percentage of those with a positive test would prove to have glucose intolerance. Conversely, screening with higher cut-offs would provide greater likelihood of finding glucose abnormalities among those who screened positive (higher PPV), at the cost of reduced sensitivity and NPV. Higher specificity cut-offs also tend to be more cost-effective [20]. GCTcap cut-offs tended to be about 1.1 mmol/l (20 mg/dl)

higher than the comparable GCTplasma cut-offs, with somewhat lower sensitivity and specificity.

Finally, we projected costs for GCTplasma screening with the 7.8 mmol/l (140 mg/dl) cut-off. Of our 1,573 participants, 622 (40%) would have exceeded the cut-off and had a follow-up OGTT, of whom 280 (45%) would have had glucose intolerance (66 diabetes, 214 prediabetes$_{110}$). Initial screening would incur Medicare costs of $7.77 per participant=$12,222; follow-up OGTTs would incur Medicare costs of $17.99 per positive screen=$11,190. Total costs would therefore be $23,412 or $84 per case identified.

Discussion

Principal findings The infrequency of screening for early glucose intolerance in non-pregnant individuals [13] may be due in part to lack of a screening strategy suitable for the general population. We demonstrate that a screening approach modelled on that for gestational diabetes could be such a strategy. Screening with GCTplasma provided AROC 0.79, 0.82 and 0.90 to detect prediabetes$_{110}$, dysglycaemia$_{110}$ and previously unrecognised diabetes respectively. Screening performance was generally consistent across different times after meals and different times of day, as well as in subgroups with higher and lower pretest probability of glucose intolerance. GCTplasma screening appears to be accurate, convenient and widely applicable, and the test would be relatively inexpensive in populations such as ours ($84 per case of diabetes or prediabetes identified).

Table 2 Impact of diabetes risk factors on GCTplasma AROC for detection of prediabetes110, dysglycaemia110 and diabetes, and on likelihood of diabetes statuses as shown

Group, risk factors	n	AROC (95% CI)			Likelihood, OR (95% CI)			
		Prediabetes110	Dysglycaemia110	Diabetes	GCTplasma ≥7.8 mmol/l[b]	Prediabetes110	Dysglycaemia110	Diabetes
All	1,573	0.79 (0.76–0.82)	0.81 (0.79–0.84)	0.90 (0.86–0.93)				
Black	912	0.82 (0.79–0.85)	0.85 (0.82–0.88)	0.92 (0.88–0.96)	0.69 (0.56–0.85)	1.25 (0.96–1.62)	1.30 (1.02–1.66)	1.47 (0.90–2.42)
White	661	0.75 (0.70–0.80)	0.78 (0.73–0.82)	0.86 (0.78–0.94)	0.73 (0.59–0.89)	0.80 (0.62–1.03)	0.76 (0.60–0.97)	0.67 (0.42–1.07)
Women	914	0.80 (0.76–0.83)	0.82 (0.79–0.85)	0.92 (0.87–0.96)	1.00	1.00	1.00	1.00
Men	659	0.78 (0.73–0.82)	0.80 (0.76–0.84)	0.87 (0.80–0.93)				
Age <40 years	398	0.77 (0.70–0.85)	0.80 (0.73–0.87)	0.89 (0.77–1.00)	2.64 (1.98–3.53)	2.84 (1.89–7.28)	2.61 (1.80–3.77)	1.57 (0.74–3.32)
Age 40–55 years	724	0.77 (0.73–0.82)	0.80 (0.76–0.83)	0.89 (0.81–0.96)	4.68 (3.44–6.36)	4.53 (2.98–6.91)	4.58 (3.14–6.68)	3.67 (1.78–7.60)
Age >55 years	461	0.76 (0.71–0.81)	0.80 (0.76–0.84)	0.88 (0.83–0.94)	1.00	1.00	1.00	1.00
BMI<25 kg/m^2	349	0.77 (0.68–0.87)	0.80 (0.72–0.88)	0.91 (0.80–1.00)	1.80 (1.37–2.35)	2.44 (1.65–3.62)	2.39 (1.67–3.44)	1.89 (0.84–4.21)
BMI 25–35 kg/m^2	888	0.78 (0.75–0.82)	0.80 (0.77–0.84)	0.90 (0.84–0.95)	2.14 (1.56–2.93)	3.58 (2.31–5.53)	4.07 (2.74–6.06)	5.14 (2.28–11.57)
BMI >35 kg/m^2	461	0.78 (0.72–0.83)	0.81 (0.77–0.86)	0.87 (0.80–0.94)	2.32 (1.72–3.15)	1.81 (1.27–2.57)	1.92 (1.39–2.64)	2.09 (1.18–3.70)
TG+[a]	196	0.67 (0.59–0.75)	0.72 (0.65–0.80)	0.88 (0.78–0.98)	1.20 (0.98–1.47)	1.74 (1.35–2.26)	1.80 (1.42–2.28)	1.82 (1.12–2.94)
TG−[a]	1,375	0.80 (0.77–0.83)	0.82 (0.80–0.85)	0.89 (0.85–0.94)	1.48 (1.21–1.82)	1.45 (1.13–1.88)	1.57 (1.24–1.99)	2.02 (1.24–3.27)
HDL+[a]	740	0.79 (0.75–0.82)	0.81 (0.78–0.85)	0.89 (0.84–0.94)	2.06 (1.66–2.57)	1.87 (1.43–2.44)	2.15 (1.69–2.74)	3.27 (2.03–5.27)
HDL−[a]	833	0.79 (0.75–0.83)	0.81 (0.78–0.85)	0.90 (0.84–0.96)	1.76 (1.43–2.15)	2.62 (2.00–3.43)	2.90 (2.26–3.73)	3.90 (2.20–6.89)
Family Hx+[a]	724	0.76 (0.72–0.80)	0.80 (0.76–0.83)	0.88 (0.82–0.93)				
Family Hx−[a]	849	0.81 (0.77–0.85)	0.83 (0.79–0.86)	0.92 (0.86–0.97)				
SBP ≥130 mmHg[a]	473	0.77 (0.72–0.82)	0.82 (0.78–0.86)	0.92 (0.88–0.95)				
SBP <130 mmHg[a]	110	0.79 (0.75–0.82)	0.80 (0.77–0.83)	0.85 (0.78–0.92)				
Waist+[a]	798	0.78 (0.74–0.81)	0.81 (0.78–0.84)	0.87 (0.82–0.92)				
Waist−[a]	775	0.78 (0.73–0.83)	0.80 (0.76–0.84)	0.92 (0.86–0.99)				

To assess the performance of GCTplasma in subgroups with different pretest probability of glucose intolerance, detection of diabetes, dysglycaemia110, and prediabetes110 was examined in groups with differences in risk factors such as age, BMI, family history of diabetes in a first-degree relative, etc. For each subgroup the following are shown: (1) likelihood of having GCTplasma ≥7.8 mmol/l (140 mg/dl) (approximately the 70% specificity cut-off for dysglycaemia110); (2) likelihood of each category of glucose intolerance; and (3) AROC for detection of the different categories of glucose intolerance

With regard to black participants, many were women and had a family history of diabetes in a first-degree relative. In our dataset, women were somewhat less likely to fail the cut-off or to have glucose intolerance; in multivariate analyses adjusted for age, BMI, sex, and family history, black race contributed independently to risk of having GCTplasma ≥7.8 mmol/l (140 mg/dl), p=0.012

[a] Increased risk cut-offs according to NCEP metabolic syndrome criteria

[b] Approximate 70% specificity cut-off to detect prediabetes110

Family Hx, diabetes in first-degree relative; SBP, systolic blood pressure; TG, triacylglycerol

Table 3 AROCs for detection of glycaemic status as shown from tests that would be convenient for screening

[a] Excludes diabetes; $n=1,501$ (1,500 for RCG)

[b] FPG was measured only during the OGTT and was therefore compared with plasma glucose measured at 1 h during the OGTT (1hPG)

Test	n	AROCS		
		Prediabetes$_{110}$[a]	Dysglycaemia$_{110}$	Diabetes
GCTplasma	1,573	0.788 (0.760–0.816)	0.815 (0.790–0.839)	0.895 (0.857–0.934)
GCTcap	1,573	0.733 (0.702–0.763)	0.763 (0.736–0.790)	0.861 (0.819–0.903)
RPG	1,573	0.698 (0.665–0.731)	0.728 (0.699–0.757)	0.826 (0.779–0.873)
RCG	1,572	0.620 (0.585–0.656)	0.648 (0.616–0.681)	0.742 (0.682–0.803)
HbA$_{1c}$	1,573	0.675 (0.640–0.710)	0.707 (0.675–0.739)	0.817 (0.754–0.881)
1hPG[b]	1,573	0.861 (0.838–0.884)	0.880 (0.860–0.800)	0.926 (0.893–0.960)
FPG[b]	1,573	0.799 (0.768–0.831)	0.828 (0.801–0.855)	0.930 (0.885–0.975)

Comparisons with other studies Previous studies of screening have focused on risk factor questionnaires, glucose-related measures and risk factor combinations of demographics, anthropometrics and laboratory measurements. Questionnaires are inexpensive and some have been reported to provide AROC for diabetes of ~0.80 [21], comparable to that of RPG in the present study, with most providing AROC 0.70–0.75 [22]. In our population, the Diabetes Risk Calculator [23] provided AROC 0.70 for diabetes and 0.67 for prediabetes$_{110}$. Such inefficiency has led to greater interest in glycaemic indicators such as HbA$_{1c}$ [24], which identified retinopathy almost as well as fasting or 2 h post-challenge glucose in a Pima Indian population [25], but in other populations performed less well than fasting glucose in identifying diabetes [26] and was very insensitive in detecting IGT [27], comparable to findings in our study. Problems in use of HbA$_{1c}$ probably reflect large inter-individual variability [28].

Use of glucose levels for screening has revealed that post-challenge glucose is a more uniform predictor of progression from IGT to diabetes as compared with fasting glucose [29]. Moreover, fasting glucose measurements often fail to recognise both IGT and diabetes [30, 31], and poor sensitivity is obtained even with lower cut-off levels [32, 33]. Previous studies of RPG and RCG have frequently not included AROC values [34, 35], but RCG can be efficient when combined in an equation with postprandial time, age, sex and BMI [36]. Such an equation provided AROC comparable to that of GCTplasma in the present study, but busy practitioners might find the equation inconvenient.

There has also been interest in screening with risk factor-based predictive models such as the metabolic syndrome. However, the AROCs for predictive models have generally been lower than those for GCTplasma in the present study; indeed, in the San Antonio Heart Study, the best model to predict incident diabetes was no better than the 1 h OGTT glucose value alone [37, 38], a measurement similar to GCTplasma. Moreover, it might be easier to implement GCT screening than risk factor-based screening in real-world practice. Risk factor guidelines would require an extra visit for fasting morning samples (glucose, lipids), which patients might be reluctant to schedule [14]. Risk factor-based screening demands consistent methodology, but lipid values vary considerably (data from the College of American Pathologists show a coefficient of variation of 8–16% for HDL vs 2–3% for glucose [39]). Risk factor-based screening may be poorly applicable to multi-ethnic populations [40] and it might also be difficult for providers to tell whether risk factor-based evaluation has been conducted. In contrast, GCT screening lacks such limitations: patients need not be fasting, the test can be done at any time of day, glucose measurements are highly consistent and the process of screening is readily identifiable.

Policy recommendations for screening must be driven by evidence of clinical benefit, predictive utility and reasonable cost. In the Diabetes Prevention Program, the direct medical costs of identifying one participant with IGT (RCG screening followed by OGTT) were US$139 [41]. The Center for Disease Control group projected the minimum cost of identifying a case of diabetes or prediabetes as $176 (comparing RCG, HbA$_{1c}$, FPG and OGTT) [42] or $172 (comparing RCG, FPG and HbA$_{1c}$) [35]. However, GCTplasma screening followed, if positive, by an OGTT would incur direct costs of only $84 per case identified; the GCTplasma approach is both more accurate and less expensive.

Limitations Our study has limitations. Having studied blacks and whites, we cannot be sure that the findings will apply to other racial or ethnic groups. We also had few tests that were initiated after 15.00 hours. Since glucose tolerance is better later in the day [43], it is possible that a GCTplasma in the late afternoon might be falsely negative in predicting results from OGTTs performed in the morning, but our conditions do reflect the situation most likely to be convenient for patients and providers. To limit possible confounding by variation in day-to-day metabolic status, we also excluded participants with illness severe enough to make them miss work, since GCTplasma accuracy could be reduced if participants were screened when ill (possibly more insulin-resistant) and follow-up OGTTs performed when they were well again. We did not measure intra-participant variability

Table 4 AROCs and effect of cut-offs on sensitivity, specificity, positive predictive value and negative predictive value by diabetes status and test

Glucose intolerance	GCTplasma						GCTcap					
	Cut-off, mmol/l (mg/dl)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AROC (95% CI)	Cut-off, mmol/l (mg/dl)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AROC (95% CI)
Diabetes	6.7 (120)	97	42	7	>99	0.895 (0.857–0.934)	7.8 (140)	97	40	7	>99	0.861 (0.819–0.903)
	7.2 (130)	94	52	9	>99		8.3 (150)	93	52	9	99	
	7.8 (140)	92	63	11	99		8.9 (160)	86	61	9	99	
	8.3 (150)	85	72	13	99		9.4 (170)	81	69	11	99	
	8.9 (160)	82	81	17	99		10.0 (180)	78	78	15	99	
	9.4 (170)	79	86	21	99		10.6 (190)	74	85	19	99	
	10.0 (180)	74	91	27	99		11.1 (200)	61	90	23	98	
	10.6 (190)	64	94	33	98		11.7 (210)	54	93	28	98	
Dysglycaemia$_{110}$	6.7 (120)	91	49	35	95	0.815 (0.790–0.839)	7.8 (140)	89	46	33	93	0.763 (0.736–0.790)
	7.2 (130)	85	61	40	93		8.3 (150)	80	59	37	91	
	7.8 (140)	77	72	45	91		8.9 (160)	70	67	39	88	
	8.3 (150)	64	80	49	88		9.4 (170)	61	75	43	86	
	8.9 (160)	53	87	56	86		10.0 (180)	51	84	49	85	
	9.4 (170)	43	91	60	84		10.6 (190)	40	89	53	83	
	10.0 (180)	37	95	70	83		11.1 (200)	29	93	56	81	
	10.6 (190)	28	97	74	82		11.7 (210)	23	96	62	80	
Prediabetes$_{110}$	6.7 (120)	89	47	28	95	0.788 (0.760–0.816)	7.8 (140)	87	44	26	93	0.733 (0.702–0.763)
	7.2 (130)	83	58	31	94		8.3 (150)	77	56	29	91	
	7.8 (140)	73	68	34	92		8.9 (160)	67	64	30	89	
	8.3 (150)	59	76	37	89		9.4 (170)	56	72	32	88	
	8.9 (160)	46	83	39	87		10.0 (180)	45	80	34	86	
	9.4 (170)	35	87	38	85		10.6 (190)	31	86	33	84	
	10.0 (180)	28	91	42	84		11.1 (200)	21	90	32	83	
	10.6 (190)	19	94	41	83		11.7 (210)	16	93	33	82	

Lower cut-offs provide greater sensitivity but reduced PPV since specificity is lower, leading to more false-positives

Sens, sensitivity; Spec, specificity

of the GCT, but such variability, along with that of the OGTT, should be accounted for in the AROC analyses. We also, to date, have not validated our findings in a separate population, and so generalisability of our results might be reduced because our participants were self-selected. However, the prevalence of unrecognised diabetes and prediabetes$_{110}$ in our study was no higher than that in NHANES III, GCTplasma AROCs were generally unaffected by the presence or absence of diabetes risk factors and boot-strapping analyses showed little bias.

Implications Americans have a high lifetime risk of diabetes [44]; many patients already have early diabetes complications and abnormal CVD risk factors at first presentation [45, 46]; risk factor management can decrease CVD [47]; progression from prediabetes to diabetes can be prevented or delayed [9, 10]; and screening for prediabetes should be cost-effective [48]. Although such findings contributed to the call by NIDDK/ADA to screen for prediabetes [49], screening is infrequent [13], due in part to the lack of a suitable screening test. Use of the GCT could solve this problem. It should be noted that because of the importance of identifying gestational diabetes at the first opportunity, GCT screening during pregnancy uses high sensitivity cut-offs. In contrast, GCT screening of non-pregnant individuals can use cut-offs that provide higher specificity (and greater cost-effectiveness [20, 34]), since patients missed at an initial screen would probably be detected on repeat screening 2 to 3 years later, which would still be early in their natural histories.

Conclusions Lack of a good strategy to identify early glucose intolerance, possibly 10 years or more prior to current identification of diabetes, is a major impediment to better care. GCT screening would be an accurate, convenient and relatively inexpensive way to find prediabetes and previously unrecognised diabetes, providing a major opportunity to improve the health of the ~40 million Americans who have these problems. Moreover, recognition early in the patient's natural history would allow the use of therapies to slow the progression of glucose intolerance and the development of associated microvascular and macrovascular complications.

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