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Stepwise Screening for Asymptomatic Diabetes Using Opportunistically Available Random Plasma Glucose and HbA1c

By

Brian T. Legvold

Master of Science in Public Health

Epidemiology

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B.Sc.

University of Colorado, Denver

2018

Faculty Thesis Advisor: Alvaro Alonso, MD, PhD

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Abstract

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Background

Oral glucose tolerance tests (OGTTs) are inconvenient but sensitive for identifying diabetes (DM), whereas more convenient HbA1c tests may be inaccurate.

Objectives

We asked if an alternative two-step strategy, measuring HbA1c only if opportunistically available random plasma glucose (RPG) is ≥100 mg/dl, could improve screening.

Methods

The Screening for Impaired Glucose Tolerance (SIGT) dataset, where 1,573 adults without known DM had measurements of RPG, HbA1c, and OGTTs; was used to evaluate the two-step strategy, using Receiver Operating Characteristic (ROC) analysis adjusted for optimism to identify DM per American Diabetes Association (ADA) OGTT criteria.

Results

Participants were 58% female and 58% black, with mean age 47.9 years, BMI 30.3 kg/m^2 and HbA1c 5.4%; 4.6% had DM by ADA OGTT criteria. The ROC area under the curve was 0.82 for HbA1c to identify DM among all 1,573 participants, but 0.86 in those with RPG ≥100 mg/dl (n=576), vs. 0.58 in those with RPG <100 mg/dl (n=997) (modeled interaction $p<0.001$). DM participants with RPG ≥100 vs <100 mg/dl had mean fasting plasma glucose 131 vs. 116 mg/dl and 2-hour plasma glucose 225 vs. 183 mg/dl, and HbA1c 6.4% vs. 5.6%, respectively, (all $p<0.025$) – less severe disease in those with RPG <100 mg/dl. Limiting OGTTs to those with RPG ≥100 mg/dl and HbA1c ≥5.5% would provide 74% sensitivity and 82% specificity overall and reduce the number of OGTTs needed by 80%. The participants with unrecognized DM who were not identified by this method (n=19) had a mean HbA1c of 5.5% (±0.6%), a fasting glucose of 115 mg/dl (±19.4 mg/dl) and an 2hr OGTT of 195 mg/dl (±56.3 mg/dl).

Conclusions

Use of RPG followed by HbA1c improves the accuracy and efficiency of screening, identifying both individuals who should and should not have an OGTT. Such a strategy might improve recognition of diabetes and prediabetes, permitting initiation of preventive management.

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Background

Diabetes is a public health epidemic, affecting 34.1 million Americans adults (13% of the adult population) of whom over 20% are undiagnosed (1). This high number of undiagnosed cases belies the importance of early diagnosis and treatment as illustrated by the findings from the Diabetes Prevention Program (DPP), the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) trials, and their respective follow-up observational studies. The DPP (2–4) trial demonstrates how a reduction in progression from prediabetes to diabetes can be achieved with early treatment, while the DCCT (5–7) and UKPDS (8,9) trials show how long-term, sustained reduction in complications from diabetes can be achieved, provided early and intensive diabetes treatment.

Despite established screening recommendations from the American Diabetes Association (ADA) aimed at early detection, screening rates in at-risk asymptomatic individuals remain suboptimal (10), and are likely attributable to both provider and patient factors. Moreover, the current recommended screening tests for diabetes in asymptomatic individuals – the oral glucose tolerance test (OGTT), fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) – all face certain limitations. OGTT and FPG are burdensome and limited by convenience, leading to an overreliance on HbA1c, which is problematic given its poorer sensitivity (11). Although diabetes risk assessment tools have been developed to assist clinicians in identifying high-risk patients for testing, they fail to address the underlying issue of sensitivity with regard to diagnosis based on HbA1c.

Recent findings have indicated that random plasma glucose (RPG) may be an effective tool in assessing an individual's risk of diabetes and in predicting the diagnosis of diabetes within 5-years (12,13). Additionally, RPG is already included in many routine blood tests performed by primary care physicians, making it readily available and requiring no additional cost. Given this, and the biological relationship between average circulating plasma glucose and observed HbA1c; we theorized that an elevated RPG may be indicative of worse overall glycemic control and consequently the accuracy of HbA1c when describing beta-cell function. Thus, we investigated if stepwise use of opportunistically available RPG followed by an HbA1c test, if indicated, could improve the diagnostic accuracy of diabetes screening versus HbA1c alone.

Research Design and Methods

Study Population

Participants were recruited for the Screening for Impaired Glucose Tolerance Study (SIGT) from the community around Atlanta, Georgia in the United States, using a variety of methods including fliers, media announcements, posters and presentations from 1 January 2005 through 31 March 2008. Enrollment criteria included: participants be age 18 to 87 years old, have no known diagnosis of diabetes, not currently taking glucocorticoids, not pregnant or nursing, and healthy enough to have worked in the past week regardless of employment status. These efforts resulted in a cohort of 4,024 volunteers initially displaying interest, with 1,658 participants completing the first visit and 1,581 participants completing both visits (14).

Protocol

The study was conducted at the general clinical research centers of Emory University Hospital and Grady Memorial Hospital. The first visit was scheduled during the normal workday hours, with no requirement for fasting ahead of time. Participants then provided a plasma sample for measuring RPG and had capillary blood glucose tested and were scheduled 2-weeks later for a 75g 2-hour OGTT. Participants returned in a fasting state to begin the test by 11:00-hours. Samples collected were included: fasting, 1-hour and 2-hour OGTT, and HbA1c. To avoid confounding and changing of behaviors, participants were not provided with the results of their first visit until after the second visit was concluded.

Measures

Plasma glucose samples were collected in tubes containing NaF/Oxalate preservatives and placed in -80˚C freezers within 30 minutes of collection. Samples were analyzed using a LX-20 system (Beckman-Coulter, Brea, CA, USA) and performed at the central clinical laboratory of Grady Health System. Whole blood samples were collected and HbA1c was measured using an assay certified by the National Glycohemoglobin Standardization Program and traceable to the DCCT (Beckman Synchron, Fullerton, CA, USA).

Classification

True glycemic metabolic classification was done according to the 2020 ADA criteria for diagnosis by FPG and OGTT: normal glucose metabolism (NGM) defined as FPG <100 mg/dl and 2-hour OGTT plasma glucose (2h PG) <140 mg/dl; pre-diabetes (preDM) defined as FPG 100-125 mg/dl, and/or 2h PG 140-199 mg/dl, and not meeting criteria for diabetes (DM); DM was defined as FPG ≥126 mg/dl, and/or 2h PG ≥200 mg/dl (15); dysglycemia was defined as meeting the criteria for either preDM or DM. BMI was calculated based on participant height and weight at first visit, while age, race and sex were self-reported at the second clinic visit.

Statistical Analysis

Of the 1,581 participants who completed both visits, 8 had incomplete OGTT data. Since this accounted for only 0.5% of the study population and no trends in missingness were observed, the 8 were excluded from further analysis without use of any methods for adjustment of imputation of missing data.

Normality of continuous variables was assessed in the complete cohort. The cohort was then stratified by random plasma glucose (≥100 mg/dl) and normality was again assessed in each stratum. Stratification at 100 mg/dl was based on previous work by Bowen et al. (12) and evaluation of the events per variable ratio according to Harrell et al. (16). Using logistic regression, we modeled the odds of participants having undiagnosed type 2 diabetes using HbA1c and RPG ≥100 mg/dl as the primary exposures. Statistically significant interaction between HbA1c and RPG was assessed with a Likelihood-ratio test, controlling for age, sex, race and BMI. Each stratified cohort was modeled using HbA1c alone and HbA1c with participant sex (female vs male), race (black vs white), age and BMI as covariates, here forth referred to respectively as the reduced and full models.

Discriminatory capability of each model was evaluated based on receiver operating characteristics (ROC) and summarized with the c-statistic, the area under the curve (AUC); while goodness-of-fit was estimated using the Hosmer-Lemeshow statistic (17). Validation involved modeling 1,000 bootstrapped samples to get an apparent AUC, followed by scoring the original study population using the bootstrapped model, to produce a scored AUC. The mean difference in the apparent AUCs from the bootstrapped cohorts and the scored AUCs from the original study population resulted in an estimation of optimism for the given model. The AUC for each model was then adjusted for its respective estimated optimism (16).

Comparisons of sensitivity and specificity between the whole study population and the cohort with an RPG of at least 100 mg/dl was done by adding all those in the RPG less than 100 mg/dl cohort as “testing negative”. These additional negatives were

then allocated to either true negative (n=982) of false negative (n=15) according to their DM status per OGTT.

Two-sample t-test were used for determining the statistical significance of differences in continuous variables of the participant demographics. Mantel-Haenszel χ^2 tests were used to evaluate the statistical significance in the distribution of categorical variables. A universal significance level of $\alpha = 0.05$ was used. All statistical analysis was done using SAS Enterprise Guide version 8.1. Figure were built using MS Excel and SAS Enterprise Guide version 8.1, and tables were built using MS Word.

Results

Participant Demographics

Of the 1,573 study participants (female: 58%, black race: 58%, age: 47.9 ± 12.2 yrs, BMI: 30.3 ± 6.8 kg/m^2), 62% (n=977) were normoglycemic, 5% (n=72) were found to have previously unrecognized diabetes with a further 33% (n=524) having unrecognized pre-diabetes. Among those with either form of unrecognized dysglycemia, 48% had isolated impaired fasting glucose, 20% had isolated impaired glucose tolerance, while 32% had impaired fasting glucose and impaired glucose tolerance. Applying current ADA diagnostic guidelines via HbA1c alone identified 34 participants as possibly having diabetes, with either FPG or 2h PG confirming a total of 24 cases (sensitivity: 0.33, specificity: 0.99).

The unrecognized diabetes cohort was similar to the group without DM in terms of the proportion of female participants (49% vs. 59%; p-value = 0.09) or black participants (67% vs 58%; p-value = 0.13). However, statistical differences were observed in the mean age of those with unrecognized DM (53.9 ± 10.9 years) versus those without diabetes (47.6 ±12.1 years; p-value < 0.0001) and in the mean BMI of those with unrecognized DM (34.4 ± 7.0 kg/m^2) versus those without diabetes (30.1 ±6.7 kg/m^2; p-value < 0.0001).

Interaction Assessment

Likelihood-ratio testing of the interaction between an RPG of at least 100 mg/dl and observed HbA1c for the prediction of DM was statistically significant in models with and without adjusting for sex, race, age and BMI (p-values 0.001 and 0.002 respectively). To account for the interaction, all further analysis was stratified on an RPG of at least 100

mg/dl. Participant demographics following stratification on an RPG of at least 100 mg/dl found that 997 (63%) of participants fell into the lower strata and 576 (37%) into the upper strata. Statistically significant differences in sex, age and BMI were observed (p-value <0.0001 for all), while no difference in racial makeup was observed (p-value = 0.06) (Table 1).

Figure 1 illustrates how the majority (n=741, 76%) of all normoglycemic participants had an RPG below 100 mg/dl, while 59% (n=340) of the participants with an elevated RPG were dysglycemic—accounting for 79% (n=57) of all DM and 54% (n=283) of all preDM—despite being only 37% (n=576) of the study population. In other words, screening the population for DM with an RPG ≥100 mg/dl translates to a PPV of 10%, an NPV of 98%, a sensitivity of 79%, and a specificity of 65%.

Among those with unrecognized DM, no statistically significant difference was appreciable between strata in sex, race, age or BMI. However, the cohort with an RPG of at least 100 mg/dl had a larger proportion of those with DM identified as meeting the diagnostic threshold for both fasting glucose and glucose tolerance (p-value = 0.006).

The 15 cases of DM (21% of all cases) within the lower stratum had glycemic measures of: HbA1c 5.6% (±0.6%), FPG 116 mg/dl (±19.3 mg/dl), 2h PG 183 mg/dl (±56.3 mg/dl). The mean glycemic measures for the upper stratum's 57 cases of DM (79% of all cases) were significantly higher than that of the lower stratum: HbA1c 6.4% (±1.0%), FPG 131 mg/dl (±25.6 mg/dl), 2h PG 225 mg/dl (±47.8 mg/dl) (P <0.025). Relative to the cohort with an RPG ≥100 mg/dl, the significantly lower HbA1c among those with an RPG <100 mg/dl also appear to have a greater degree of overlap in the

distribution of observed HbA1c values between those with and those without DM, as illustrated by Figure 2.

Model Fit

Logistic regression modeling of the odds of DM by HbA1c in the whole study population showed improved fit when adjusting for sex, race, age and BMI (goodness-of-fit p-values 0.004 and 0.12; crude vs adjusted, respectively). However, in the stratified cohorts, model fit was notably better without adjusting for those same. While the models for the cohort with an RPG below 100 mg/dl were not statistically significant in their lack of fit (p-values 0.19 and 0.11; crude vs adjusted, respectively), they performed worse than the models for the cohort with an RPG of at least 100 mg/dl (p-values 0.35 and 0.27; crude vs adjusted, respectively).

When assessing normality, age, BMI and HbA1c appeared to be approximately non-normally distributed, which was addressed by log transforming each variable. This uniformly resulted in a reduced fit for all models leading us to use the non-transformed variables in subsequent analysis.

Receiver Operating Characteristics

The complete study population revealed an AUC of 0.82 (SE±0.03) in the reduced model—without adjusting for covariates—and an AUC of 0.84 (SE±0.03) in the full model—with adjustment for sex, race, age and BMI. Bootstrap validation methods indicated no statistically significant optimism bias in the reduced model, while the full model had an estimated optimism of 0.006 (95% CI: 0.004, 0.008) for an optimism adjusted AUC of 0.84.

Stratum specific modeling of those with an RPG below 100 mg/dl and analysis of the receiver operating characteristics found an AUC of 0.60 (SE±0.08), an estimated optimism of 0.02 (95% CI: 0.010, 0.021), for an optimism adjusted AUC of 0.58 in the reduced model; and an observed AUC of 0.70 (SE±0.09), an estimated optimism of 0.07 (95% CI: 0.067, 0.076), for an optimism adjusted AUC of 0.63 in the full model. For the cohort with an RPG of at least 100 mg/dl, the estimated optimism when not adjusting for covariates failed to reach statistical significance, thus the observed AUC of 0.86 (SE±0.03) equaled the AUC adjusted for optimism. When adjusting for covariates among those with an RPG of at least 100 mg/dl, the observed AUC was 0.87 (SE±0.03), the estimated optimism was 0.01 (95% CI: 0.007, 0.011) and the optimism adjusted AUC was 0.86 (Table 2).

Further analysis of the receiver operating characteristics found at an HbA1c cutoff of ≥6.5%, in conjunction with an RPG of 100 mg/dl or more, the reduced model identified 24 participants as possibly having DM, with OGTTs confirming 21 as cases for a positive predictive value (PPV) and a negative predictive value (NPV) of 88% and 99%, respectively. By comparison, 10 participants had an RPG <100 mg/dl and an HbA1c ≥6.5%, with 3 confirmed by OGTT as having DM for a PPV of 30% and an NPV of 99%. Relative to the whole study population, the cases identified through stepwise screening with an HbA1c cutoff of 6.5% and an RPG cutoff of 100 mg/dl resulted in a sensitivity of 29% and specificity of >99% (Table 3).

By reducing the screening cutoff of HbA1c to 5.5% and maintaining the RPG cutoff of at least 100 mg/dl, the reduced model identified 317 participants as possible cases of DM, with OGTTs confirming 53 cases, for a PPV of 17% and an NPV of 98%.

Relative to the whole study population, this translates to an overall sensitivity of 74% and a specificity of 82%. Additional examination of the resulting 'false positives' (n=264) revealed that 64% (n=170) met the ADA glucose guidelines for preDM, of whom 58% (n=99) met the World Health Organization's guidelines for prediabetes (FPG ≥110 mg/dl and/or a 2h PG ≥140 mg/dl).

Discussion

In a cohort of 1,573 individuals with no known diagnosis of DM, the diagnostic accuracy of stepwise screening for DM (per OGTT) based on a single RPG ≥100 mg/dl and subsequent screening of participants with HbA1c (n=576) was superior to screening by HbA1c alone in the complete cohort (n=1,573). By including other DM risk factors such as sex, race, age and BMI, the diagnostic accuracy of HbA1c was slightly enhanced, though still inferior to stepwise screening. Furthermore, after accounting for the optimism inherent in predictive models, the impact additional risk factors had on diagnostic accuracy, when included in stepwise screening, was negated. These results indicate a strong association between a single observed RPG ≥100 mg/dl and unrecognized DM. Incorporating opportunistically available RPG into current DM screening guidelines could be an efficient method to improve identification of unrecognized DM and earlier initiation of preventive management.

By applying the ADA guidelines for diagnosis of DM using FPG and 2h PG, we found 72 undiagnosed cases of asymptomatic DM in our study population. What is more, based on an HbA1c ≥6.5%, diagnostic criteria for DM as recommended by the ADA, we only identified 24 (33%) of the undiagnosed cases of DM that met FPG or 2hr OGTT criteria, with an additional 10 possible undiagnosed cases who did not meet the diagnostic criteria for either FPG or 2hr OGTT. Similar findings have been reported where HbA1c demonstrated a sensitivity of just 25% when compared with FPG and 2h PG among a population with undiagnosed DM (11), while another study in overweight and obese adults found HbA1c identified only 53% of the participants who met FPG or 2h PG (18). In fact, the ADA's 2020 Standards of Medical Care in Diabetes note the

consistent lack of congruity between HbA1c, FPG and 2h PG (15). However, those same Standards of Medical Care state that HbA1c, FPG, and 2h PG can all be used equally as a method of screening for DM.

Currently, the ADA recommends screening of asymptomatic patients by either an informal analysis of select risk factors or the use of a more formalized risk assessment tool (15). While no large scale randomized controlled trials have been conducted to evaluate the effectiveness of community wide screening for DM, numerous studies have demonstrated how early and aggressive treatment can alter the natural history of the disease (2–9,19). Furthermore, studies such as the DPP, the Finnish Diabetes Prevention study, and the Da Qing Diabetes Prevention Study have shown how prevention of DM through cost-effective treatment of patients at high risk for developing the disease can be achieved (4,20–22). Despite the recommended screening guidelines and research supporting the effectiveness of early treatment, it is estimated that over 20% of all DM cases in US adults remain undiagnosed and untreated (1).

Our results show that those who had an RPG of 100 mg/dl or more, compared with those who had a lower RPG, had a higher prevalence of dysglycemia in general. By applying an additional restriction of HbA1c, the resulting ‘false positives’ predominately had preDM. Furthermore, those cases of DM that missed in the RPG below 100 mg/dl cohort had demonstrably less severe disease.

Though the stepwise screening method purposed here is not perfect, it would be a substantial improvement over current screening techniques. Additionally, not only were we able to improve sensitivity using lower HbA1c cutoffs in conjunction with an RPG of at least 100 mg/dl, but that we were able to so while maintaining high specificity and

reducing the proportion of the population needing an OGTT to confirm diagnosis by more than half.

The shortcomings of our current DM screening practices need to be addressed if we are to make meaningful strides towards more efficient management of the disease. RPG has been shown in multiple settings to have potential as an effective tool at both screening for DM and predicting future cases (12,13). By incorporating other objective and empirical measures, such as RPG, clinicians could improve identification of high-risk patients whose HbA1c fails to reach the diagnostic threshold, and recommend they receive an OGTT to confirm their lack of diagnosis.

There are few studies that have collected data on HbA1c, FPG and 2h PG , and fewer still that also include documentation of RPG. In light of this, the large cohort of 1,573 well characterized participants used in this study is a major strength. Even when datasets do include RPG as a measure, it is frequently biased due to the sample being collected on the same day as another sample which requires fasting. As part of the SIGT study protocol, HbA1c and RPG samples were collected on a separate day approximately 2 weeks apart from when the FPG and 2hr OGTT were collected.

This study is not without limitations. Our study was conducted in a single American city. Thus, the findings may have limited applicability in other regions of the world. Additionally, the study recruited volunteers from the local community through advertisement campaigns, which may have led to bias from participants self-selecting into the study. Undiagnosed DM was determined based on FPG and 2h PG , both of which face issues of their own in terms of consistency. Identified cases with an RPG

below 100 mg/dl were sparse, in turn limiting the comparisons in cases that can be made to between strata.

To further understand the potential role RPG may be able to play in DM screening, more research is needed. Existing data sets from previous studies investigating DM often do not include values of RPG despite many of these studies having collected the data as either part of eligibility screening or during the course of the study as part of other common lab work. Yet, in spite of these shortcomings of the data, evidence is mounting that RPG could have a clinically meaningful role as part of stepwise screening for DM.

Tables

Table 1 Participant demographics

	All		Diabetes Only	
	RPG < 100 mg/dl	RPG ≥ 100 mg/dl	RPG < 100 mg/dl	RPG ≥ 100 mg/dl
n	997	576	15	57
per cent of all	63.4	36.6	20.8	79.2
Age (years)	46.2 (±12.4)	50.8 (±11.2)	52.1 (±11.5)	54.3 (±10.8)
BMI ($kg•m^{-2}$)	29.6 (±6.6)	31.4 (±6.9)	32.9 (±6.9)	34.8 (±7.0)
Black (%)	59.8	54.9	53.3	70.2
Female (%)	62.4	50.7	46.7	49.1
Mean A1c (%)	5.4 (±0.4)	5.6 (±0.6)	5.6 (±0.6)	6.4 (±1.0)
RPG (mg/dl)	87.6 (±8.4)	118.6 (±20.7)	93.9 (±3.9)	141.3 (±37.1)
RCG (mg/dl)	93.4 (±15.5)	120.4 (±26.4)	95.7 (±14.0)	139.2 (±41.2)
Fasting PG (mg/dl)	91.6 (±10.5)	101.7 (±15.8)	116.2 (±19.3)	130.7 (±25.6)
2hr PG (mg/dl)	102.7 (±31.2)	129.6 (±47.8)	182.9 (±56.3)	225.4 (±47.8)
1hr GCT (mg/dl)	123.1 (±34.6)	151.0 (±42.9)	182.2 (±41.3)	212.5 (±53.2)
Dysglycemia (%)	25.7	59.0		
≥100 mg/dl, FPG (ADA)	18.3	51.0	80.0	94.7
≥110 mg/dl, FPG (WHO)	3.9	21.7	67.7	87.7
≥140 mg/dl, 2hr OGTT	11.8	33.0	73.3	96.5
FPG (ADA) & 2hr OGTT	4.4	25.0	53.3	91.2
FPG (WHO) & 2hr OGTT	1.8	15.3	40.0	84.2
Prediabetes (%)	24.2	49.1		
Diabetes (%)	1.5	9.9		
≥126 mg/dl, FPG	0.7	6.1	46.7	61.4
iIFG	0.6	1.6	40.0	15.8
≥200 mg/dl, 2hr OGTT	0.9	8.3	60.0	84.2
iIGT	0.8	3.8	53.3	38.6
FPG & 2hr OGTT	0.1	4.5	6.7	45.6

Note: All values presented as either mean (±sd) or percent.

Table 2 Screening accuracy of reduced model by HbA1c cut point

		Total		RPG <100 mg/dl		RPG ≥100 mg/dl	
n		1,573		997		576	
Cases		72		15		57	
AUC (±SE)		0.82 (±0.03)		0.60 (±0.08)		0.86 (±0.03)	
Optimism		-0.001		0.015		-0.001	
95% CI		(-0.003, 0.001)		(0.010, 0.021)		(-0.003, 0.001)	
Adj AUC		0.82		0.58		0.86	
		Sens	Spec	Sens	Spec	Sens	Spec
HbA1c (%)	4.9	1.00	0.06	1.00	0.07	1.00	0.04
	5.0	0.96	0.10	0.87	0.11	0.98	0.08
	5.1	0.96	0.16	0.87	0.18	0.98	0.13
	5.2	0.92	0.24	0.73	0.27	0.96	0.19
	5.3	0.89	0.34	0.67	0.38	0.95	0.27
	5.4	0.85	0.49	0.47	0.53	0.95	0.41
	5.5	0.83	0.58	0.47	0.63	0.93	0.49
	5.6	0.78	0.69	0.47	0.73	0.86	0.61
	5.7	0.74	0.77	0.47	0.81	0.81	0.69
	5.8	0.69	0.83	0.40	0.86	0.77	0.78
	5.9	0.64	0.89	0.33	0.91	0.72	0.85
	6.0	0.57	0.93	0.27	0.94	0.65	0.89
	6.1	0.54	0.95	0.27	0.96	0.61	0.94
	6.2	0.49	0.97	0.20	0.97	0.56	0.96
	6.3	0.46	0.98	0.20	0.99	0.53	0.98
	6.4	0.39	0.99	0.20	0.99	0.44	0.99
	6.5*	**0.33**	**>0.99**	**0.20**	**>0.99**	**0.37**	**>0.99**
	6.6	0.28	>0.99	0.07	>0.99	0.33	>0.99
	6.7	0.24	>0.99	0.00	>0.99	0.30	>0.99
	6.8	0.19	>0.99	-	-	0.25	>0.99
	6.9	0.14	>0.99	-	-	0.18	>0.99
	7.0	0.14	>0.99	0.00	>0.99	0.18	1.00
	7.1	-	-	-	-	-	-
	7.2	-	-	-	-	-	-
	7.3	0.13	>0.99	-	-	0.16	1.00
	7.4	0.10	>0.99	0.00	>0.99	0.12	1.00
	7.5	0.08	1.00	-	-	0.11	1.00
	7.6	0.07	1.00	-	-	0.09	1.00
	7.7	0.06	1.00	-	-	0.07	1.00
	7.8	0.04	1.00	-	-	0.05	1.00
	9.9	0.03	1.00	-	-	0.04	1.00
	11.0	0.01	1.00	-	-	0.02	1.00

*Current ADA criteria for HbA1c based diagnosis of diabetes. Note: Blank cells reflect no participants among the specified cohort were observed having a HbA1c at the given level. Random plasma glucose (RPG), sensitivity (Sens), specificity (Spec), and area under the curve (AUC).

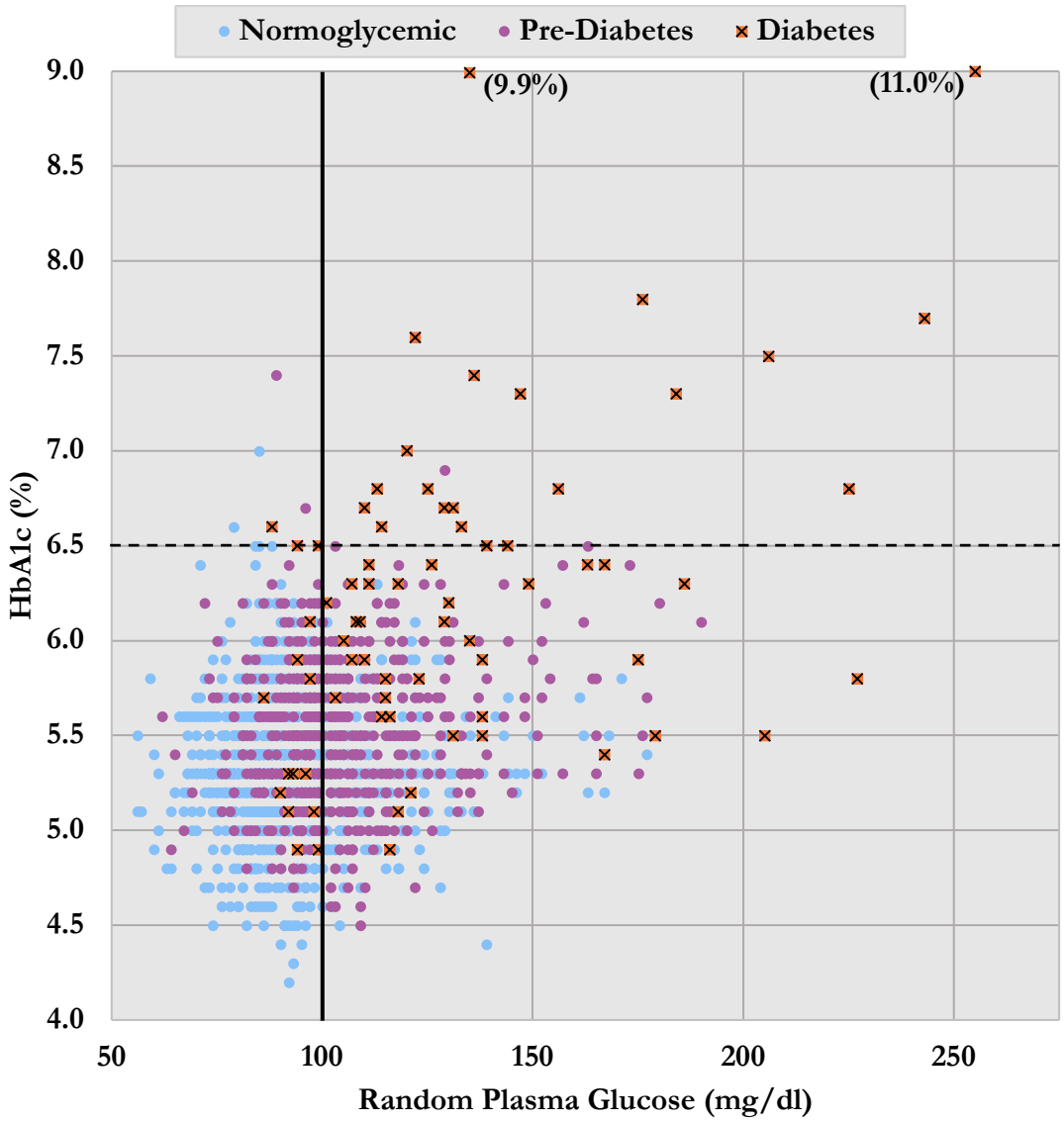
Table 3 Screening accuracy by HbA1c cut point, relative to complete study population

	Model							
	HbA1c Alone				HbA1c + RPG ≥100 mg/dl			
HbA1c (%)	Sens	Spec	Test Pos	True Pos	Sens	Spec	Test Pos*	True Pos
4.9	1.00	0.06	1478	72	0.79	0.67	554	57
5.0	0.96	0.10	1422	69	0.78	0.68	535	56
5.1	0.96	0.16	1330	69	0.78	0.70	509	56
5.2	0.92	0.24	1203	66	0.76	0.72	477	55
5.3	0.89	0.34	1049	64	0.75	0.75	435	54
5.4	0.85	0.49	822	61	0.75	0.80	358	54
5.5	0.83	0.58	685	60	0.74	0.82	317	53
5.6	0.78	0.69	528	56	0.68	0.86	253	49
5.7	0.74	0.77	398	53	0.64	0.89	206	46
5.8	0.69	0.83	301	50	0.61	0.92	158	44
5.9	0.64	0.89	218	46	0.57	0.95	121	41
6.0	0.57	0.93	153	41	0.51	0.96	93	37
6.1	0.54	0.95	108	39	0.49	0.98	67	35
6.2	0.49	0.97	86	35	0.44	0.99	53	32
6.3	0.46	0.98	58	33	0.42	>0.99	42	30
6.4	0.39	0.99	44	28	0.35	>0.99	31	25
6.5†	**0.33**	**>0.99**	**34**	**24**	**0.29**	**>0.99**	**24**	**21**
6.6	0.28	>0.99	25	20	0.26	>0.99	20	19
6.7	0.24	>0.99	21	17	0.24	>0.99	18	17
6.8	0.19	>0.99	17	14	0.19	>0.99	15	14
6.9	0.14	>0.99	13	10	0.14	>0.99	11	10
7.0	0.14	>0.99	12	10	0.14	1.00	10	10
7.1‡	-	-	-	-	-	-	-	-
7.2‡	-	-	-	-	-	-	-	-
7.3	0.13	>0.99	10	9	0.13	1.00	9	9
7.4	0.10	>0.99	8	7	0.10	1.00	7	7
7.5	0.08	1.00	6	6	0.08	1.00	6	6
7.6	0.07	1.00	5	5	0.07	1.00	5	5
7.7	0.06	1.00	4	4	0.06	1.00	4	4
7.8	0.04	1.00	3	3	0.04	1.00	3	3
9.9	0.03	1.00	2	2	0.03	1.00	2	2
11.0	0.01	1.00	1	1	0.01	1.00	1	1

*Denotes number of participants that meet cutoff criteria for HbA1c and have an RPG ≥100 mg/dl. †Current ADA criteria for HbA1c based diagnosis of diabetes. ‡No participants with an HbA1c at the given level. Note: the sensitivity (Sens) and specificity (Spec) in the "HbA1c + RPG ≥ 100 mg/dl" model reflect the added 982 true negatives and 15 false negatives among those with a random plasma glucose (RPG) less than 100 mg/dl. Positive (Pos)

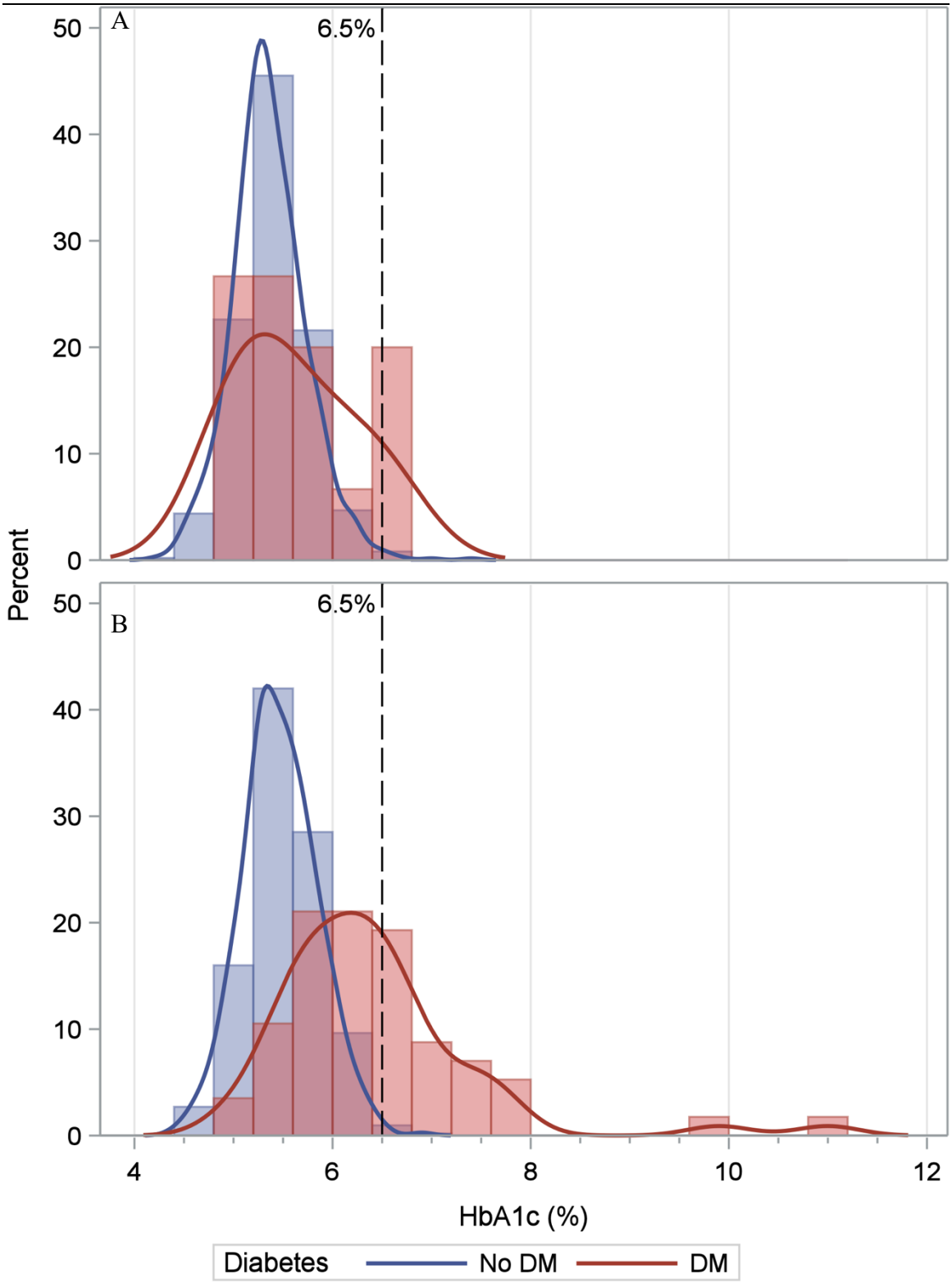
Figures

Figure 1 Random Plasma Glucose versus HbA1c, by Dysglycemia



	DM +	DM -	Total
RPG ≥100 mg/dl	57	519	576
RPG <100 mg/dl	15	982	997
Total	72	1,501	1,573
Positive Predictive Value:	9.9%	Negative Predictive Value:	98.5%
Sensitivity:	79.2%	Specificity:	65.4%

Figure 2 Distribution of HbA1c by RPG ≥100 mg/dl and Type 2 Diabetes Mellitus



A: Random plasma glucose less than 100 mg/dl
B: Random plasma glucose of at least 100 mg/dl

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