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Glucose Challenge Test as a Predictor of Type 2 Diabetes

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by

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Abstract

***Background*:** The Centers for Disease Control and Prevention estimates that 30 million Americans are living with diabetes and by 2050, 1 out of 3 U.S. adults could develop diabetes. Current screening and diagnostic methods for diabetes mellitus include the oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c), and fasting plasma glucose (FPG) levels, but each test when used alone will miss a portion of patients who have the disease. It has been suggested that the 50-g glucose challenge test (GCT) could also serve as a useful diabetes screening test particularly in light of its greater convenience compared to the FPG and OGTT. Given the expected increases in the prevalence of diabetes, it is particularly important to identify convenient and efficient screening tests which can effectively predict those individuals at highest risk for the development of diabetes.

Objective: To determine the predictive utility of the GCT in identifying incident diabetes over five years and to determine whether other important risk factors, including age, gender, race, body mass index, waist circumference and lipid levels, modify the predictive utility of the GCT.

Methods: We performed a prospective observational study at the Atlanta Veterans Affairs Medical Center (2009-2012). Eligible participants were those who did not have diabetes at baseline based on an OGTT. Data on incident diabetes was collected during 5 years of follow-up. Incident diabetes was defined by patient medical records and ICD-9 codes. Receiver operating characteristics were used to assess the predictive utility of the GCT, HbA1c, and components of the OGTT (fasting, 1-hour, and 2-hour measures). The GCT consisted of a 50 gram glucose load with plasma and capillary (finger stick) glucose measurements performed one hour later.

Results: Of 1384 eligible participants, 94% were male, 73.4% Black, and median age and body mass index was 56.0 years and 29.5 kg/m^2, respectively. Among those with follow up within 5 years, 133 (9.6%) participants had a new diagnosis of diabetes. The area under the receiver operating characteristics curves (AROC) for the GCTplasma, GCTcap, HbA1c, and the grouped measures from the OGTT (fasting, 1-hour, and 2-hour) were 0.634, 0.643, 0.725, 0.657, 0.691 and 0.662, respectively. When comparing AROC values in predicting incident diabetes at five years, the GCTplasma performed as well as the GCTcap, 2hr-OGTT, and FPG ($p>0.05$), but had a significantly lower predictive utility than that of HbA1c and 1hr-OGTT ($p <0.01$). Among subgroups of age, body mass index, waist circumference, and triglycerides AROC values for diabetes risk were greater in patients aged <50 (0.684) and BMI ≥35 (0.713) compared to their respective reference subgroups.

Conclusion: The GCT performed as well as the currently used 2hr-OGTT and FPG tests at predicting future incidence of diabetes. Given its convenience as a non-fasting, 1-hour test, the GCT may provide a practical and efficient approach in identifying those at risk of incident diabetes in a clinical setting.

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Author's Statement Page

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Chapter 1: Introduction

Background

Diabetes mellitus is a metabolic disorder in which blood glucose levels rise above normal [1, 2]. Type 2 diabetes is a result of the body not being able to use insulin effectively (insulin resistance) and or the body's inability to produce adequate amounts of insulin (insulin deficiency). Insulin is a hormone produced by the pancreas and facilitates the transfer of glucose from the bloodstream and into the cells of insulin-dependent tissues. If diabetes is left uncontrolled, glucose levels will rise and can lead to the development of serious health complications and other diseases, such as blindness, kidney disease, heart disease, and stroke [1, 2].

According to the CDC, over 200,000 deaths per year in the United States are attributed to diabetes. Since 1980, the number of diagnoses of diabetes in adults has quadrupled and it is projected that 1 out of 3 adults could have diabetes by 2050 [1]. Among the 30 million Americans living with diabetes, approximately 8 million (28%) are undiagnosed, 90 to 95 percent of which have type 2 diabetes[1, 2]. Furthermore, an estimated 86 million individuals have prediabetes, a high risk condition for the development of type 2 diabetes [1]. The risk of diabetes also increases with age, is higher in males than females, and disproportionately affects Hispanics and African Americans compared to non-Hispanic whites.

Early detection of diabetes and prediabetes is key to prevent or delay the progression from prediabetes to diabetes and to ensure early intervention to combat the risk for diabetes-related complications and. Large randomized controlled trials have shown that intensive glycemic management in patients with diabetes leads to significant reductions in diabetes-related complications [3] [4] and that earlier initiation of intensive treatment provides long-term

reductions in risk compared to later initiation of intensive glycemic management [5] [6]. As such, identification of effective screening approaches is essential for early diagnosis of diabetes and in the interest of public health.

The American Diabetes Association (ADA) and National Institute of Health (NIH) have identified several factors that can lead to increased risk diabetes. Age, gender, race, BMI, waist circumference, and blood pressure all have been proven to influence the risk of developing type 2 diabetes. Current clinical practices use hemoglobin A1C (HbA1c), fasting plasma glucose (FPG), and the oral glucose tolerance test (OGTT) to screen for and diagnose type 2 diabetes. These methods have proven effective but also have individual disadvantages. The use of a glucose challenge test (GCT) may serve as a more efficient and simple tool to screen for diabetes and prediabetes given its convenience and low cost. The GCT, a standard screening test for gestational diabetes during pregnancy, entails the ingestion of a 50-gram oral glucose load at any time of day, irrespective of fasting or postprandial state, followed by a blood glucose measurement one hour later. In a screening study by Phillips et al [7], the GCT was shown to be more accurate in detecting glucose intolerance (diabetes or prediabetes) compared to other standard methods. In combination with other publications, there is supporting evidence that the GCT is not only successful in screening for diabetes but could be a useful predictor of future incidence of diabetes.

Purpose of the Study:

The purpose of this study was to: 1) assess and compare the utility of the GCT, HbA1c and OGTT (fasting, 1-hour, and 2-hour values) to predict incident diabetes among non-diabetic patients, and 2) to determine whether other important risk factors including age, gender, race, BMI, waist circumference and lipid levels modify the predictive utility of the GCT.

Research Aims

1. To determine the predictive utility of the glucose challenge test to predict the 5 year incidence of type 2 diabetes among non-diabetic patients.
2. To compare the utility of the glucose challenge test against the hemoglobin A1c test and oral glucose tolerance test (fasting, 1-hour, and 2-hour values) in predicting incident diabetes over 5 years, among non-diabetic patients.
3. To determine the predictive value, area under the receiver operating characteristics curve, within subgroups of age, gender, race, body mass index, waist circumference and blood pressure in detecting incidence of diabetes.

Hypotheses

1. The glucose challenge test will have greater accuracy in predicting 5-year incident diabetes, as determined by receiver operating characteristics, than hemoglobin A1c and the oral glucose tolerance test.
2. Body mass index will have the largest predictive value among the subgroups in detecting diagnoses of diabetes.

Chapter 2: Review of Literature

Reducing the rate of progression to type 2 diabetes is critical in combating the many health problems associated with the disease. The American Diabetes Association classifies prediabetes as, blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes [8]. The prevalence of prediabetes is estimated to be over 80 million in the United States and this group is not only at increased risk of developing type 2 diabetes but also

cardiovascular disease and stroke [1]. Consequently, diabetes along with cardiovascular disease and stroke all fall within the top 10 leading causes of death in the United States. Thus it is of great importance to continue to use our best methods to screen for diabetes and develop methods to effectively predict future incidences of diabetes.

Predicting Diabetes

Developing accurate and effective measures to predict future incidence of diabetes could be beneficial in reducing the increasing burden of type 2 diabetes. Growing interest and evidence suggests that current screening practices and methods can be useful in predicting diabetes in non-diabetic populations [9-11]. Hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT) are all currently used in the clinical setting to screen and diagnose type 2 diabetes. Several recent publications have taken interest in the utility of these test to predict future incidences of diabetes among non-diabetic populations.

HbA1c vs FPG

Edelman D. et al [10] in 2004 published a study that assessed the use of HbA1c to independently predict future risk cases of type 2 diabetes. This prospective study conducted at Durham Veterans Affairs Medical Center (DVAMC) followed 1253 patients ages 45-64 for 3 years. A baseline visit was conducted measuring HbA1c, those with HbA1c greater than or equal to 6.0% were invited back and a FPG was taken. An annual phone call was made to patients during year 1 and 2 to check for diagnoses of diabetes and a repeat visit identical to the baseline exam was performed during year 3. There were 56 patients at baseline that were determined to have unrecognized diabetes (HbA1c $\geq$ 7.0% or FPG $\geq$ 126 mg/dl) and were still included throughout the 3 year follow-up but not in the analysis.

New incidence of diabetes were calculated over the 3 year period by self-reporting, or HbA1c ≥ 7.0% or FPG ≥ 126 mg/dl at the 3 year visit. Over the 3 year period, 73 new cases of diabetes were identified. To assess HbA1c in its ability to predict future cases of diabetes, the baseline results were stratified into 3 groups: normal (≤ 5.5%), high-normal (5.6- 6.0%), and elevated (6.1-6.9%). The results showed that there was a correlation between rising HbA1c and incidences of diabetes. The elevated subgroup of HbA1c had a significantly higher incidence rate of 7.8 compared to the normal subgroup, 0.8. A multivariable logistic regression model was also used to assess the known risk factor, age, sex, family history, BMI, and hypertension while comparing those who did and did not develop a new diagnoses of diabetes. Out of these 5 risk factors only BMI was seen to be associated with elevated risk after controlling for HbA1c. Overall, HbA1c was seen in this study to predict future incidence of diabetes in this cohort.

OGTT (0, 30, 60, 120 min)

In 2009, Abdul-Ghani M. et al compared fasting plasma glucose (FPG) to the 75g-OGTT post-load plasma glucose levels in a study using the results from the Botnia Study. The study consisted of 2,442 non-diabetic participants from the Botnia Study in Western Finland. The baseline visit collected plasma glucose and insulin levels measured at 0, 30, 60, and 120 minutes during the OGTT. Participants were then followed for 7-8 years for incidence of diabetes using ADA criteria. Receiver operating characteristics (ROC) was used to measure the predictive power at each post-load time point. Tree modeling analysis was also used and categorized participants into 4 categories: normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and combined glucose intolerance (CGI) (IFG+IGT). These groups allowed for detailed comparisons to be made across the different levels of prediabetes.

The area under the curve (ROC AUC) was calculated for each time point strongest (0, 30, 60, 120 minutes) and concluded that the 1-hour (60 minute) post-load value was the predictor of future incidence of diabetes with an ROC AUC of 0.795. The remaining time points also indicated statistically significant results: 30 minute (0.735), 120 minute (0.688) and FPG (0.672). Hemoglobin A1c (HbA1c) was also measures and resulted in an ROC AUC slightly better than FPG, 0.679.

1-hour vs 2-hour plasma glucose and FPG

In 2010, Priya M. et al published a study that evaluated the 1-hour and 2-hour post-load plasma glucose and FPG's ability to predict progression to diabetes and prediabetes among NGT subjects. The study was performed in Chennai, South India and consisted of 1,179 participants selected from a diabetes specialty center. All participants were non-diabetic at baseline (FPG ≤ 100 mg/dl) and had undergone an OGTT with a 1-hour and 2-hour plasma glucose sample between 1997- 2010. The participants were then followed for 7-8 years and assessed for diagnoses of diabetes or prediabetes at the end of follow-up using ADA criteria. ROC analysis was used to compare the predictive ability of FPG, 1-hour plasma glucose, and 2-hour plasma glucose. Sensitive and specificity at multiple cut off values was also assessed using ROC curves. Incidence of prediabetes and diabetes were reported per 1,000 person-years, continuous variables were displayed as averages and categorical variables as percentages or counts.

The results of this study concluded that the 1-hour plasma glucose level had a larger AUC in comparison to the 2-hour plasma glucose and FPG in predicting prediabetes and diabetes. The AUC for the 1-hour, 2-hour, and FPG in predicting diabetes was 0.689, 0.608, and 0.622 respectively. The 1-hour cutoff for optimal sensitive and specificity cutoff was determined to be 155 mg/dl for prediction of diabetes. Using this 1-hour cut of participants were further

stratified into three categories: < 143 mg/dl, ≥ 143 md/dl - < 155 mg/dl, and ≥ 155 mg/dl. Further analysis of these subgroups showed that those with 1-hour plasma glucose levels ≥ 155 mg/dl had a larger proportion to develop diabetes (19.5%) and shorter time to diagnoses compared to the < 143 mg/dl subgroup (6.6%).

1-hour plasma glucose vs IFG

A more recent study published in 2015 by Fiorentino T. V. et al. [11] also took interest in the 1-hour post load plasma glucose measurement. This study consisted of 2 sample groups to assess the 1-hour post load plasma glucose level in predicting future development of type 2 diabetes compared to IFG and IGT. The first group consisting of 595 white nondiabetic adults from the European Network on Functional Genomics of type 2 diabetes (EUGENE2) project and the second group contained 392 white adults that were current participants the Cat-Anzaro Metabolic Risk Factors (CATAMERI) study. Each of the participants in both sample groups had a 75g OGTT performed with blood samples taken at 0, 30, 60, 90, and 120 minute intervals. Participants were then classified as having normal glucose tolerance (NGT), isolated IFG, or IGT according to ADA criteria [8] in reference to the 1-hour plasma glucose. Those who fell into the NGT group were then separated into a NGT 1h-low group if 1-hour plasma glucose levels were below 155 mg/dl and NGT 1h-high if above 155 mg/dl.

In first group (EUGENE2 project) a cross-sectional study analysis was preformed to observe the insulin sensitivity among the cohort. The categorical variables in this group were compared using a Chi-square test and a general linear model was used to make multiple comparisons for the variables age, gender, and BMI. In the second group (CATAMERI study), a longitudinal study analysis was preformed to observe the risk of metabolic and cardiovascular outcomes. A Cox-proportional hazards analysis was performed and included age, gender and

BMI to estimate the hazard ratio to develop type 2 diabetes of the NGT 1h-high, isolated IFG and IGT groups compared to the NGT 1h-low group. The results from the CATAMERI cohort showed that those in the NGT 1h-high category are at increased risk for developing type 2 diabetes compared to NGT 1h-low. The hazard ratio for NGT 1h-high, isolated IFG, and IGT were 4.02, 1.91, and 6.67 respectively. The incidence rate among the entire NGT group was 6.4%, but once stratified into the subgroups, NGT 1h-high (16.7%) has a significantly higher rate than the NGT 1h-low (2.9%) subgroup. The results of this study are of interest because the use of the 1-hour plasma glucose measurement has possibly identified an at risk group that under current ADA criteria would be overlooked and not identified. Evidence is also growing around the 155 mg/dL 1-hour plasma glucose cutoff as a means to identify future risk of type 2 diabetes.

Screening for Diabetes

There are several screening methods used in detecting and diagnosing diabetes and prediabetes. The oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c), and fasting plasma glucose (FPG). It is recommended by the American Diabetes Association that these test be repeat upon confirmation to assure accurate testing and greater likelihood of concurrence [12]. These test results are also used in conjunction with signs and symptoms of diabetes to make a well informed clinical diagnoses of prediabetes or type 2 diabetes [8].

Several studies have shown that a substantial amount of patients can be missed by using just one test and that some test capture more undiagnosed patients than other. The ADA reports that HbA1c, FPG, and OGTT identify approximately 30-40%, 50%, and 90% of previously undiagnosed patients, respectively [13]. These results are supported by the 2003-2006 NHANES data, 2010 IRAS study [14], and a 2010 study in Qingdao, China [15]. These results further

conclude that improved methods for the detection of diabetes are in the interest of the public health community.

Screening using OGTT

The OGTT involves the ingestion of a 75-gram glucose load that must be administered while fasting, followed by a blood glucose measurement two hours later. Results less than 140 mg/dl are normal, 140 mg/dl to 199 mg/dl indicates prediabetes, and greater than 200 mg/dl, diabetes [8]. While this test is considered to be the most sensitive, it is often times not used in clinical practice because it is inconvenient due to the required fasting and time constraint [7] [16]. Acute stress and diet the day before the test can also alter the results making them not consistently reproducible and nausea is a potential side effect from the glucose drink.

Screening using FPG

The fasting plasma glucose test is an easy and common laboratory test done to determine blood glucose levels. It entails one plasma glucose collection under fasting conditions. Results less than 100 mg/dl are normal, 100 mg/dl to 125 mg/dl indicate prediabetes, and 126 mg/dl or higher, diabetes [8]. Though relatively simple to perform, like the OGTT, FPG can be easily altered by day to day diet, illness, or stress resulting in inaccurate measurements [12].

Screening using HbA1c

The HbA1c is a test that measures the average blood glucose level over the past 2 to 3 months. Unlike the OGTT and FPG, no fasting or drinking is required making this test more convenient to administer [8, 12]. An HbA1c value of less than 5.7% is normal, 5.7% to 6.4% indicates prediabetes, and 6.5% or higher, diabetes. Though it is deemed the most convenient

test, there are still limitations that include incomplete correlation between HbA1c and average glucose levels in certain race/ethnicities and ages [12]. African Americans tend to have higher HbA1c levels compared to non-Hispanic whites even with comparable FPG [12]. Elevated HbA1c levels are also found among the aging population [17].

Investigational Screening using Glucose Challenge Test (GCT)

In the screening study by Phillips et al. [7], the glucose challenge test was used as an alternate screening test to identify prediabetes, dysglycemia, and diabetes. The results indicated that the GCT was an accurate, convenient, and inexpensive alternative to screen for diabetes and prediabetes. The study included 1,573 participants that were administered a GCT followed by an OGTT at a later visit. Fasting plasma glucose (FPG) along with hemoglobin A1c and lipid values were also measured and recorded for each patient and diagnoses were made using ADA criteria. Receiver operating characteristics (ROC) analysis was used to compare and determine the effectiveness of the screening measurements by calculating the area under receiver operating characteristic curves (AROCs). The GCT out preformed hemoglobin A1C, FPG, and random plasma glucose (RPG) in detecting diabetes, prediabetes, and dysglycemia. The AROC results indicated great generalizability to other populations and were unaffected by time of day or fasting.

Chapter 3: Manuscript

Abstract

***Background*:** The Centers for Disease Control and Prevention estimates that 30 million Americans are living with diabetes and by 2050, 1 out of 3 U.S. adults could develop diabetes. Current screening and diagnostic methods for diabetes mellitus include the oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c), and fasting plasma glucose (FPG) levels, but each test when used alone will miss a portion of patients who have the disease. It has been suggested that the 50-g glucose challenge test (GCT) could also serve as a useful diabetes screening test particularly in light of its greater convenience compared to the FPG and OGTT. Given the expected increases in the prevalence of diabetes, it is particularly important to identify convenient and efficient screening tests which can effectively predict those individuals at highest risk for the development of diabetes.

Objective: To determine the predictive utility of the GCT in identifying incident diabetes over five years and to determine whether other important risk factors, including age, gender, race, body mass index, waist circumference and lipid levels, modify the predictive utility of the GCT.

Methods: We performed a prospective observational study at the Atlanta Veterans Affairs Medical Center (2009-2012). Eligible participants were those who did not have diabetes at baseline based on an OGTT. Data on incident diabetes was collected during 5 years of follow-up. Incident diabetes was defined by patient medical records and ICD-9 codes. Receiver operating characteristics were used to assess the predictive utility of the GCT, HbA1c, and components of the OGTT (fasting, 1-hour, and 2-hour measures). The GCT consisted of a 50 gram glucose load with plasma and capillary (finger stick) glucose measurements performed one hour later.

Results: Of 1384 eligible participants, 94% were male, 73.4% Black, and median age and body mass index was 56.0 years and 29.5 kg/m^2, respectively. Among those with follow up within 5 years, 133 (9.6%) participants had a new diagnosis of diabetes. The area under the receiver operating characteristics curves (AROC) for the GCTplasma, GCTcap, HbA1c, and the grouped measures from the OGTT (fasting, 1-hour, and 2-hour) were 0.634, 0.643, 0.725, 0.657, 0.691 and 0.662, respectively. When comparing AROC values in predicting incident diabetes at five years, the GCTplasma performed as well as the GCTcap, 2hr-OGTT, and FPG ($p>0.05$), but had a significantly lower predictive utility than that of HbA1c and 1hr-OGTT ($p <0.01$). Among subgroups of age, body mass index, waist circumference, and triglycerides AROC values for diabetes risk were greater in patients aged <50 (0.684) and BMI ≥35 (0.713) compared to their respective reference subgroups.

Conclusion: The GCT performed as well as the currently used 2hr-OGTT and FPG tests at predicting future incidence of diabetes. Given its convenience as a non-fasting, 1-hour test, the GCT may provide a practical and efficient approach in identifying those at risk of incident diabetes in a clinical setting.

Introduction

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels. If left uncontrolled, diabetes can lead to the development of serious health complications, including cardiovascular disease, kidney failure, blindness and stroke [1, 2, 18]. Diabetes is a growing health concern in the United States, with over 200,000 deaths per year, and is ranked the 7th leading cause of death in 2013 [1]. Since 1980, the number of diabetes diagnoses in U.S. adults has quadrupled, and 1 of 3 adults is projected to have diabetes by 2050 [1]. An estimated 8 million Americans currently have diabetes but are undiagnosed [1, 2].

Early detection of type 2 diabetes and prediabetes is vital to prevent or delay the progression from prediabetes to diabetes and to ensure early interventions to prevent or reduce the complications associated with diabetes [18, 19]. Large randomized controlled trials have shown that early initiation of intensive treatment, using medications such as sulfonylureas, insulin, or metformin, provides long-term reductions in risk and complications compared to later initiation of intensive glycemic management [4-6]. The American Diabetes Association (ADA)[12] and US Preventive Services Task Force (USPSTF)[2] have both outlined guidelines on screening for diabetes, but it would also be in the public health interest to determine if current methods could also predict future incidence of diabetes among the non-diabetic population.

In an observational cohort study by Phillips et al [7] the glucose challenge test (GCTplasma), similar to that used for routine screening of gestational diabetes in pregnancy [20, 21], was evaluated as a potential screening test for type 2 diabetes and prediabetes in a non-pregnant population. The study found that the GCTplasma was more accurate at detecting diabetes and prediabetes than hemoglobin A1c (HbA1c), the 2-hour oral glucose tolerance test (2hr-OGTT) and fasting plasma glucose (FPG) – all standard tests for diabetes screening and diagnosis. In addition to identifying undiagnosed diabetes, there has also been recent interest in identifying those individuals with particularly high risk for future development of diabetes, and therefore the predictive ability of current screening methods to identify this subpopulation requiring closer and screening [9-11, 22, 23].

The purpose of this study was to determine the predictive utility of the GCT to identify incident diabetes mellitus among non-diabetic patients, compare the utility of the GCTplasma, GCTcap, HbA1c, and the combined measures of the OGTT (Fasting, 1-hour, and 2-hour values),

and to determine whether other important risk factors including age, gender, race, body mass index, waist circumference, and lipid levels, modify the predictive utility of the GCT.

Methods

Participants

This prospective observational study included the cohort of participants in a previously conducted diabetes screening study [24] at the Atlanta Veterans Affairs Medical Center (VAMC). The purpose of that screening study was to compare the diagnostic utility of the GCT against standard clinical screening methods. The participants were recruited from June 2009 to December 2012 during primary care visits at the Atlanta VAMC. Participants were eligible if they were 45 years or older and had a BMI greater than 25 and no current clinical diagnoses of diabetes. Participants underwent a 50-gram 1-hour GCT and a 75-gram 2-hour OGTT. Among the original cohort of 1535 participants, the subset identified as non-diabetic at their baseline visit (n=1384) by OGTT, according to the ADA criteria [8], served as the study cohort for the current study

Study Design and Measures

Data was collected from the participant's medical records for up to 5 years following the initial screening visit. The primary outcome of interest was incident diabetes. A new diagnosis of diabetes was defined as: a) any use of the diabetes ICD-9 code 250.xx [25] in conjunction with a primary care attending outpatient visit and/or b) any two uses of the ICD-9 code 250.xx or c) an outpatient prescription of a diabetes drug.

Collected demographic information included race, gender, and age. Race was categorized into 3 groups black, white, and other. Body mass index, waist circumference, triglycerides, high density lipoproteins (HDL) cholesterol, and low density lipoproteins (LDL) cholesterol

measurements were also obtained via medical records, if available. These variables were chosen because of their known link to increased risk of diabetes [2, 26, 27]. All 1384 participants had complete results for the GCT, OGTT, HbA1c, and FPG. Two additional test measurements, the 1-hr OGTT glucose and GCT capillary (GCTcap) glucose, which consisted of a point-of-care finger stick glucose measurement in place of a standard venous blood draw, were also available for a portion of the study population. All laboratory testing were preformed using standard VAMC equipment and protocols.

Analysis

This study analyzed the performance of GCTplasma to predict future incidence of diabetes and compared its utility to the 2hr-OGTT, HbA1c, and FPG. Descriptive statistics were calculated for all variables which were included in the logistic analysis models (Table 2). Generalized estimating equations (GEE) [28] were used to model the likelihood of being diagnosed with diabetes given the results from the GCTplasma, GCTcap, 2hr-OGTT, 1-hr OGTT, HbA1c, and FPG. This method of analysis was chosen to account for correlation of the data and its ability to handle missing values among the covariates. All of the participants did not have complete follow up history throughout the 5 years, in turn, two assumptions were made during the analysis. First, if a participant was diagnosed in a given year we assumed that participant remained a patient with diabetes for the following years. Second, if a person did not have a follow up visit in a given year, we assumed that a diagnosis of diabetes was not made in that year. The predictive utility of the tests and covariates was evaluated by using receiver operating characteristic (ROC) analysis and comparing area under receiver operating characteristic curves (AROCs) [29]. All analyses were performed using the SAS analysis system (Cary, NC). A p-value <0.05 was considered statistically significant for all analyses.

Results

Among the cohort of 1384 participants, 94% were male, 73.4 % Black and the median age was 56.0 years with a mean BMI and waist circumference of 29.5 kg/m^2 and 100.0 cm, respectively. Over the 5 years of follow up, 133 (9.6%) participants had incidence of diabetes. Compared to those who remained diabetes-free, participants with incident diabetes were heavier (1.0 kg/m^2 BMI difference, $p<0.01$), had larger waist circumference (6.0 inches difference, $p<0.01$), and higher triglyceride levels (17.00 mg/dl difference, $p<0.01$), (Table 2).

The GCTplasma, GCTcap, 1hr-OGTT, 2hr-OGTT, HbA1c and FPG were all predictors of incident diabetes. GCTplasma produced an AROC of 0.634, the GCTcap, 1hr-OGTT, 2hr-OGTT, HbA1c, and FPG produced AROCs of 0.643, 0.691, 0.662, 0.725, and 0.657, respectively (Table 4). Out of the 1348 participates, 1324 had GCTcap and 1194 had 1hr-OGTT measurements. We found no statistical significant differences when comparing GCTplasma AROC values and subsequent tests, except for HbA1c – GCTplasma and 1hr-OGTT - GCTplasma, with an AROC difference of 0.091($p<0.01$) and 0.057($p<0.01$), respectively. (Table 5).

There were 746 participants who were normal glucose tolerant (NGT) at baseline, 92.6% male, 74.9% Black, with median age, BMI, and waist circumference of 55.0 years, 29.0 kg/m^2, 98.0 cm, respectively. 38 (5.1%) of those who were NGT at baseline had incidence of diabetes over the 5 years of follow up. Compared to those that remained diabetes-free, those with incidence of diabetes had significantly larger waist circumference (8.0 cm difference, $p<0.01$), GCTplasma (13.0 mg/dl difference, $p<0.01$), GCTcap (30.0 mg/dl, $p<0.01$), 1hr-OGTT (20.0 mg/dl difference, $p<0.01$), and HbA1c (0.2% difference, $p<0.01$).

Within the subgroups of age, BMI, waist circumference and triglycerides, the average of each subgroups AROC values mimicked that of GCTplasma (0.634). Those within subgroups age <50 and BMI ≥35 were all found to have slightly larger AROC values in predicting diabetes (0.684 and 0.713 respectively) (Table 6). Overall, GCTplasma predicted incident diabetes among subgroups of risk factors.

GCTplasma's predictive ability over time was calculated by producing AROC values for each year of follow up. The test produced AROCs of 0.683, 0.702, 0.706, 0.699, and 0.693 for years 1 through 5 respectively. Though a slight increase through year 3 and a marginal drop off thereafter, the GCTplasma was consistent throughout 5 years of follow up.

Discussion

We found that the 50-gram GCT, currently used as a standard screening test for gestational diabetes in pregnancy, may also be a good predictor of 5-year incident diabetes in the non-pregnant population, with the 1hr post challenge glucose (GCTplasma) giving an AROC of 0.634. The only other recommended screening tests to produce a higher AROC value were HbA1c (AROC 0.725) and 1hr-OGTT (AROC 0.691). GCTplasma performed equally well as the 2hr-OGTT and FPG with no statistical difference between the tests. Furthermore, the GCTplasma test has two distinct advantages over the 2hr-OGTT. First, the test can be performed regardless of fasting conditions or time of day, and second, the GCTplasma test is administered over 1 hour versus the 2hr-OGTT. Clinicians can administer the GCTplasma test at any time of day and during any visit in patients with high risk of diabetes (regardless of fasting status). Overall, the GCTcap performed equally as well as the GCTplasma, is convenient and can be administered via a simple finger stick versus an intravenous blood draw, and is more affordable [24, 30].

Our results concluded that HbA1c had an AROC difference of 0.091 when compared to GCTplasma. This can be partly attributed to the circularity that exists in the use of HbA1c in the prediction of incident diabetes as it is also mostly commonly used in the diagnosis of diabetes. The majority of clinicians use the HbA1c test for the diagnosis of diabetes, primarily because of its convenience [31]. Although the OGTT is the "gold standard test", clinicians use it less frequently because of the time and preparation needed to administer the test. The association between HbA1c and our outcome of interest, incident diabetes, is likely one reason we observed a larger AROC.

Our findings are consistent with those in the literature that examined the predictive utility of currently used diabetes diagnostic tests. In comparison a study by Adul-Ghani M. et al [9], which also used ROC to assess the predictive ability of the OGTT, HbA1c, and FPG, our AROC values were on average slightly smaller. Adul-Ghani M et al did have similar AROC results for the 2hr OGTT (0.688) and FPG (0.672), while we observed a higher AROC value for HbA1c and lower value for the 1hr OGTT. In a study by Priya et al [22] the three measures of the OGTT (fasting, 1-hour, and 2-hour) were evaluated on their ability to predict progression to diabetes. The AROCs for 1-hour, 2-hour, and FPG measures (0.689, 0.608, and 0.622, respectively) were smaller than those observed in our study, while both still concluded that the 1hr-OGTT was a better predictor. Edelman et al [10] assessed the use of HbA1c in comparison to FPG as a predictor of future cases of diabetes. While ROC analysis was not used, they also concluded that HbA1c is a predictor of future incidence of diabetes. Body mass index was also a statistically significant predictor, which was supported by our findings as well.

Our study has important limitations. First our study may lack of generalizability to other populations because the study population consisted predominantly of black males from one

healthcare system, which may limit the extent to which of our findings are reliable for women and other race groups. The VA Medical Center population is also subject to different risks compared to the general public. Second, lack of complete follow-up information over the 5 years after the initial screening was a limitation. Follow up information, including time at incident diabetes diagnosis, was collected only for patients who presented with a new diagnosis of diabetes during the years of follow up. Patients who either were not diagnosed with diabetes during follow up or were lost to follow up were grouped together as having no diagnosis of diabetes at follow up. Consequently, we could not distinguish between participants with follow up and no diagnosis and those without follow up visit (lost to follow up) and unknown diagnosis. Making the assumptions mentioned previously could lead to misclassification of participants and over-estimations in our results. Ideally, the study should include follow up data for each participant and counts of those loss to follow up to calculate a more accurate predictive value.

In conclusion, the GCTplasma and GCTcap are both useful predictors of type 2 diabetes. Both worked as well as the gold standard OGTT and the widely used FPG. The convenience of the GCT for patients and clinicians alike could prove beneficial in identifying those at increased risk of developing type 2 diabetes. Additional research will need to be conducted to assess the clinical application and true benefit of the GCT.

Tables 1-7

Table 1 – Blood Test Levels for Diagnosing Diabetes and Prediabetes			
	A1c	**FPG**	**OGTT**
Diabetes	≥ 6.5%	≥ 126 mg/dl	≥ 200 mg/dl
Prediabetes	6.5% - 5.7%	125-100 mg/dl	200 – 140 mg/dl
Normal	< 5.7%	< 100 mg/dl	< 140 mg/dl

Table 1 - OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose).
Source: American Diabetes Association

Table 2a – Comparison of Baseline Characteristics for Study Participant with Incidence of Diabetes and without Incidence of Diabetes over 5 years.				
Variable	**Total (n=1384)**	**Diabetes (+) n=133**	**Diabetes (-) n=1251**	**P-Value**
Age (years) (n=1384)	56.0	56.0	56.0	0.73
Gender (n=1384) Male (%) Female (%)	 1301 (94%) 83 (6%)	 128 (96.3%) 5 (3.7%)	 1173 (93.7%) 78 (6.2%)	0.25
Race (n=1384) Black White Other	 73.4% 24.5% 2.1%	 85.7% 13.5% 0.75%	 72.1% 25.7% 2.2%	 <0.01
BMI (kg/m^2) (n=1384)	29.5	31.0	29.0	<0.01
Waist Circumference (cm) (n=1378)	100.0	105.0	99.0	<0.01
Triglycerides (mg/dl) (n=1324)	105.0	121.0	104.0	0.01
LDL (mg/dl) (n=1308)	110.9	108.0	111.0	0.22
HDL (mg/dl) (n=1330)	42.0	39.5	42.0	0.02
GCTplasma (mg/dl) (n=1384)	129.0	142.0	127.0	<0.01
GCTcap (mg/dl) (n=1324)	155.0	179.0	153.0	<0.01
FPG (mg/dl) (n=1384)	97.0	101.0	96.0	<0.01
1-hr OGTT (mg/dl) (n=1194)	140.0	170.0	136.0	<0.01
2-hr OGTT (mg/dl) (n=1384)	107.0	121.0	105.0	<0.01
HbA1c (%) (n=1384)	5.80	6.10	5.70	<0.01

Table 2a – BMI (Body Mass Index), LDL (low-density lipoprotein), HDL (high-density lipoprotein), GCT (glucose challenge test), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose). All continuous variables reported as median values. Wilcoxon rank sum test used to compare incidence of diabetes groups.

Table 2b – Comparison of Baseline Characteristics for Normal Glucose Tolerant Participants with Incidence of Diabetes and without Incidence of Diabetes over 5 years				
Variable	**Total (n=746)**	**Diabetes (+) (n=38)**	**Diabetes (-) (n=708)**	**P-Value**
Age (years) (n=746)	55.0	55.5	55.0	0.59
Gender (n=746) Male (%) Female (%)	 691 (92.6%) 55 (7.4%)	 36 (94.7%) 2 (5.3%)	 655 (92.5%) 53 (7.5%)	0.61
Race (n=746) Black White Other	 74.9% 22.8% 2.3%	 33 (86.8%) 5 (13.2%) 0	 74.3% 23.3% 2.4%	0.19
BMI (kg/m^2) (n=746)	29.0	30.5	29.0	0.23
Waist Circumference (cm) (n=741)	98.0	105.0	97.0	0.02
Triglycerides (mg/dl) (n=707)	99.0	119.0	98.0	0.09
LDL (mg/dl) (n=698)	113.1	103.0	113.6	0.15
HDL (mg/dl) (n=707)	43.0	40.0	43.0	0.13
GCTplasma (mg/dl) (n=746)	120.0	132.0	119.0	<0.01
GCTcap (mg/dl) (n=720)	147.5	177.0	147.0	<0.01
FPG (mg/dl) (n=746)	91.0	92.0	91.0	0.17
1hr OGTT (mg/dl) (n=653)	126.0	146.0	126.0	<0.01
2hr OGTT(mg/dl) (n=746)	97.0	107.0	96.0	0.17
HbA1c (%) (n=746)	5.70	5.90	5.70	<0.01

Table 2b – BMI (Body Mass Index), LDL (low-density lipoprotein), HDL (high-density lipoprotein), GCT (glucose challenge test), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose). All continuous variables reported as median values. Wilcoxon ranks sum test used to compare incidence of diabetes groups.

Table 3 – Baseline Demographics and Characteristics of Study Participants stratified by diagnoses in each year of follow up					
Variable	**Year 1 (n=66)**	**Year 2 (n=26)**	**Year 3 (n=25)**	**Year 4 (n=8)**	**Year 5 (n=8)**
Age (years)	56.7	56.5	55.4	57.6	49.4
Gender					
Male (%)	63 (95.5%)	25 (96.2%)	24 (96.0%)	8 (100%)	8 (100%)
Female (%)	3 (4.5%)	1 (3.8%)	1(4.0%)	0	0
Race					
Black (%)	83.3%	92.3%	88%	62.5%	100%
White (%)	15.2%	7.7%	12%	37.5%	0
Other (%)	1.5%	0	0	0	0
BMI (kg/m^2)	31.5	32.4	30.4	31.0	31.5
Waist Circumference (cm) (n=1378)	105.1	106.6	100.9	103.4	104.5
Triglycerides (mg/dl) (n=1324)	153.2	132.2	135.9	151.1	142.1
LDL (mg/dl) (n=1308)	104.5	109.1	118.8	105.4	118.6
HDL (mg/dl) (n=1330)	40.7	41.8	40.3	37.1	41.7
GCTplasma (mg/dl)	149.2	150.2	152.2	136.0	124.9
FPG (mg/dl)	102.9	103.0	99.2	99.0	105.0
2-hr OGTT(mg/dl)	131.7	116.6	121.5	106.0	93.8
HbA1c (%)	6.1	6.2	6.1	5.9	6.0

Table 3 – BMI (Body Mass Index), LDL (low-density lipoprotein), HDL (high-density lipoprotein), GCT (glucose challenge test), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose).
*All continuous variables reported as mean values.

Table 4-Comparison of Sensitivity, Specificity and AROC by Test: All Participants		
	AROC	**95% CI**
GCTplasma	0.634	(0.609-0.657)
GCTcap	0.643	(0.617-0.668)
1-hr OGTT	0.691	(0.665-0.717)
2-hr OGTT	0.662	(0.637-0.688)
HbA1c	0.725	(0.699-0.750)
FPG	0.657	(0.632-0.682)
Comparison of Sensitivity, Specificity and AROC by Test: Normal Glucose Tolerant Participants		
GCTplasma	0.661	(0.609-0.713)
GCTcap	0.685	(0.629-0.741)
1-hr OGTT	0.655	(0.604-0.706)
2-hr OGTT	0.612	(0.561-0.663)
HbA1c	0.731	(0.685-0.776)
FPG	0.563	(0.517-0.609)

Table 4 – GCTplasma (glucose challenge test plasma), GCTcap (glucose challenge test capillary), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose), AROC (area under receiver operating characteristic curve).

∗ Incident diagnosis of diabetes was defined as: a) any use of the diabetes ICD-9 code 250.xx in conjunction with a primary care attending outpatient visit and/or b) any two uses of the ICD-9 code 250.xx and/or c) an outpatient prescription of a diabetes drug.

Table 5a – Comparison of ROC-contrast probabilities						
	GCTplasma	**GCTcap**	**1hr-OGTT**	**2hr-OGTT**	**HbA1c**	**FPG**
GCTplasma	X	0.48	<0.01	0.23	<0.01	0.19
GCTcap		X	<0.01	0.16	<0.01	0.13
1hr-OGTT			X	0.09	0.06	0.17
2hr-OGTT				X	<0.07	0.81
HbA1c					X	<0.01
FPG						X

Table 5a - GCTplasma (glucose challenge test plasma), GCTcap (glucose challenge test capillary), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose).

Table 5b – Comparison of ROC-contrast probabilities: Normal Glucose Tolerant Participants						
	GCTplasma	**GCTcap**	**1hr-OGTT**	**2hr-OGTT**	**HbA1c**	**FPG**
GCTplasma	X	0.32	<0.01	0.76	0.36	0.02
GCTcap		X	<0.01	0.54	0.22	0.05
1hr-OGTT			X	<0.01	0.02	<0.01
2hr-OGTT				X	0.23	0.01
HbA1c					X	<0.01
FPG						X

Table 5b - GCTplasma (glucose challenge test plasma), GCTcap (glucose challenge test capillary), OGTT (oral glucose tolerance test), HbA1c (hemoglobin A1c), FPG (fasting plasma glucose).

Table 6 – Patient Characteristics and GCTplasma Prediction of Incident Diabetes		
Variable	**AROC**	**95% CI**
*Age (years)		
<50 (n=342)	0.684	(0.635-0.733)
50-59 (n=534)	0.669	(0.634-0.704)
≥60 (n=508)	0.548	(0.508-0.587)
Gender		
Female (n=83)	0.469	(0.391-0.548)
Male (n=1301)	0.638	(0.614-0.662)
Race		
Black (n=1016)	0.637	(0.612-0.663)
White (n=339)	0.679	(0.625-0.733)
Other (n=29)	0.821	(0.758-0.885)
*BMI (kg/m^2)		
BMI <30 (n=692)	0.677	(0.641-0.713)
BMI 30-35 (n=455)	0.531	(0.490-0.571)
BMI ≥35 (n=237)	0.713	(0.673-0.754)
*Waist Circumference (cm)		
Normal[A] (n=774)	0.653	(0.619-0.688)
Elevated[A] (n=604)	0.609	(0.577-0.641)
*Triglycerides (mg/dl)		
<150 (n=957)	0.634	(0.605-0.662)
≥150(n=367)	0.623	(0.581-0.665)
*HDL (mg/dl)		
Normal[B] (n= 746)	0.658	(0.625-0.690)
Low[B] (n=584)	0.597	(0.563-0.631)

Table 6 – BMI (Body Mass Index), HDL (high-density lipoprotein), AROC (area under receiver operating characteristics curve).

*Stratified according to NCEP metabolic syndrome criteria [32]

[A] Waist circumference, Elevated= male >102 cm, female >88 cm

[B] HDL, Low= male <40 mg/dl, female <50 mg/dl

Table 7 – Sensitivity and Specificity across GCTplasma cutoff values		
Cut-off (mg/dl)	**Sensitivity**	**Specificity**
120	0.74	0.42
130	0.62	0.52
140	0.52	0.63
150	0.41	0.74
160	0.36	0.81
170	0.30	0.87
180	0.22	0.91

Table 7 – Crude sensitivity and specificity of GCTplasma values only. GCTplasma (glucose challenge test – plasma)

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