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Amanda Zhang April 10, 2019

The 1 Hour Oral Glucose Tolerance Test Predicts Development of Dysglycemia and T2DM

by

Amanda Zhang

Lawrence S. Phillips, M.D.
Advisor

Department of Biology

Lawrence S. Phillips, M.D.

Advisor

Amanda Starnes, D.V.M.

Committee Member

Jennifer Sarrett, Ph.D.

Committee Member

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An abstract of
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Abstract

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Background: Inadequate insulin secretion due to pancreatic beta cell dysfunction underlies the development and progression of type 2 diabetes (T2DM), a major public health problem. Since current methods of assessing beta cell function are time-consuming, labor- intensive, and expensive, we investigated whether the plasma glucose at 1 hour in an oral glucose tolerance test (1hOGTT) could be an equally accurate but more convenient and less costly alternative.

Methods: The areas under receiver operating characteristic curves (ROC AUCs) were used to compare the accuracy of predicting the progression towards T2DM over 3 years in 489 participants with complete data in the European Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) Study.

Results: The ROC AUCs for 1hOGTT were 0.647 (95% CI 0.580-0.713) for prediction of progression from normal glucose metabolism to dysglycemia (pre-T2DM or T2DM), 0.794 (0.727-0.862) for non-high risk dysglycemia to high risk dysglycemia, and 0.908 (0.851-0.965) for non-T2DM to T2DM, all comparable or superior to more complex assessments, including the euglycemic insulin clamp, OGTT modeling, insulinogenic index, and beta cell glucose sensitivity. The findings were similar in paired analyses of data from 369-743 participants.

Conclusions: Prediction of progression toward T2DM with the simple, convenient 1hOGTT is comparable to prediction with complex and costly methods. Consideration should be given to use of the 1hOGTT for screening and to complement more complex measures in understanding mechanisms to support discovery of new treatments.

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Acknowledgements

First, I would like to thank Dr. Phillips, who has given me generous help and support over the past year. When I first started to collaborate with Dr. Phillips, I knew little about T2DM and even less about the disposition index (DI) and the 1 hour oral glucose tolerance test (1hOGTT). As my mentor, he not only taught me concepts involved with my project, he also guided my way of thinking and how I approached problems in research.

Secondly, I would like to thank members of Dr. Phillips' team, Dr. Dong Li and Mr. Brian Legvold. Brian helped me learn to code in SAS from scratch and guided my construction of the ROC curves and corresponding results. Dr. Li helped clean the dataset for my analysis and checked our results.

Thirdly, I would like to thank our collaborators, Dr. Beverly Balkau for providing us with the RISC dataset and Dr. Andrea Mari as well as Dr. Kristina Utzschneider for helping us understand the different standard approaches to assess beta cell function.

Lastly, I would like to thank my committee members, Dr. Starnes and Dr. Sarrett, for their time and advice.

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Introduction

Glucose as a Metabolic Fuel

Glucose is absorbed as a result of food digestion. Once in the bloodstream, cells in different tissues and organs can convert this nutrient to a source of energy through nonaerobic and arerobic metabolism. More particularly, muscle tissue is known to utilize a large amount of glucose. If not directly utilized, glucose can be stored as a potential source of energy as glycogen or fat (Poian, 2010).

Regulation of Glucose Levels by Insulin

The human body requires that blood glucose be maintained in a narrow range, mostly 5.6 to 6.9 mM (100 to 125 mg/dL). Insulin is released from the beta cells within the islets of the pancreas, where alpha and delta cells are also housed. Within the normal blood glucose range, a rise in glucose above a threshold of about 4 mM (72 mg/dl) stimulates the release of insulin, and a fall in glucose decreases the release of insulin. Insulin is an "anabolic" hormone, facilitating energy storage and decreasing breakdown of different body tissues and organs. With respect to metabolic regulation, low levels of insulin reduce lipolysis and ketogenesis, higher levels of insulin are required to restrain hepatic glucose production, and the highest levels of insulin are required to promote glucose disposal into fat and muscle. In addition, insulin inhibits gluconeogenesis, the generation of glucose from non-carbohydrate carbon substrates, and stimulates glycogenesis, the process where glucose molecules are added to chains of glycogen for storage.

T2DM as a Disorder of Glucose Regulation – Hyperglycemia

Inadequate secretion of insulin leads to the development of hyperglycemia. Prolonged hyperglycemia leads to the development of T2DM and other complications, involving different body tissues and organs. Microvascular disease includes eye damage, kidney damage, and nerve damage, while macrovascular disease includes coronary artery disease, peripheral vascular disease, and stroke.

Natural History of Development of T2DM

Compared to earlier time periods, people in current day society tend to be older, more overweight, and sedentary (World Health Organization, 2018). All of these factors could be viewed as results of the "success of society" – people are living longer, have more to eat, and don't have to do as much physical labor. However, this "success" leads to insulin resistance, the need for a higher concentration of insulin to regulate blood glucose levels, and underlies the "diabetes epidemic" (Phillips, 2014).

Nevertheless, not all patients with insulin resistance develop T2DM. Increased insulin secretion is a compensatory mechanism for increased insulin resistance. If compensation is adequate, the glucose levels will be properly regulated. Inadequate insulin secretion by the beta cells of the pancreas – beta cell dysfunction – may also be due to reduced beta cell mass. This is also a primary factor in the onset and progression of T2DM.

Within a Gila River Indian Community, 404 individuals with normal glucose tolerance were studied (Weyer et al., 1999). Various methods, like the OGTT and hyperinsulinemic-euglycemic clamp, were used on subsets of the population to assess the insulin secretion and

action of each individual. Insulin secretion is the amount of insulin the beta cell secretes in response to plasma glucose levels. Insulin action was the effectivity of the insulin at triggering glucose reuptake, and in this case, in relation to estimated metabolic body size. Changes in insulin secretion relative to changes in insulin action were shown in Figure 1. The progressors were 17 Pima Indian subjects in whom glucose tolerance deteriorated from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to diabetic (DIA), of which 11 are shown. Glucose and insulin sensitivity of the body decreased within these individuals and led to this progression. There were also 31 non-progressors who retained NGT, of which 23 are shown. Glucose and insulin sensitivity of the body were maintained in this case. Combining insulin secretion and insulin action in order to study stages of dysglycemia is the foundation of the disposition index (DI).

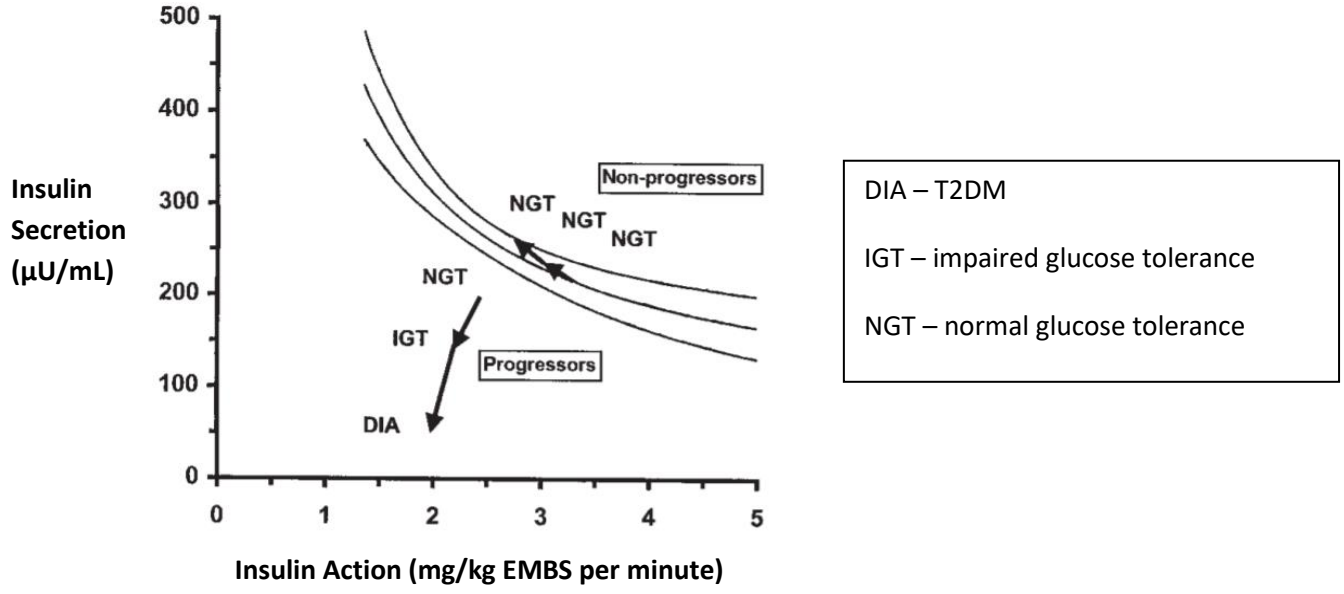

Figure 1 Insulin secretion versus insulin action for non-progressors and progressors (from Weyer, 1999).

Consequences of Diabetes (mostly T2DM, with about 5% type 1 diabetes [T1DM])

Diabetes is a major health problem within the United States and around the world, with more than 100 million adults in the United State now living with prediabetes or diabetes, and the prevalence is increasing. Diabetes leads to numerous serious complications, such as cardiovascular disease, nerve damage, kidney damage and eye damage (National Center for Health Statistics, 2017). Not only does diabetes burden individual health, diabetes management is costly and consumes healthcare resources. It is estimated that the lifetime added expense for the treatment of diabetes and its complications is around $55,000 to $130,000 per individual over a lifetime. In addition to these direct costs, impacted individuals will have to spend time and energy following regimens that help to regulate the disease. These individuals have a high degree of absenteeism in their employment, which leads to the loss of productivity.

What is Needed to Make T2DM Less of a Problem

Identification of earlier stages of dysglycemia (prediabetes and diabetes) would allow for preventative management. However, since the disease is asymptomatic in its beginning stages, a screening mechanism is required for identification purposes. In addition, improving our understanding of the mechanisms of the disease could allow for the development of new and better treatments.

Standard Analyses of Insulin Secretion and Insulin Action – Clamps, OGTTs, and Acute C-Peptide Responses to Intravenous Glucose (ACpRg)

With the hyperglycemia clamp approach, the plasma glucose concentration is raised and maintained at a constant hyperglycemic level by adjusting the glucose infusion. This requires plastic catheters in both arms, one for samples to measure insulin and other factors, and one

for glucose infusions. Blood samples are then collected at different time points, usually every few minutes for measurement of glucose to adjust the glucose infusion and for measurements of interest (i.e., glucose, insulin, C-peptide). Alternatively, with the hyperinsulinemic-euglycemic clamp, insulin is infused intravenously at a constant rate while plasma glucose concentration is held constant by a variable glucose infusion. This also requires plastic catheters in both arms, one for samples to measure glucose and other factors, and one for glucose and insulin infusions. Similarly, blood samples are then collected at different time points, usually every few minutes for measurement of glucose to adjust the glucose infusion and for measurements of interest.

For the oral glucose tolerance test (OGTT), rather than intravenous injections, patients orally consume a glucose drink, and blood samples for the measurement of interest are taken at different time points. These measurements can then be used to calculate different indexes or create different models.

With the ACpRg, the C-peptide response is measured before and after intravenous administration of a bolus of glucose. The mean is then calculated. Insulin and C-peptide are released from the pancreas at the same time and in about equal amounts. However, C-peptide is excreted at a more constant rate over a longer time, so this measure is usually more reliable.

With all of these methods, the need to collect data over different time points, and sometimes at short intervals, makes the approaches expensive, labor intensive and time consuming.

We Measure Circulating Glucose Levels to Define Status

The development of T2DM usually follows a trend from normal glucose metabolism (NGM) to pre-T2DM to T2DM. The 75g OGTT is a standardized way to assess the fasting plasma glucose level and the glucose level at 2 hours after a glucose drink in order to determine the stage of glucose metabolism of an individual. This allows for the diagnostic classification as NGM, pre-T2DM, or T2DM.

The baseline glucose level is mostly reflective of insulin secretion because it is measured after a night of fasting, so hepatic glucose production is suppressed which allows for accurate assessment of insulin secretion. In contrast, the glucose level at the 2 hour mark is reflective of insulin action because it accounts for reducing glucose levels after the 75g glucose drink by promoting glucose disposal – mainly into muscle. The measurement of the 1 hour glucose level has been ignored in most cases, except when screening for T2DM in pregnant women.

Hypothesis

We hypothesize that the 1-hour OGTT plasma glucose level – as a simple combination of insulin secretion and insulin action – will be as accurate at predicting the progression of the disease, from NGM to pre-T2DM to T2DM, as other standard tests.

What is Already Known about the 1 Hour Glucose Level

The plasma glucose concentration at 1 hour during the OGTT has shown to be a strong predictor of future risk for T2DM, as in the San Antonio Heart Study as well as the Botnia Study (Abdul-Ghani et al., 2007; Abdul-Ghani et al., 2009). Other research has supported this by showing that the 75g OGTT 1h plasma glucose measurement has the potential to serve as a

sensitive screening tool for identifying people who are at a high-risk of developing T2DM over the next few years (Manco et al., 2018). However, despite these conclusions, little comparison has been made between the 1hOGTT and a comprehensive list of DIs as well as other methods from OGTT data. In addition, a direct comparison between the 1hOGTT and the glucose challenge test (GCT), measuring glucose levels after glucose is administered at any time of day, could validate the GCT as a new method to screen for early stages of dysglycemia.

Measuring the 1hOGTT Plasma Glucose Would be Convenient, Easy, and Inexpensive

Measuring the 1hOGTT plasma glucose would be convenient. Rather than having multiple intravenous lines and obtaining multiple measurements at different time points, the 1hOGTT simply requires an oral glucose drink and a single glucose measurement. In addition, the 1hOGTT doesn't require complicated setups or multiple recordings like in the clamp method as well as in the OGTT approach. Therefore, it is a relatively inexpensive.

If Comparable to Standard Tests, Might be Able to Use the 1hOGTT for Both Screening and Monitoring of Mechanism

If the 1hOGTT can assess the insulin secretion and action as effectively as other standard tests, then we might be able to use variations of this approach to both screen populations at risk and study mechanisms of T2DM within large groups of study subjects, due to its simplicity.

Materials and Methods

General Design

We used the Relationship between Insulin Sensitivity and Cardiovascular Disease **(**RISC) dataset to study how accurately the 1hOGTT and other more complex approaches predicted the progression of T2DM over 3 years. This dataset is ideal because it is a prospective study over 3 years, with baseline as well as follow-up data, and includes all of the methods. The accuracy was accessed using ROC curves, which is an unbiased way to compare different diagnostic tests.

Human Subjects Considerations

The first step was to gain permission from the Emory University Institutional Review Board (IRB) to conduct this thesis project by demonstrating that human subjects were protected during data collection and would be protected during analysis. In addition, it was a way of making sure that I was educated about the importance of protecting human subjects in clinical research. Next, I was added to the T2DM Related Research at Emory (DARE) protocol. This process allowed us to request permission to utilize data originating from outside data sources in our study.

While waiting to hear back from the RISC team, we obtained a dataset from the University of Indiana. In order to gain access to this dataset, we had to write an outline of our project and list the variables we needed for our study. However, this dataset was not a prospective study, so it only allowed us to conduct correlation analyses between the various methods. Hence, we did not further analyze this dataset once we obtained the RISC dataset.

In order to gain access to the RISC dataset, we had to go through a set of procedures. First, we had to submit an outline of our research plan to their project management board, detailing the research problem to be investigated, what objectives would be achieved through this research, how will the research process would be carried out, and what was required from the RISC project. Once the project was approved, a contract was signed with the list of variables requested, and the data were transferred to us.

Assessment Tools

In the OGTT, there is first a fasting lab draw of blood to test the fasting glucose level. An 8 ounce syrupy glucose drink that contains 75g of glucose is then administered. Subsequently, blood glucose levels are measured at different time points, usually at baseline before the glucose drink, and at different times afterwards, such as at 30, 60, 90, and 120 min. T2DM individuals will have higher levels of glucose in comparison to pre-T2DM and normal individuals (Figure 2).

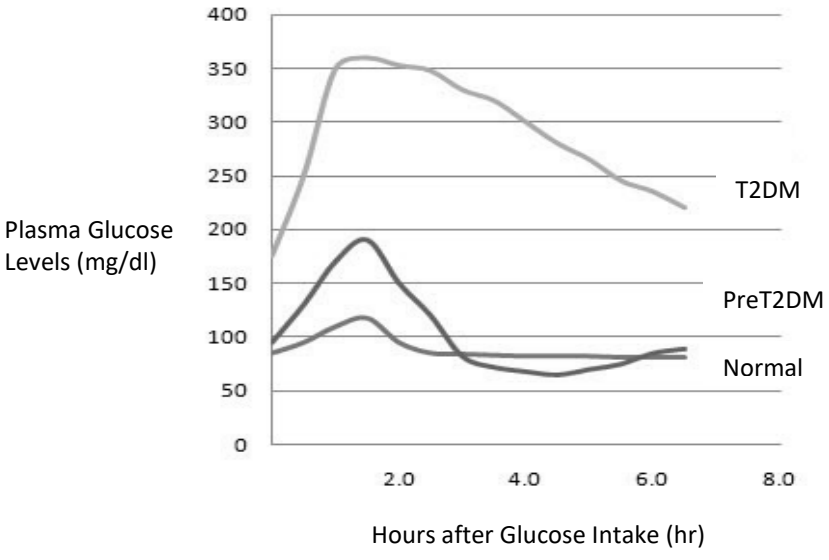

Figure 2 Diabetic, prediabetic, and normal glucose metabolism on a 1hOGTT curve.

For the clamp method, the plasma glucose concentration is maintained at a constant level. In the hyperglycemic clamp, the glucose concentration is acutely raised to 11.11 mM (200 mg/dl) by a continuous infusion of glucose. This hyperglycemic state is maintained by the adjustment of a variable glucose infusion, which will depend on the rate of insulin secretion and glucose metabolism. Because the plasma glucose concentration is held constant at a high level, hyperglycemic clamps are often used to assess insulin secretion. In hyperinsulinemic-euglycemic clamps, the plasma insulin concentration is acutely raised and maintained constant by a continuous infusion of insulin. Meanwhile, the plasma glucose concentration is held constant at 5.27 mM (95 mg/dl) by a variable glucose infusion. When the steady-state is achieved, the glucose infusion rate equals the glucose uptake by all the tissues in the body, a measure of insulin action.

In a DI of insulin secretion versus insulin action, the relationship resembles a hyperbola (figure 3). T2DM individuals have the lowest insulin secretion relative to insulin action compared to moderate T2DM (prediabetic) individuals and those with normal glucose metabolism. Thus, T2DM individuals will also fall on a curve that sits closest to the x and y axes (Figure 3).

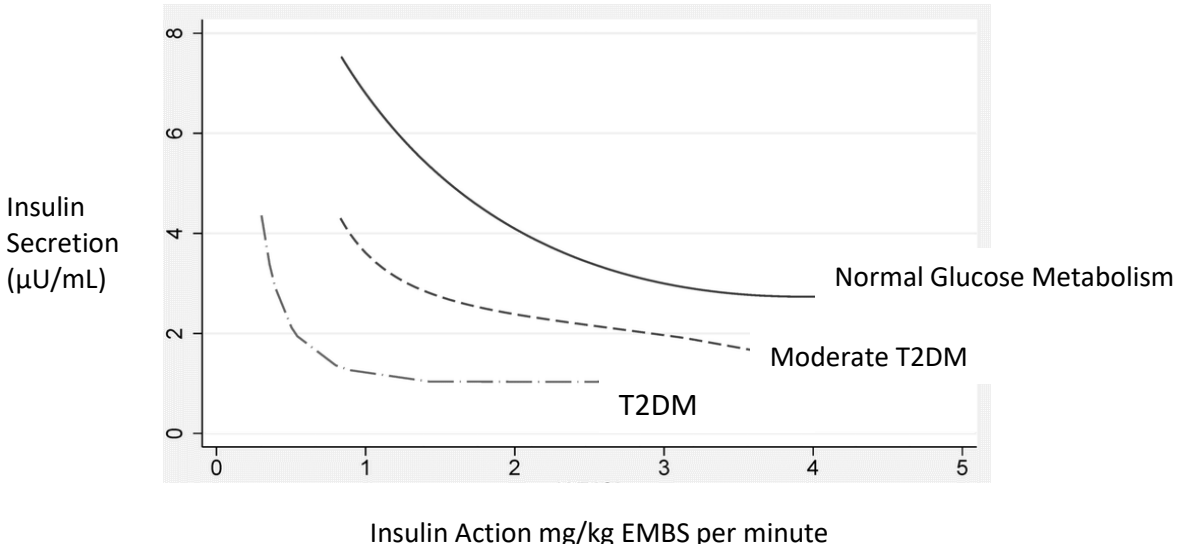

Figure 3 Normal glucose metabolism, moderate T2DM, and T2DM on a DI plot.

RISC Dataset

The original project involved the European Group in the Study of Insulin Resistance (The EGIR Study). However, the study eventually expanded its focus on the relationship between insulin sensitivity and cardiovascular disease. Insulin resistance is thought to be a key predictor for the development of T2DM and cardiovascular disease (CVD), a leading cause of morbidity and premature mortality. The RISC Study collected data from an extended European collaborative research group to study insulin resistance and CVD risk in 1500 healthy people aged 30 to 60 years from 20 centers in 13 countries.

This rich dataset was a European prospective study over 3 years. At baseline, the cohort was clinically healthy; individuals who were receiving treatment or who had a serious medical condition were not eligible to participate. At follow-up, those who received glucose-lowering treatment were excluded. At the baseline and follow-up examinations, participants underwent

a 75g OGTT after an overnight fast. Plasma glucose, serum insulin, and C-peptide concentrations were assessed at five time points during the OGTT (0, 30, 60, 90, 120 min). A hyperinsulinemic-euglycemic clamp was also performed at baseline.

Data Cleaning

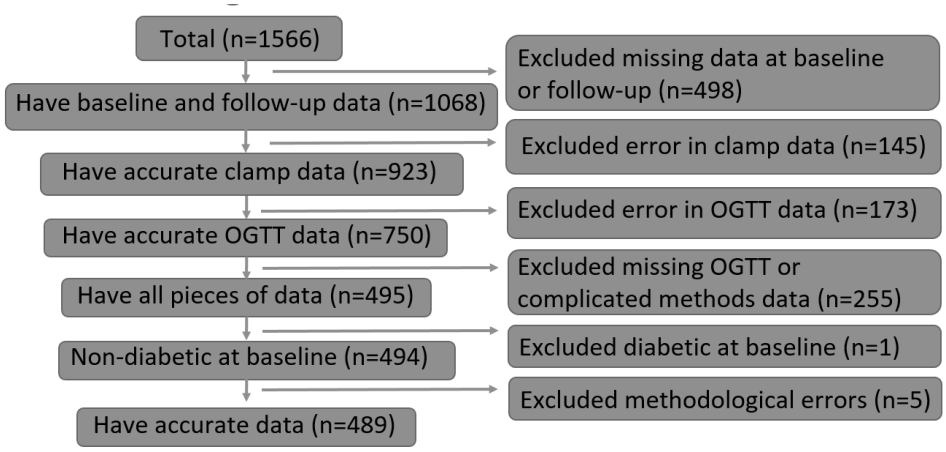

Figure 4 CONSORT Diagram (data cleaning steps).

We show above our **CON**solidated **S**tandards **O**f **R**eporting **T**rials (CONSORT) diagram. Due to the large number of participants in the dataset, there were errors in data collection as well as missing data in general. Hence, before we started our analysis, we had to further clean the data. We started out with 1,566 participants total. After excluding 498 participants with missing data at baseline or 3 year follow-up, we were left with 1,068 participants. Then, we removed 145 participants with errors in their clamp data and were left with 923 participants. We then removed 173 participants with errors in their OGTT data and were left with 750 participants. Following that, we removed 255 participants who were missing OGTT data or data used in the more complicated methods, and this left us 495 participants. Lastly, we removed one participant because he or she was diabetic at baseline, so there was no room for this participant to progress and therefore was not of interest to us for the study. This left us with

494 participants. Lastly, for some assessments, measured values such as glucose levels may have fallen after the glucose drink or ACpRg bolus. Since negative values couldn't be included in the statistical analyses, 5 participants with such values were excluded. This left us with 489 patients to conduct our analysis on.

For the paired analyses, we made sure that within each set of comparison, all participants had accurate 1hOGTT data as well as data needed for a certain complex method. This approach increased the number of individuals studied, which improved the accuracy and generalizability of the results. The number of participants in each paired analysis ranged from 369-743 (actual numbers for each paired analysis of the three progression definitions will be provided within the results section).

Metabolic Tests

Metabolic Test Abbreviations			
		Name	**Abbreviation**
		1-hour oral glucose tolerance test	1hOGTT
DI	Clamp	Acute insulin release * moles of glucose metabolized/ml of insulin in plasma	GISR * M/I
		Acute insulin release * moles of glucose metabolized/ml of insulin in plasma	AIR * M/I
	Hybrid	Beta-cell glucose sensitivity * moles of glucose metabolized/ml of insulin in plasma	beta-cell glu sens * M/I
	Modeled	Beta-cell glucose sensitivity * oral glucose insulin sensitivity	beta-cell glu sens * OGIS
Unmodeled		$Insulin_{30-0}/glucose_{30-0}$	Insulinogenic index
Modeled		Beta-cell glucose sensitivity	beta-cell glu sens

Figure 6 Different tests, their categorization, and their abbreviations.

After discussions with experts in the field, Dr. Andrea Mari, PhD, at the Institute of Neuroscience in Padova, Italy and Dr. Kristina M. Uzechneider, M.D., at the University of Washington School of Medicine in Seattle, WA, who have studied ways of assessing beta cell function, we selected several methods along with the 1hOGTT to analyze RISC data.

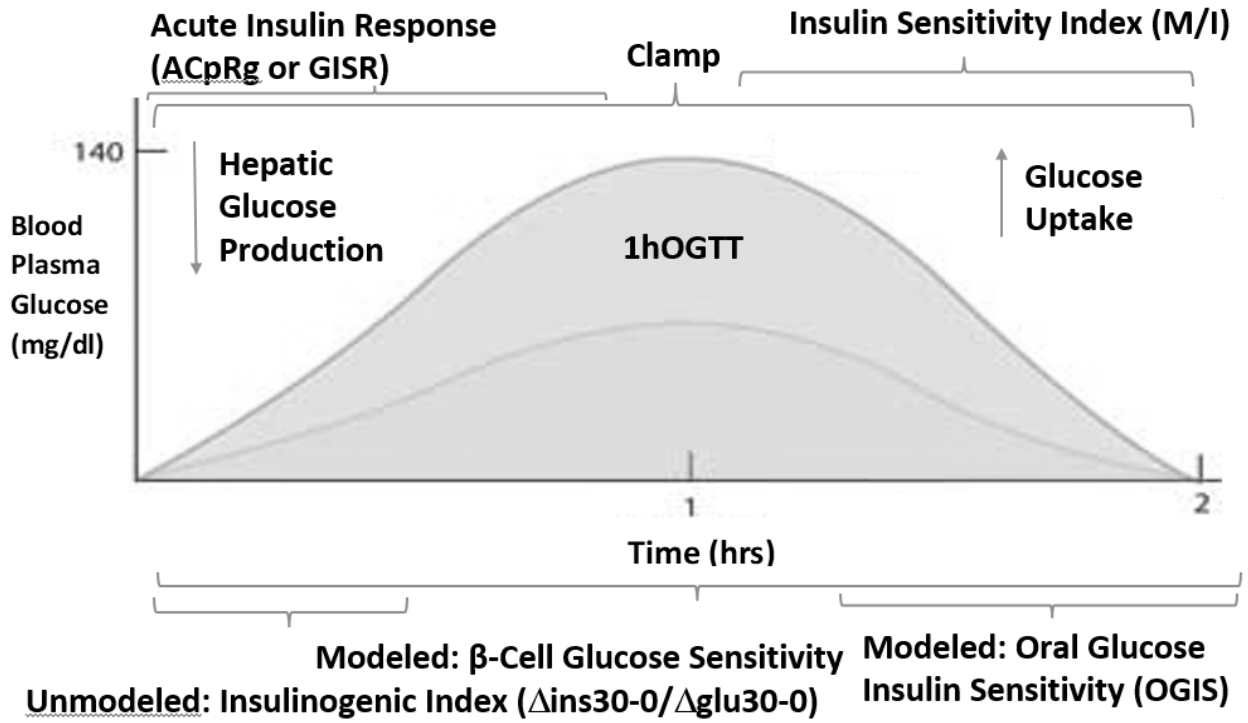

Figure 7 Tests in relation to each other and what they measure.

Figure 7 shows what each method evaluates in terms of glucose production and glucose uptake, relative to each other. Clamp data collected over several hours includes both immediate effects on glucose intake such as decreased hepatic glucose production and insulin secretion, as well as later effects such as increased glucose uptake (insulin action). The glucose-induced secretory response (GISR) measures the acute response to glucose administration. GISR was expressed as [ISRtot_BSA / tmax] / AIRg, where ISRtot_BSA was the integral of

incremental insulin secretion after a glucose bolus per m^2 of estimated body surface area and tmax was the duration of the period after a glucose dose (8 minutes). AIRg was expressed as the mean incremental insulin secretion during a glucose dose. Mean incremental concentration was calculated from areas under the curves, using trapezoidal integration. The pre-dosage value to calculate increments was the value at 120 min; if this value was missing the mean in the interval 80-120 min was used. The insulin sensitivity index (M/I), where M is the mean glucose concentration over the last 40 min of the clamp and I is the steady-state serum insulin concentration measured over the same time period, indicates insulin action by measuring glucose uptake. Dr. Utzchneider has published on the use of the insulinogenic index as a strong measure of insulin secretion and thus beta cell function. This index looks at the difference of insulin from baseline to the 30 minute mark divided by the difference in glucose from baseline to the 30 minute mark (Utzchneider et al., 2009). Using his modeling approach, Dr. Mari has used beta cell glucose sensitivity as an indicator of beta cell function. Within his model, a glucose input, potentiation, and early secretion all contributed to the insulin secretion of the beta cells (Mari et al., 2010). However, he also studied the oral glucose insulin sensitivity (OGIS), which measures insulin action on the body based on an oral glucose intake. Hence, we constructed four versions DIs: GISR * M/I, AIR * M/I, beta cell glucose sensitivity * OGIS, and beta cell glucose sensitivity * M/I. In addition, we also studied the insulinogenic index as well as beta cell glucose sensitivity alone. These methods were then compared to the 1hOGTT.

Classification of Glucose Metabolism

In order to study disease progression – development of hyperglycemia over time – we had to define the various ways we were going to study progression. Different fasting plasma glucose levels as well as 75 g OGTT two-hour glucose levels were used to establish the ranges for the different stages of hyperglycemia (American Diabetes Association, 2016)

Categorization of Dysglycemia			
		Dysglycemia	
Time	**Normal Glucose Metabolism (NGM)**	**Prediabetes (Pre-DM)**	**Diabetes (DM)**
Baseline	<100 mg/dl	Impaired Fasting Glucose (IFG): 100 – 125 mg/dl	>125 mg/dl
2 hour	<140 mg/dl	Impaired Glucose Tolerance (IGT): 140 – 199 mg/dl	>199 mg/dl

Figure 8 The definitions of different metabolic states and their corresponding glucose levels at baseline and 2 hours.

At 0 time, less than 100 mg/dl is considered normal glucose metabolism, between 100 mg/dl and 125 mg/dl is considered impaired fasting glucose, while above 125 mg/dl is considered diabetic. On the other hand, at two hours after a 75g glucose drink, less than 140 mg/dl is considered normal glucose metabolism, between 140 ng/dl and 199 mg/dl is considered impaired glucose tolerance, and above 199 mg/dl is considered diabetic.

Definitions of Progression toward T2DM

Definitions of Progression	
Type	**Definition**
non-T2DM to T2DM	(NGM or pre-DM [IFG or IGT or IFG+IGT]) to DM
non-high risk dysglycemia to high risk dysglycemia	(NGM or isolated IFG or isolated IGT) to (IFG+IGT or DM)
NGM to dysglycemia	NGM to (pre-DM [IFG or IGT or IFG+IGT] or DM)

Figure 8 The definitions of the three types of progression

Based on these cutoffs, we developed three definitions of progression of hyperglycemia from studies at baseline and repeat studies 3 years later.

(a) Progression from non-T2DM to T2DM: This included participants who were non-diabetic at baseline and became diabetic at 3 years. In essence, we looked at all individuals outside the T2DM category at baseline who ended up in the T2DM category at 3 years.

(b) Progression from non-high risk dysglycemia to high risk dysglycemia: This included individuals who started out as non-high risk dysglycemia and later had high risk dysglycemia. Non-high risk dysglycemia is normal glucose metabolism or either isolated impaired fasting glucose or isolated impaired glucose tolerance. In contrast, high risk dysglycemia is impaired fasting glucose and impaired glucose tolerance or diabetes.

(c) Progression of normal glucose metabolism to dysglycemia: This included participants who had normal glucose metabolism and later became dysglycemic. In other words, we looked at individuals who started in the normal glucose metabolism category and later moved outside that category.

Analysis of Tests to Predict an Outcome

(1) Sensitivity looks at how often a test ends up positive in the case that the disease is actually present while (2) specificity looks at how often a test ends up negative when the disease is not present. Unlike positive and negative predictive values, which assess the accuracy of the test based on the number of times it is negative or positive and therefore is

impacted by the population, sensitivity and specificity assess the accuracy of the test based on those who have or do not have the disease and therefore is independent of the population.

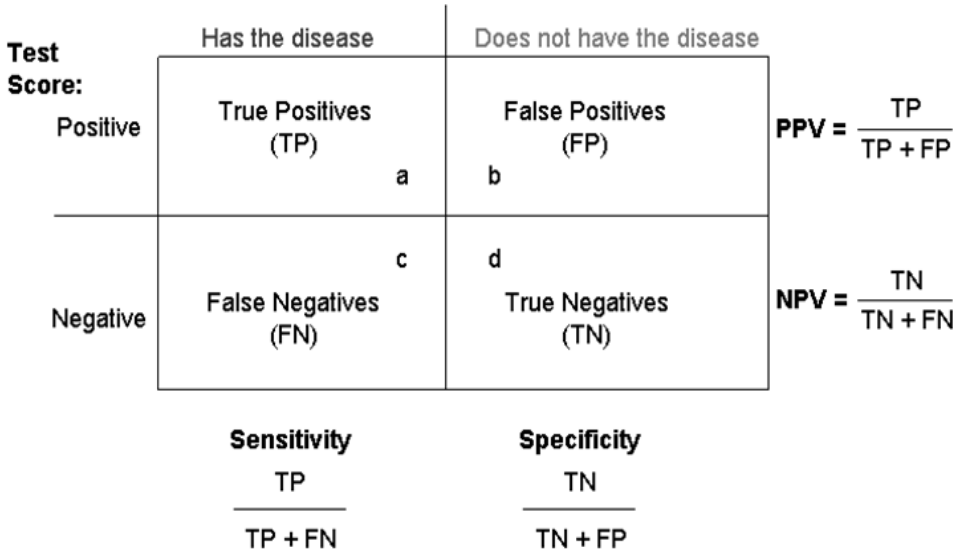

Figure 9 The relationship between sensitivity, specificity, PPV, and NPV in terms of test scores and the presence of the disease.

Receiver Operating Characteristic Curve Analysis

We used the area under the receiver operating characteristic curve as an evaluation of the accuracy of the diagnostic tests for prediction of progression. Hence, we used this statistical tool to analyze how accurately each test assessed beta cell function and thus predicted the progression of hyperglycemia. The ROC curve is based on sensitivity and specificity, so it is a powerful tool because it is unbiased and independent of the population.

The ROC curve is a plot of sensitivity (true positives) vs 1 – specificity (false positives), for all cutoff points, creating a curve. If the ratio of true positives to false positives is high, then the curve will fall close to the y axis until it reaches a point of high sensitivity. As a result, if the

curve stays close to both the x and y axes, then there will be a greater area under the curve (AUC). A higher AUC indicates that the diagnostic test is stronger. The diagonal line across the middle gives an AUC of 0.5, meaning that the diagnostic test is as good as random chance. On the other hand, if the curve falls on the axes, the AUC is 1.0 and the test is completely accurate when making diagnoses.

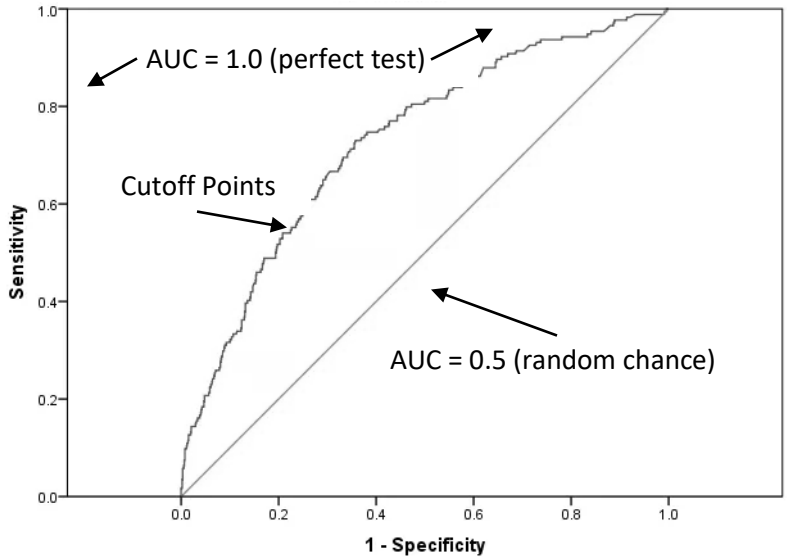

Figure 10 ROC curve plot with AUC and cutoff points.

Analysis

All analyses utilized SAS version 9.4 (Cary, NC).

Results

Participant Characteristics

Demographics									
		Baseline				Follow-Up			
		All (n=489)	NGM (n=341)	Pre-T2DM (n=148)	T2DM (n=1)	All (n=489)	NGM (n=293)	Pre-T2DM (n=192)	T2DM (n=5)
Sex (% male)		47%	51%	39%	0%	47%	52%	39%	60%
Age		44.82	43.73	47.43	47.00	48.15	46.42	50.74	50.40
BMI (kg/m^2)		25.74	25.20	27.03	26.60	25.74	25.19	26.54	26.96
Fasting Glucose Level (mmol/l)		5.15	4.95	5.61	7.20	5.31	4.98	5.77	6.35
1 Hour Glucose Level (mmol/l)		8.12	7.52	9.46	15.90	8.34	7.51	9.50	11.50
2 Hour Glucose Level (mmol/l)		6.00	5.55	7.00	10.80	6.12	5.50	6.92	11.18
Insulin Secretion	ACpRg	782.28	802.59	728.04	664.90	782.28	800.17	756.95	580.70
	GISR	63.06	64.18	60.44	37.03	63.06	67.06	56.79	38.68
	Insullinogenic Index	100.24	105.72	85.34	41.63	100.24	110.68	82.76	38.68
Insulin Action	M/I	143.10	149.98	123.84	78.68	143.10	150.65	130.33	99.39
	OGIS	439.87	457.86	386.66	348.50	439.87	457.79	407.07	402.60
DI	ACpRg*M/I	111944.27	120372.45	90160.47	52314.33	111944.27	120545.61	98653.29	57715.77
	GISR*M/I	9023.89	9625.72	7484.89	2913.52	9023.89	10102.59	7401.44	3844.41

Figure 11 Patient demographics after data cleaning.

As expected, individuals in the prediabetic and diabetic categories were generally older and heavier. In addition, these individuals have higher glucose levels as a result of reduced insulin secretion and or action, which leads to a lower DI.

ROC Analysis

The 1hOGTT AUC is similar to if not higher than other AUCs under the 3 definitions of T2DM progression. Likewise, the difference between 1hOGTT and complicated methods that performed well were not significantly different. In addition, the 1hOGTT confidence intervals were relatively narrow, indicating that this method is quite precise with respect to other methods.

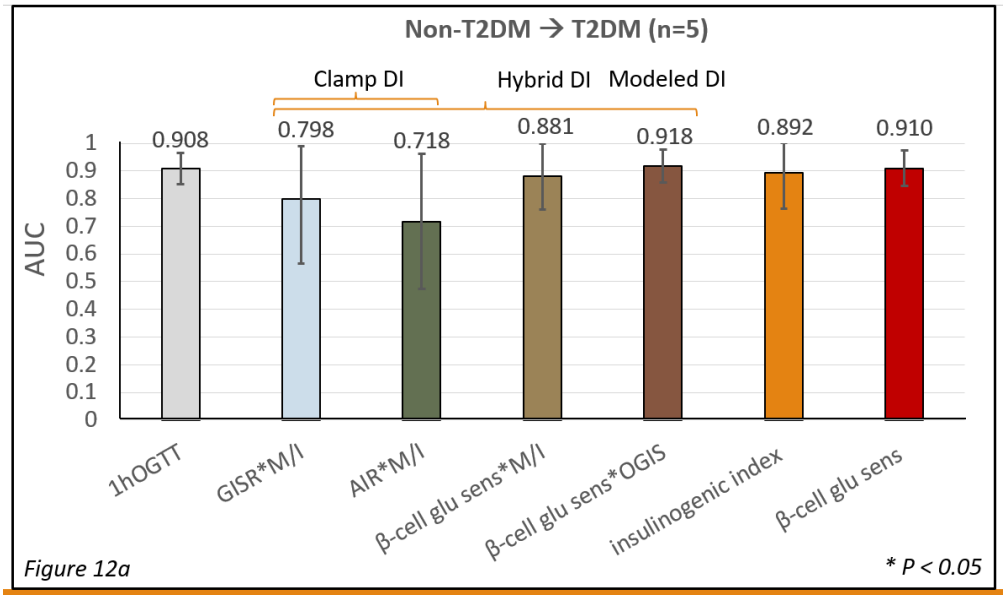

Figure 12a

For the non-T2DM to T2DM definition, the 1hOGTT most accurately predicted the progression of dysglycemia with a AUC of 0.908. In addition, the 95% confidence interval was relatively narrow from 0.851-0.965. The AUCs of other more complicated methods that performed better were not significantly different from that of the 1hOGTT.

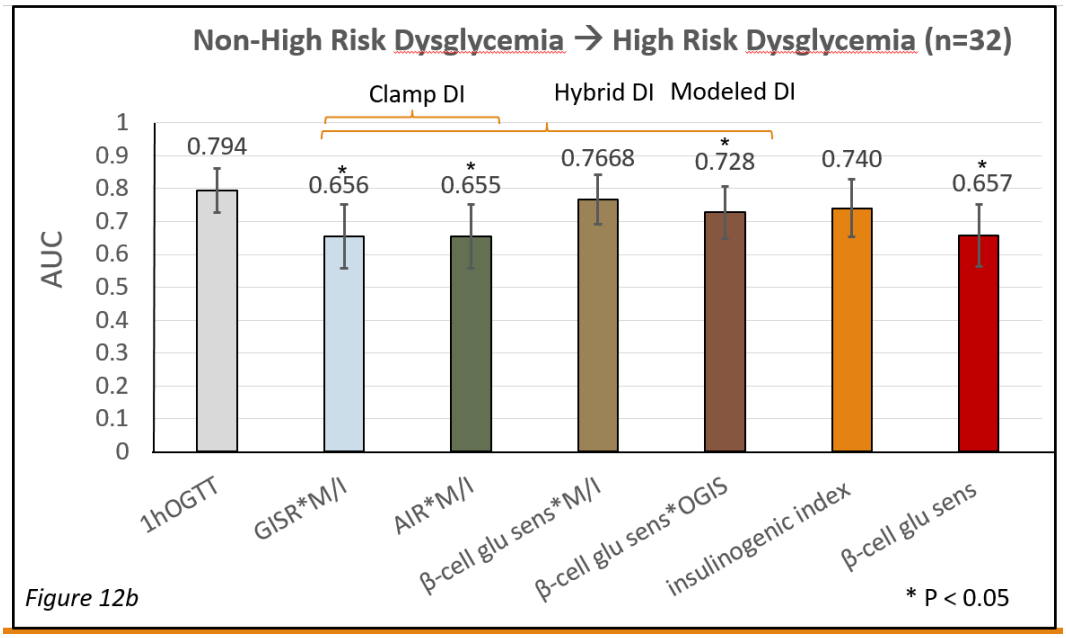

Figure 12b

For the non-high risk dysglycemia to high risk dysglycemia definition, the 1hOGTT most accurately predicted the progression of dysglycemia with a AUC of 0.794. In addition, the 95% confidence interval was relatively narrow from 0.727-0.862. The AUCs of other more complicated methods that performed better were not significantly different from that of the 1hOGTT.

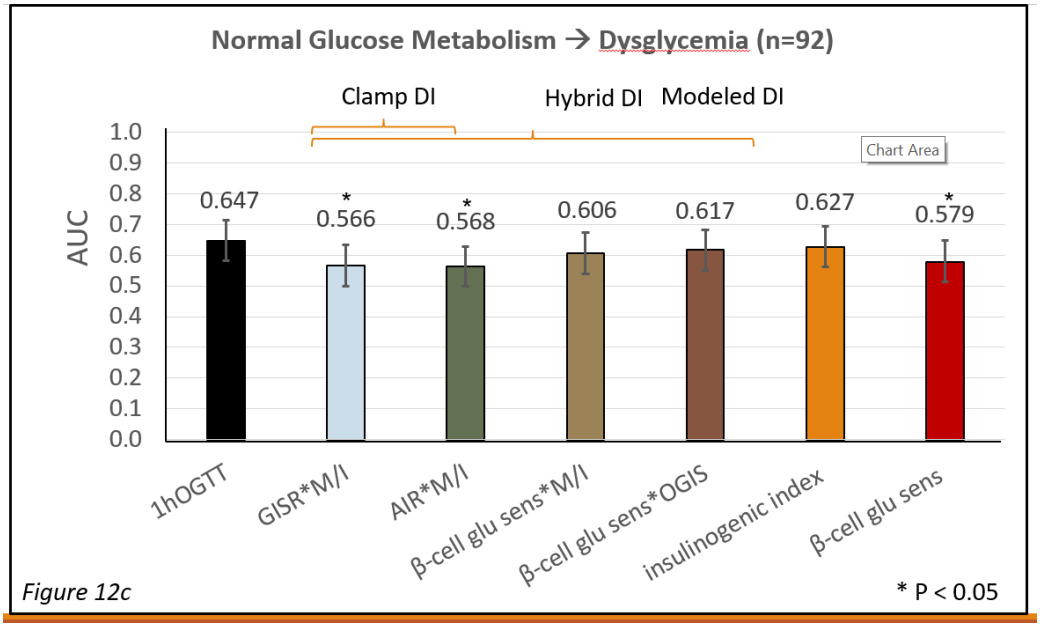

Figure 12c

For the NGM to dysglycemia definition, the 1hOGTT most accurately predicted the progression of dysglycemia with a AUC of 0.647. In addition, the 95% confidence interval was relatively narrow from 0.580-0.713. The AUCs of other more complicated methods that performed better were not significantly different from that of the 1hOGTT.

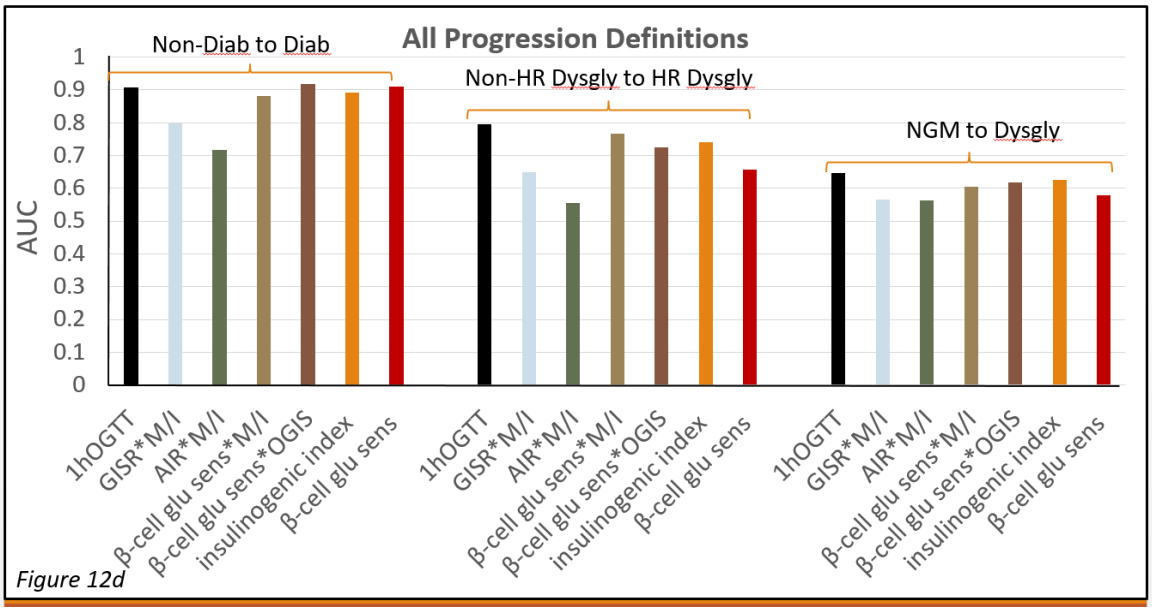

Figure 12 A) AUCs of tests for non-diabetic to diabetic definition. (B) AUCs of tests for non-high risk dysglycemia to high risk dysglycemia. (C) AUCs of tests for normal glucose metabolism to dysglycemia. (D) AUCs of tests for all definitions.

When the AUCs for all methods of each definition of progression were compared, it is evident that the 1hOGTT AUC is the highest within each definition. In addition, it seems that all methods are more accurate at predicting progression under the definition of non-T2DM to T2DM.

AUC and Confidence Intervals		
Non-T2DM to T2DM (n=5)		
	AUC	**95% Confidence Interval**
1hOGTT	0.908	0.851-0.965
GISR*M/I	0.798	0.605-0.991
ACpR*M/I	0.718	0.474-0.963
β-cell glu sens*M/I	0.881	0.761-1.000
β-cell glu sens*OGIS	0.918	0.860-0.976
insulinogenic index	0.892	0.764-1.000
β-cell glu sens	0.910	0.848-0.973
Non-High Risk Dysglycemia to High Risk Dysglycemia (n=32)		
	AUC	**95% Confidence Interval**
1hOGTT	0.794	0.727-0.862
GISR*M/I	0.656	0.559-0.753
ACpR*M/I	0.655	0.555-0.756
β-cell glu sens*M/I	0.767	0.691-0.843
β-cell glu sens*OGIS	0.728	0.648-0.808
insulinogenic index	0.741	0.654-0.828
β-cell glu sens	0.657	0.563-0.753
Normal Glucose Metabolism to Dysglycemia (n=92)		
	AUC	**95% Confidence Interval**
1hOGTT	0.647	0.580-0.713
GISR*M/I	0.566	0.471-0.635
ACpR*M/I	0.563	0.495-0.631
β-cell glu sens*M/I	0.606	0.538-0.675
β-cell glu sens*OGIS	0.617	0.551-0.683
insulinogenic index	0.627	0.486-0.625
β-cell glu sens	0.579	0.511-0.647

Figure 13 Summary of all AUCs and 95% confidence intervals.

Paired Analysis

Since the population size was significantly reduced after ensuring that all participants had each piece of data needed for the different tests, we conducted a sensitivity analysis where

we paired each complicated method to the 1hOGTT for comparison. This way, we had larger sample sizes because we only needed to ensure that all participants had information for the 1hOGTT and the complicated method being compared in that pair. The results from these paired analyses are similar to the previous analysis. The 1hOGTT AUC was still similar if not a little better than complicated measures.

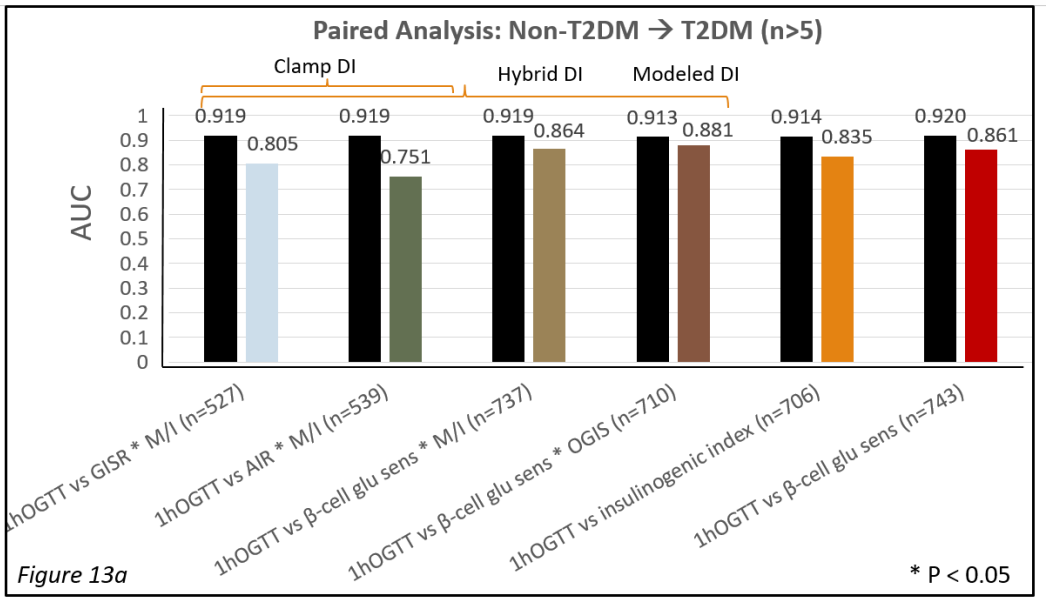

Figure 13a

The number of participants who qualified was 527 for 1hOGTT vs GISR*M/I, 539 for 1hOGTT vs ACpR*M/I, 737 for 1hOGTT vs beta cell glucose sensivity*M/I, 710 for 1hGOTT vs beta cell glucose sensivity*OGIS, 706 for 1hOGTT vs insulinogenic index, and 743 for 1hOGTT vs beta cell glucose sensitivity. The 1hOGTT AUC was higher than that of any other method witin the paired analysis. For the non-T2DM to T2DM definition, the 1hOGTT AUC were all above 0.900, unlike the AUCs of other methods. The AUCs of complex methods that were more accurate were not statistically significant from that of the 1hOGTT.

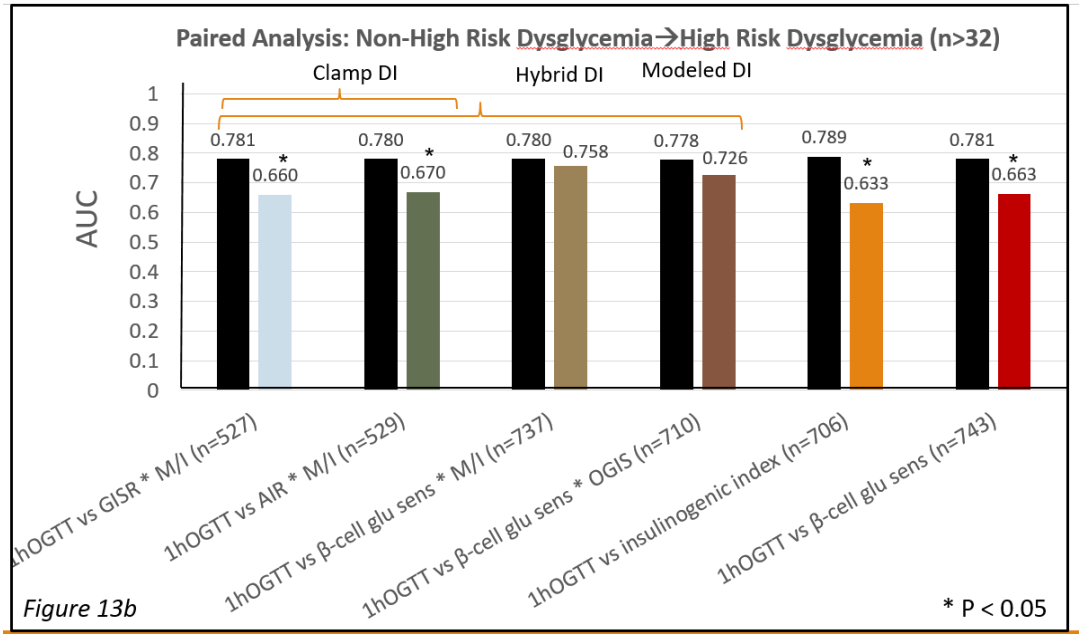

Figure 13b

The number of participants who qualified was 527 for 1hOGTT vs GISR*M/I, 529 for 1hOGTT vs ACpR*M/I, 737 for 1hOGTT vs beta cell glucose sensivity*M/I, 710 for 1hGOTT vs beta cell glucose sensivity*OGIS, 706 for 1hOGTT vs insulinogenic index, and 743 for 1hOGTT vs beta cell glucose sensitivity. The 1OGTT AUC was higher than that of any other method witin the paired analysis. For the non-high risk dysglycemia to high risk dysglycemia definition, the 1hOGTT AUC were all above 0.700, unlike the AUCs of other methods. The AUCs of complex methods that were more accurate were not statistically significant from that of the 1hOGTT.

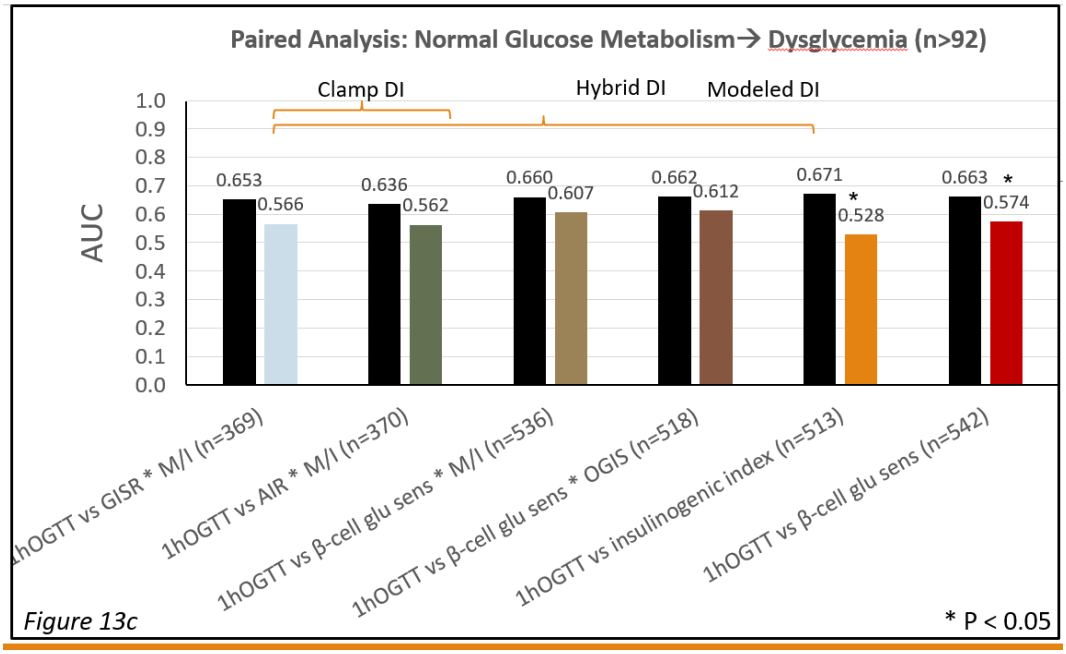

Figure 13 (A) Paired comparison of AUCs of tests for non-diabetic to diabetic definition. (B) Paired comparison of AUCs of tests for non-high risk dysglycemia to high risk dysglycemia. (C) Paired comparison of AUCs of tests for normal glucose metabolism to dysglycemia.

The number of participants who qualified was 369 for 1hOGTT vs GISR*M/I, 370 for 1hOGTT vs ACpR*M/I, 536 for 1hOGTT vs beta cell glucose sensivity*M/I, 518 for 1hGOTT vs beta cell glucose sensivity*OGIS, 513 for 1hOGTT vs insulinogenic index, and 542 for 1hOGTT vs beta cell glucose sensitivity. The 1OGTT AUC was higher than that of any other method witin the paired analysis. For the NGM to dysglycemia definition, the 1hOGTT AUC were all above 0.600, unlike the AUCs of most other methods. The AUCs of complex methods that were more accurate were not statistically significant from that of the 1hOGTT

Discussion

Summary of Findings

With three definitions of progression of hyperglycemia, the 1hOGTT was a strong predictor – the ROC AUC were 0.647 (95% CI 0.580-0.713) for prediction of progression from normal glucose metabolism to dysglycemia (pre-T2DM or T2DM), 0.794 (0.727-0.862) for non-high risk dysglycemia to high risk dysglycemia, and 0.908 (0.851-0.965) for non-T2DM to T2DM. The 1hOGTT ROC AUCs appeared to be similar to if not greater than those of more complex methods. In addition, these differences were generally non-significant between the 1hOGTT and complex methods that performed well. Lastly, results were similar in paired analyses of larger populations.

Comparison to What is Already Known About 1hOGTT

Although the 1hOGTT was expected to reflect insulin secretion and insulin action to a certain degree due to its position between the fasting glucose level and 2 hour glucose level, it was surprising to see that its ROC AUCs were not statistically different than those of the complicated methods that performed well. It was more unexpected that, in some cases, the ROC AUCs of the 1hOGTT were higher than those of more complicated methods, especially the DIs – a widely used approach for evaluating insulin secretion as well as insulin action. The ROC DIs from the RISC dataset is comparable to those found in previously published papers, so this validates our results (Abdul-Ghani et al., 2007; Utzchneider et al., 2009).

What is Already Known About the 1hGCT

The 1hGCT is currently used to screen for T2DM in pregnant women. The 1hGCT is measured after a glucose drink an hour later and can be administered anytime during the day. To some degree, it should correlate with the 1hOGTT since both approaches measure plasma glucose levels 1 hour after an oral intake of glucose. However, since the 1hGCT does not take place after a night of fasting, it cannot be used to understand mechanisms as accurately as the 1hOGTT since it lacks a fasting glucose level.

Limitations

Although the longitudinal dataset had a large number of participants as well as the necessary pieces of data, 3 years is a short time frame to study T2DM progression. In addition, the study population was predominantly European. In other words, the participants were mostly white, more active, and slimmer in comparison to the populations in the US and the rest of the world, so the generalizability of our findings to other groups needs to be studied.

Future Directions

It would be informative to use other longitudinal datasets over longer spans of time to verify our results. This longer time span would allow for more accurate results. Such data can be found in the San Antonio Heart Study and the Utzschneider dataset (Abdul-Ghani et al., 2007; Utzschneider et al., 2009). In addition, we should perform more sensitivity analysis beyond the paired analysis to ensure that other factors do not affect the generalizability of the results. For example, we could see how factors like BMI and lipids affect the AUCs and therefore determine how generalizable our results of a European population are to the US.

Furthermore, it would be beneficial to study the progressors within each of our definitions to see if there are groups of individuals who share certain characteristics. This would be informative because, in the future, these diagnostic tests might be more accurate in predicting progression in individuals with these characteristics. Lastly, we should look for a dataset with prospective 1hGCT data, so that we can consider using it as a screening tool due to the flexibility of when it is administered.

Conclusions

Despite its limitations, the 1hOGTT was found to have relatively high accuracy in comparison to other more complicated measures. Thus, this means that the 1hOGTT could complement the DI in understanding beta cell function and mechanisms of T2DM in the future. This would allow work aimed at the discovery of new and better treatments. Furthermore, similar tests to the 1hOGTT, such as the 1hGCT which does not require overnight fasting, could be used to screen for early stages of dysglycemia in the future.

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