

Performance of HBA1C versus Oral Glucose Tolerance Test (OGTT) As a Screening Tool to Diagnose Dysglycemic Status

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Abstract

Background: The objectives of this study were to examine the diagnostic accuracy of HbA1c using OGTT as a reference standard to identify subjects of dysglycemic status and also evaluate the agreement between HbA1c and OGTT in diagnosing dysglycemic status among high-risk Indian patients.

Methods: We reviewed a sample of high-risk adult, aged 18 Yrs and older, who underwent 75-g OGTT and had an HbA1c value within 3 months. Data were collected on baseline characteristics such as, age, sex, blood pressure, BMI, WC, history of diabetes in first-degree relatives, previously documented cardiovascular diseases, history of smoking, hypertension, plasma lipid profiles, and statin usage.

Results: We evaluated the agreement represented by the ROC curves between the classification of prediabetes and diabetes defined by OGTT and HbA1c. In diabetes group, the AUC was 0.72 indicating that HbA1c was an acceptable test to diagnose diabetes. The agreement, represented by kappa value of 0.309 , was

considered a fair agreement between the two tests. However in diagnosing prediabetes, AUC from the ROC curve is 0.51. Thus, HbA1c could not be used to discriminate subjects with IGT. The Kappa value of 0.151, indicated that there was no agreement between the two tests in diagnosing prediabetes.

Conclusion: Our study found that diabetes prevalence is higher when diagnosed using OGTT than when using HbA1c which implies the limitations of HbA1c as a screening tool for diabetes in high-risk patients. This is the first study to explore the role of HbA1c in diagnosing dysglycemic status in high-risk patients. OGTT should continue to advocate as a screening tool for identification of dysglycemic status in particular population.

Introduction

Hypertension (HTN) and diabetes mellitus (DM) are very common pathological entities, which very frequently co-exist. Both DM and HTN are associated with increased cardiovascular (CV) morbidity and mortality. HTN and DM demonstrate substantial

similarities in their clinical manifestations as well as the underlying pathophysiological mechanisms, such as inflammation and oxidative stress, obesity, and insulin resistance¹. As much as one-third of hypertensive subjects are also insulin resistant and fulfill the diagnostic criteria for the metabolic syndrome. The American Diabetes Association (ADA) defines prediabetes as either impaired fasting glucose (IFG) (i.e., fasting glucose levels of 100–125 mg/dl), impaired glucose tolerance (IGT) (i.e., glucose levels post 2-h oral glucose loading of 140–199 mg/dl), or an elevated hemoglobin A1c (HbA1c) level of 5.7% to 6.4%².

Prediabetes is a well-established risk factor for progression to overt DM, which is in turn associated with development of HTN and vice versa. However, the role of prediabetes as an independent risk factor for the development of HTN necessitates further elucidation.³ Currently, there are three glucose-based diagnostic methods with specific cut-off points for diagnosing dysglycemic status. HbA1c is the latest method and the most convenient screening tool for dysglycemia, but it is also known to be less sensitive than the oral glucose tolerance test (OGTT). It is still debatable whether HbA1c or OGTT should be the preferred test for diagnosing diabetes⁴. The results from the Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) study which included more than 40,000 participants with gradable retinal photographs from five countries did not support the superiority of OGTT over HbA1c or fasting plasma glucose (FPG). Also, the effect of race/ethnicity on HbA1c level were apparent⁵. Unfortunately, no study was done to evaluate the clinical utility of HbA1c compared with OGTT to diagnose dysglycemia in Indian participants. The objectives of this study were to

examine the diagnostic accuracy of HbA1c using OGTT as a reference standard to identify subjects of dysglycemic status and also evaluate the agreement between HbA1c and OGTT in diagnosing dysglycemic status among high-risk Indian patients.

Material and Methods

We reviewed (record based retrospective study) a sample of 150 high-risk adult, aged 18 Yrs and older, who underwent 75-g OGTT and had an HbA1c value within 3 months from 1 Oct. 2019 to 31 Dec. 2019.

Most subjects had high risk for diabetes such as having a body mass index (BMI) ≥ 25 kg/m² or having abdominal obesity and family history of diabetes. Subjects were excluded from this study if they had a history of diagnosed diabetes, had hematologic or endocrinologic disorders or on medications that would interfere with glucose metabolism. Subjects that are pregnant during the OGTT were also excluded.

Data were collected on baseline characteristics such as, age, sex, blood pressure, BMI, WC, history of diabetes in first-degree relatives, previously documented cardiovascular diseases, history of smoking, hypertension, plasma lipid profiles, and statin usage.

In this study, the definition is based on 2018 American Diabetes Association (ADA) criteria. Diabetes was defined as subjects with 2-h plasma glucose from OGTT ≥ 200 mg/dL and/or HbA1c $\geq 6.5\%$ and/or FPG of ≥ 126 mg/dL. The term “prediabetes” refers to IFG (FPG 100–125 mg/dL), IGT (2-h plasma glucose from OGTT at 140–199 mg/dL) or an HbA1c level of 5.7–6.4%. Normal glucose tolerance (NGT) was defined as subjects who had 2-h plasma glucose less than 140 mg/dL. After fasting for at least 8–12 h, OGTT was performed 2 h after the ingestion of a standard 75-g glucose load. Plasma glucose was measured by enzymatic hexokinase method (Roche Diagnostics

Cobas analyzer). Measurement of HbA1c was done by electrochemiluminescence immunoassay. The HbA1c test was DCCT-aligned assay and was accredited by the National Glycohemoglobin Standardization Program (NGSP).

Statistical Analysis

Continuous variables were presented as mean (\pm standard deviation, SD) or median (interquartile range), and categorical variables were presented as proportions. Clinical characteristics were compared

using one-way ANOVA and post hoc analysis. *P*-value ≤ 0.05 was considered statistically significant.

Results

Of the 150 subjects without prior history of diabetes who underwent OGTT.

Table.1: Socio-demographic variable

Mean age	36.23 \pm 12.32 Yrs
Sex (M:F)	102:48

Mean age of patients was 36.23 \pm 12.32 Yrs.

Table 2: Clinical characteristics and laboratory data of analyzed subjects classified by OGTT (N = 150)

Parameter	Overall (n=150)	NGT(n=40)	IGT(n=62)	DM(n=48)	p-value
Age (Yrs)	36.23 \pm 12.32	42.25 \pm 6.23	49.11 \pm 10.65	52.23 \pm 9.82	0.01
Sex (M:F)	102:48	28:12	42:20	32:16	0.235
BMI(kg/mt ²)	24.12 \pm 2.32	22.10 \pm 1.12	25.02 \pm 2.32	26.78 \pm 2.31	0.126
Hypertension (%)	12.00%	10.00%	12.90%	12.5%	0.231
Smoking	18.67%	15.00%	25.81%	12.5%	0.365
Fasting sugar	103.23 \pm 10.24	90.6 \pm 9.12	106.12 \pm 10.01	119.12 \pm 14.20	0.001
Hb1Ac	5.76 \pm 0.6	5.4 \pm 0.4	5.7 \pm 0.6	6.1 \pm 0.8	0.001

150 participants that are categorized into 3 groups including NGT, IGT, and DM. The mean age of all subjects was 36.23 \pm 12.32 years and the mean BMI was 24.12 \pm 2.32 kg/m². Compared to the NGT group, the

IGT and DM groups were significantly older (*p* = 0.001) and tended to have higher BMI but did not reach statistical significance (*p* = 0.126).

Table 3: Sensitivity, specificity for detecting selected type 2 diabetes mellitus at different HbA1c thresholds

HbA1c	Sensitivity	Specificity
5.7	76.00%	46.00%

5.8	72.00%	56.00%
5.9	68.00%	64.00%
6.0	62.00%	70.00%
6.1	56.00%	70.00%
6.2	54.00%	80.00%
6.3	45.00%	87.00%
6.4	37.00%	90.00%
6.5	32.00%	92.00%

The agreement between HbA1c and OGTT

We evaluated the agreement represented by the ROC curves between the classification of prediabetes and diabetes defined by OGTT and HbA1c. In diabetes group, the AUC was 0.72 indicating that HbA1c was an acceptable test to diagnose diabetes. The agreement, represented by kappa value of 0.309, was considered a fair agreement between the two tests. However in diagnosing prediabetes, AUC from the ROC curve is 0.51. Thus, HbA1c could not be used to discriminate subjects with IGT. The Kappa value of 0.151, indicated that there was no agreement between the two tests in diagnosing prediabetes. Discussions

In this study we found that compared to OGTT, HbA1c has lower sensitivity but higher specificity in diagnosing diabetes. The optimal cut-off HbA1c point to diagnose diabetes was found at 6.2% per OGTT criteria which is lower than the current HbA1c-based criteria of diabetes. Such findings suggest that physicians should advocate OGTT as a screening tool for the identification of dysglycemic status in high-risk Indian patients. Alternatively, a lower cut-off point for HbA1c might be suitable for high-risk Indian patients. The natural history of T2DM is characterized by a progressive decline in beta-cell function, a process that is accelerated by obesity. In vivo studies in humans indicated that there is a 70% decrease in beta-cell glucose responsiveness by the time that individual has

developed IGT⁵. Primary prevention by lifestyle modifications and pharmacological therapy had been shown to be effective, especially in IGT patients.⁶⁻⁸ Early detection for primary prevention is therefore critical to prevent future diabetes and cardiovascular diseases.

Glycated hemoglobin was endorsed as one of the criteria for diagnosis of prediabetes and diabetes by ADA in 2010⁹ and by the World Health Organization (WHO) in 2011 based on its equal sensitivity and specificity to other methods as a predictor of prevalent retinopathy. However, it needed to emphasize that the quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values.¹⁰ Also, it should be ensured that there are no conditions present which preclude accuracy of HbA1c measurement.¹¹ The use of HbA1c can avoid the requirements for individual to fast or to have adequate carbohydrate intakes before OGTT testing. Hemoglobinopathies especially thalassemia which affects 5–10% of individuals from Southeast Asia is known to interfere with some HbA1c assay¹². But the prevalence of major thalassemia (beta-thalassemia and beta-thalassemia associated with other Hb anomalies) varies among different regions in each country¹³. Therefore, HbA1c is still a valuable tool for early diagnosis of dysglycemia in the Asia region if we understand the limitations of its use.

Finally, the data are retrospective (Record based) in nature and we cannot conclude the overall progression of future diabetes, cardiovascular diseases, or other future co-morbidities for each individual. Further prospective follow up study should be conducted to evaluate our approach in using both OGTT and HbA1c to capture dysglycemia in high-risk patients and evaluate risks for long-term diabetic and cardiovascular complications.

Conclusion

Our study found that diabetes prevalence is higher when diagnosed using OGTT than when using HbA1c which implies the limitations of HbA1c as a screening tool for diabetes in high-risk patients. This is the first study to explore the role of HbA1c in diagnosing dysglycemic status in high-risk patients. OGTT should continue to advocate as a screening tool for identification of dysglycemic status in particular population.

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