PERFORMANCE OF HbA1c VERSUS ORAL GLUCOSE TOLERANCE TEST (OGTT) AS A SCREENING TOOL TO DIAGNOSE DYSGLYCEMIC STATUS

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Abstract

Background: Increasing global prevalence of type 2 diabetes (T2D) has resulted in concerted efforts to improve predictors for development of this obesity-related disorder. Establishing markers that identify prediabetes, an intermediary state of glycaemia above that of healthy individuals but below frank T2D, is an important focus. 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. 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 0.73 indicating that HbA1c was an acceptable test to diagnose diabetes. The agreement, represented by kappa value of 0.312, was considered a fair agreement between the two tests. However in diagnosing prediabetes, AUC from the ROC curve is 0.52. Thus, HbA1c could not be used to discriminate subjects with IGT. The Kappa value of 0.153, 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.

Keywords: HbA1c, OGTT, Dysglycemia.

Introduction

Type 2 diabetes (T2D) is becoming an increasingly common disease with incidence rates that are rising rapidly in parallel with the rising global prevalence of overweight and obesity.¹ In 1994 approximately 1 million people globally were reported with T2D, which increased to 382 million in 2013, and now with a projected increase to 592 million over the next 20 years.² High T2D prevalence results in both decreased quality of life for the individual and increased government health care costs resulting from increased morbidity, largely a result of macro and microvascular conditions caused by long-term elevations in peripheral blood glucose. A disease long known in those who are 'overweight and over forty' it is gradually becoming a disease of younger adults, adolescents and even children as lifestyle changes lead to weight gain and

increased adiposity. Those who have high levels of central adiposity are at particular risk of T2D, with abdominal obesity strongly associated with important changes in body composition including lipid overspill/infiltration into critical organs such as the pancreas and liver³

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 effects 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 200 high-risk adult, aged 18 Yrs and older, who underwent 75-g OGTT and had an HbA1c value.

Most subjects high risk for diabetes such as having a body mass index (BMI) $\geq 25 \text{ kg/m}^2$ 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 and subjects with other nationalities 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 $\geq 200 \text{ mg/dL}$ and/or HbA1c $\geq 6.5\%$ and/or FPG of $\geq 126 \text{ mg/dL}$. 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

Data analyses were compiled in MS Excel, Primer, and SPSS software. Those were presented in tables and graphs wherever applicable. Data were analysed as per objectives.

Inferences were drawn with the help of appropriate of significance.

Results

Table 1: Socio-demographic variable

Mean age	39.12 $\pm$ 11.06 Yrs
Sex (M:F)	122:78

Mean age of patients was 39.12 $\pm$ 11.06 Yrs.

Table 2: Clinical characteristics and laboratory data of analyzed subjects classified by OGTT (N = 200)

Parameter	Overall (n=200)	NGT(n=55)	IGT(n=76)	DM(n=69)	p-value
Age (Yrs)	39.12 $\pm$ 11.06	43.12 $\pm$ 6.13	48.12 $\pm$ 10.02	52.80 $\pm$ 9.76	0.01
Sex (M:F)	122:78	36:22	48:30	38:26	0.123
BMI(kg/mt ²)	24.12 $\pm$ 2.32	22.18 $\pm$ 1.16	25.16 $\pm$ 2.10	26.92 $\pm$ 2.55	0.121
Hypertension (%)	12.00%	10.90%	15.78%	13.04%	0.129
Smoking	18.00%	14.55%	19.74%	13.04%	0.182
Fasting sugar	104.23 $\pm$ 10.18	92.36 $\pm$ 9.11	107.2 $\pm$ 10.16	120.2 $\pm$ 13.80	0.001
Hb1Ac	5.78 $\pm$ 0.7	5.42 $\pm$ 0.39	5.69 $\pm$ 0.59	6.12 $\pm$ 0.79	0.001

200 participants that are categorized into 3 groups including NGT, IGT, and DM. The mean age of all subjects was 39.12 $\pm$ 11.06 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 = 0.121).

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

HbA1c	Sensitivity	Specificity
5.7	75.00%	45.00%
5.8	73.00%	54.00%
5.9	70.00%	62.00%
6.0	69.00%	72.00%
6.1	54.00%	72.00%
6.2	53.00%	78.00%
6.3	46.00%	84.00%
6.4	38.00%	88.00%
6.5	34.00%	90.00%

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 0.73 indicating that HbA1c was an acceptable test to diagnose diabetes. The agreement, represented by kappa value of 0.312, was considered a fair agreement between the two tests. However in diagnosing prediabetes, AUC from the ROC curve is 0.52. Thus, HbA1c could not be used to discriminate subjects with IGT. The Kappa value of 0.153, 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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