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Diagnostic performance of four different screening tools in detecting pre-diabetes and diabetes among the first degree relatives of patients with Type 2 diabetes.

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Abstract

Knowledge on the diagnostic performance of different tests available for screening individuals in different risk categories to develop diabetes would help in selecting the most appropriate tool in the given setting. We aimed to study the sensitivity and specificity of fasting blood glucose (FBG), capillary blood glucose (CBG), glycosylated hemoglobin (HbA1c) and Finish Diabetes Risk Score (FINDRISC) in detecting pre-diabetes and diabetes as opposed to the oral glucose tolerance test (OGTT) among individuals in high diabetes risk category. First degree relatives of patients with type 2 diabetes underwent FBG, CBG, HbA1C and OGTT. Sensitivity, specificity and area under the curve (AUC) of receiver operator curve (ROC) of each screening method were calculated against the OGTT criteria. Diagnostic cut–offs levels recommended by the American Diabetes Association were used to define pre-diabetes and diabetes. Mean (SD) age and body mass index of the 157 subjects tested were 49 (11) years and 23 .6 (3.6) Kg/ m2 respectively. Sensitivity and specificity of HbA1c, FBG, CBG, and FINDRISC in detecting diabetes were 77.3% and 97.3%, 68.2% and 99.3%, 45.5% and 97.8%, 4.55 and 100%. AUC of the ROC for each tool were 0.96%, 0.87%, 0.88% and 0.65% respectively. HbA1c cut-off level of 6.5% has superior sensitivity than all other screening tools in detecting both diabetes and pre-diabetes in the first degree relatives of patients with T2DM. With AUC close to 1 (0.96%) in ROC curve, HbA1c test can be a practical and reliable alternative screening tool to OGTT to detect diabetes in this high diabetes risk category.

Introduction

The pandemic of diabetes is rapidly spreading in South Asia including Sri Lanka [1]. Due to the asymptomatic nature in the early phase of the disease, a substantial majority of individuals affected with type 2 diabetes (T2DM) remain undiagnosed until they develop debilitating and fatal complications such as blindness, end stage renal disease or premature cardiovascular disease [2]. Detection of asymptomatic individuals and timely interventions to prevent complications have shown to reduce morbidity and mortality among patients with diabetes[3]. Therefore, T2DM fulfils almost all the criteria necessary for community screening.

Guidelines recommend regular screening of individuals with high risk of developing diabetes [4]. Due to genetic predisposition, the first degree relatives of patients with diabetes are at a high diabetes risk.

Although there is consensus regarding the categories of patients who should be screened for abnormal glucose tolerance, there is still some debate over the most sensitive and specific screening tool for this purpose. Random capillary blood glucose (CBG) and fasting blood glucose (FBG) are the two most widely used blood tests carried out for diabetes screening in routine clinical setting. They have varying sensitivity and specificity when compared with the gold standard of oral glucose tolerance test (OGTT) in the diagnosis of pre diabetes and diabetes. Estimation of glycosylated hemoglobin (HbA1c) has recently been advocated as a screening tool to diagnose diabetes and pre-diabetes[5]. Although it can be performed in the non-fasting state, relatively higher cost than FBG and CBG, lack of a standardised method of estimation, ethnic variations of the “population normal value” and prevalence of different hemoglobinopathies have limited its wider utility as a screening tool to diagnose abnormalities in glucose tolerance[6].

For the purpose of low cost and simplicity in application in the primary care setting, some population based research on prevalence of diabetes has used scoring systems to select patients who need biochemical investigations for blood glucose. Finland Diabetes risk score (FINDRISC) is a validated and widely used such scoring system[7].

In the background of the pandemic of diabetes and lack of consensus on the most sensitive and specific screening tool, there is a need of research focused on the performance of different screening

tools to detect diabetes in high risk categories in the community. The objective of this study is to evaluate the diagnostic performance (sensitivity and specificity) of four different screening tools to detect glucose abnormalities (diabetes and pre-diabetes) against the oral glucose tolerance test (OGTT) in previously non-diabetic , first degree relatives of patients with type 2 diabetes from an urban locality in Southern Sri Lanka.

Methods

Participants for the study were recruited by inviting the first degree relatives above the age of 35 years of patients with known T2DM. Ethical approval for the study was obtained from the local ethics review committee. Each participant was interviewed by a medical officer with regard to the accuracy of inclusion criteria including the relationship to the index patient and verification of age with a national identity card and written informed consent were obtained.

Demographic data including gender, age, family history of diabetes (maternal, paternal, sibling) were obtained and weight, height, waist circumference were measured using standard techniques.

Exclusion criteria: Those with known diabetes and who were on long term steroids, anti-psychotic agents or diagnosed to have chronic liver, pancreatic or kidney disease or malignancies and pregnant females were excluded.

Using the modified FINDRISC questionnaire, FINDRISC score for every participant was calculated. CBG was tested using a single glucometer for all subjects in the non-fasting state. Participants were asked to come on the next day after minimum of 12 hours of fasting and 5 ml venous blood was drawn for estimation of FPG and HbA1C and 75 grams OGTT was carried out. Estimation of CBG and FBG capillary and venous glucose was carried out using glucose oxidase method and high performance liquid chromatography was used for HbA1C testing. American diabetes association (ADA) criteria were used to categorize individuals into pre-diabetes and diabetes on FBG, HbA1C and OGTT[4].

Individuals found to have diabetes were referred for medical treatment.

Sample size: The minimum number of participants necessary for the study was calculated using standard sample size calculation formula and assuming prevalence of type 2 diabetes in Sri Lanka as 10% was eighty.

Data analysis - All descriptive variables were represented as mean (SD) standard deviations. Prevalence of diabetes and pre-diabetes according to each screening method were given as percentages of study sample.

Results

Study sample included 157 first degree relatives of patients with T2DM. Mean (SD) values of age, BMI were 50 (11) years, 23.6 (3.6) kg/m2 respectively. Other characteristics of the study sample are shown in the table 1.

Table 2 shows the number and percentages of patients with pre-diabetes and diabetes based on OGTT, FBS, HbA1c, FRS and CBS. Sensitivity and specificity values of each screening tool, calculated keeping OGTT as the gold standard, in detecting diabetes and pre- diabetes are shown in table 3.

According to these findings, HbA1c had the highest sensitivity of 77.3%. Using Pearson correlation, significant positive correlations were observed between 2- hour value of blood glucose after 75 grams of glucose in OGTT and three of the screening tools; HbA1C ($r = 0.848$, $P = < 0.05$), FBS ($r = 0.873$, $P = < 0.05$), and CBS ($r = 0.846$, $P = < 0.05$) Table 4.

Receiver operating characteristics analysis revealed that HbA1C had the highest discriminatory value while FBG and CBG possess lesser but almost similar discriminatory value in recognizing abnormal glucose tolerance. (Table 5 and Table 6).

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Table 1 Descriptive data of study sample (157)

	Mean (SD)
Age (years)	49 (11)
Weight (kg)	60.8 (11.2)
BMI (kg/m^2)	23.6 (3.6)
CBG (mg/dL)	100.1 (23.9)
HbA1C (%)	5.7% (1.2%)
2 – hour plasma glucose after 75 grams of glucose in OGTT(mg/dL)	143.4 (82.3)

Table 2- Number and percentages with pre-diabetes and diabetes according to different screening tools in detecting abnormal glucose tolerance

Test	Normal	Pre – diabetes	Diabetes
OGTT	109 69.4%	26 16.6%	22 14.01%
FBG	112 71.3%	29 18.5%	16 10.2
HbA1C	107 68.2%	30 19.1%	20 12.7%
CBG	106 67.9%	37 23.7%	13 8.3%
FINDRISC	138 88.5%	17 10.9%	1 0.6%

Table 3. Sensitivity and specificity of screening tools in detecting diabetes with the 2 hour OGTT value of 200 mg/ dL as the gold standard

	Sensitivity	Specificity
HbA1C	77.3%	97.8%
FBG	68.2%	99.3%
CBG	45.5%	97.8%
FINDRISC	4.5%	100%

Table 5. Area under the curve for 4 different screening tools in detecting pre-diabetes with 2 hour OGTT value 140- 200 mg/ dL as the gold standard

Test	AUC	95% CI	P
HbA_1C	0.83	0.75 – 0.91	<0.001
FBG	0.75	0.66 – 0.84	<0.001
CBG	0.74	0.64 – 0.83	<0.001
FINDRISC	0.55	0.45 – 0.65	0.29

Table 6. Area under the curve for four different screening tools in detecting diabetes with the 2 hour OGTT value of 200 mg/ dL as the gold standard

Test	AUC	95% CI	P
HbA_1C	0.96	0.93 – 0.98	<0.001
FBG	0.87	0.77 – 0.98	<0.001
CBG	0.88	0.80 – 0.96	<0.001
FINDRISC	0.65	0.51 – 0.79	0.03

Discussion

Rising incidence of diabetes and its burden on the health care systems in the developing countries demands adoption of sensitive screening tools with acceptable diagnostic performance. This study compared the diagnostic performance of four screening tools in detecting pre-diabetes and diabetes among the first degree relatives of patients with T2DM in a developing country with high prevalence of diabetes.

Results of the study revealed that among the first degree relatives of patients with T2DM, the prevalence of diabetes according to HbA1c and FBS are 12.7 % and 10.7% and pre diabetes was 19.1% and 18.5% respectively. Of the four screening tools tested, HbA1c has the highest sensitivity in detecting diabetes and pre-diabetes (77.3% and 50%) respectively. HbA1c also had superior diagnostic performance over all other screening tools with the largest area under the curve (0.96).

With a sensitivity of 77.3% as opposed to 68.2% of FBS, testing with HbA1c could detect diabetes in additional nine subjects out of one hundred first degree relatives of patients with T2M tested who would not be diagnosed as having diabetes by testing with FBS alone.

Although with lower sensitivity in detecting those with pre-diabetes than diabetes (77.3% vs 50%) HbA1c test could also detect additional eight patients with pre-diabetes per one hundred individuals tested when compared to FBS (sensitivity of HbA1c 50 % vs sensitivity of FBS of 42%). The other most significant finding in this study was the unacceptably low sensitivity of FINDRISC in detecting diabetes (4.5%) and pre-diabetes (3.8%) in this community. However it showed the highest specificity (100%) indicating its value in ruling out those with diabetes in this community.

Published studies on the prevalence of diabetes and pre-diabetes in Sri Lanka have been carried out in the general population and none has used HbA1c as a screening tool. No study has specifically focused individuals with a high risk of developing diabetes such as the first degree relatives as in the present study. The prevalence rates of diabetes and pre-diabetes in the general community vary according the time and setting (urban vs rural) and the screening test used. A cross sectional survey conducted in Sri Lanka in 2007 in a sample of 2986 individuals has revealed a prevalence rate of diabetes in 20.3% men and 19.8 % females[8]. The population screened in this study included adults in the age range between 34-65 years and used fasting plasma glucose as the screening tool.

The lower prevalence of diabetes reported from our study could be due several factors including exclusion of patients with known diabetes and those with other risk factors such as steroid use etc. The sample studied in the present study was also drawn from a relatively rural or suburban community.

Another study using HbA1c as a screening tool in Caucasian population with high risk of diabetes has revealed a prevalence of diabetes of 25% and pre-diabetes of 40 %[9]. Although with similar HbA1c cut-off levels, higher prevalence rates reported in this study than the findings in in our study could be due to higher ethnic susceptibility to diabetes in the African Americans and Latinos and presence of several risk factors other than the positive family history of diabetes in their study sample.

Some studies which compared the diagnostic performance of HbA1c and FBG were conducted in a general population and they have used different cut-off values of HbA1c to diagnose diabetes and pre-diabetes.

A population based cross-sectional survey conducted in a rural community in Bangladesh has revealed that the HbA1c cut-off value of 6% has the sensitivity of 86% and specificity of 93.3 % which is superior to FBG in diagnosing diabetes. The sensitivity and specificity of HbA1c cut-off value of 5.6% in detecting pre-diabetes was 68% and 66.4 % respectively in this study[6]. The observed sensitivity and specificity in diagnosing diabetes and pre-diabetes in our study with HbA1c cut off value of 6.5 % and 5.7% was marginally lower than the reported figures from Bangladesh but we too found that the sensitivity of HbA1c was higher than FBS in diagnosing diabetes in our study sample.

Reduced sensitivity of HbA1c in the diagnosis of pre-diabetes has been reported in another study conducted a sample of 501 in Caucasian subjects[10]. In this study, the HbA1c cut-off value of 5.6% had sensitivity of 76% and specificity of 63% in detecting individuals with pre-diabetes (impaired glucose tolerance in OGTT) and when the cut off- value was increased to 5.9% the sensitivity has been reduced to 46% with specificity increased to 84%.

Another study carried out in Brazilian Zavente Indians (630 individuals age > 20 years), a high risk ethnicity for diabetes, has reported a sensitivity (71.3%) and specificity (90.5%) and diagnostic performance (AUC of 0.88 (95%CI: 0.83-0.93) for HbA1c in detecting diabetes[11], almost similar to the results found in our study. Due to lower specificity (51.4%) and reduced AUC (0.62 (95%CI: 0.57-0.67), they too have commented on the acceptability of HbA1c for the diagnosis of diabetes, but not for pre-diabetes in this ethnicity with high risk of diabetes.

FINDRISC has not been tested as a screening tool in any community based studies carried out in Sri Lanka or India. FINDRISC uses eight variables (age, body mass index, family history, waist circumference, use of anti-hypertensive medications, and consumption of fruits and pervious diagnosis of high blood glucose levels).

Out of the total possible score of 26 a score over 20 is regarded as a high risk and over 15 as a moderate risk. We used score over 20 as having diabetes and over 15 as pre-diabetes. But the sensitivity of these cut-off value was unacceptably low (4.5%) However its value as a cost effective screening tool has been highlighted in a major community based studies from the United States of America.

Using data from the National Health and Nutrition Examination Survey (NHANES) the sensitivity and specificity of the FINDRISC (cutoff of >/=9) was reported to be 79.1% and 48.6% for diabetes and 60.2% and 61.4% for pre-diabetes[12]. The lower sensitivity (4.5%) of the FINDRISC in the sample studied in this study could be due to several factors. These may include misinterpretation of some of the questions such as the use of anti-hypertensive agents, previous diagnosis of high blood glucose values, family history, and consumption of fruits in the FINDRISC questionnaire. However with a specificity of 100% detected in the present study, we can report that lower FINDRISC value could reliably exclude abnormal glucose tolerance among the first degree relatives of patients with diabetes in our community.

Lower sensitivity and specificity of CBG in detecting individuals with pre-diabetes and diabetes in this study is also a notable finding and this could be due to lack of standard procedure for random CBG testing and some local factors variability of skin blood flow among individuals screened . Although it is convenient, and low cost than FBG and HbA1c, our finding argues against use of CBG in preference to FBG in screening for abnormalities in glucose tolerance in this population with high diabetes risk.

In summary, the present study highlights the superior diagnostic performance of HbA1c over FBG and random CBG in detecting diabetes among the first degree relatives of patients with diabetes. With an AUC of 0.96 in the receiver operator curve, we recommend that HbA1c testing can be a reliable and practical alternative to more cumbersome OGTT to detect diabetes in this high risk category.

However, as in the reported studies from other settings, HbA1c test lacks adequate sensitivity to reliably detect those with pre-diabetes among individuals in this high risk category. We also found that the CBG and FINDRISC tools lack the required sensitivity and can only be useful in excluding those with diabetes in this community.

The main strength of this study is testing of all the routinely used diabetes screening tools such as FBG, CBG against the gold standard of OGTT and inclusion of novel HbA1c testing.

Although the number of individuals included was above the minimum required, our study sample is relatively smaller than most of the published studies in literature. All participants included in the study were first degree relatives of patients with T2DM, hence application of these findings to general community should be done after a large scale community based study to include individuals with all diabetes risk (low and high) categories in the community.

Conclusions

We report that HbA1c is a more sensitive test than FBG in the diagnosis of diabetes among the first degree relieves with T2DM. With hardly any preparation necessary, HbA1c test is a reliable and more practical alternative to OGTT which demands more time and preparation to detect individuals with diabetes among the first degree relatives of patients with T2DM in our community.

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