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Optimal HbA1c Level for Screening of Prediabetes and Diabetes in a Multiethnic Singaporean Population

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Abstract

Objectives: Many organizations including American Diabetes Association (ADA) recommend HbA1c of ≥ 6.5% as an appropriate cutoff to diagnose diabetes mellitus. Until recently, in Singapore the use of HbA1c has not been accepted due to apprehensions around the influence of ethnicity, hemoglobinopathies and other disorders that alter red cell turnover.

The aims of this study are to evaluate the use of HbA1c for diabetes screening, and to determine the optimal HbA1c cutoff for screening of prediabetes and diabetes in Singapore.

Methods: We designed a prospective study, whereby subjects were recruited from multiple community health screening events from Mar 2017-Mar 2018. The inclusion criteria include both sexes, age (20-80 years old) and ethnicity (Chinese, Malay or Indian). Laboratory tests performed were HbA1c and Fasting Plasma Glucose (FPG). The exclusion criteria were as follows: those who were pregnant; ever diagnosed with diabetes; those with chronic kidney disease; and those with hemoglobinopathies.

Results: 214 subjects were included in the final analysis. In our study, the ADA recommended HbA1c level of 5.7% had a high sensitivity (90.0%) and low specificity (60.3%) when used as a threshold for the identification of prediabetes. In contrast, an HbA1c cutoff of 6.2% predicts prediabetes and diabetes with sensitivity (75.0%) and specificity (95.4%) and the AUC was 0.884.

Conclusions: Our study findings were consistent with the recommendations of the Singapore Ministry of Health March 2019 health screening guidelines for diabetes. Our proposed HbA1c cutoff at 6.2% has similar sensitivity and specificity in screening for prediabetes and diabetes compared to the recommended 6.1%.

Keywords: HbA1c cutoff; Diabetes; Prediabetes; Multiethnic; Singapore

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Introduction

Diabetes mellitus type 2 (diabetes) is reaching pandemic proportions across the world, including Singapore. The number of diabetes patients is projected to increase from 8.8% (425 million) globally in 2017 to 9.9% (451 million) by 2045 [1].

In Singapore, 14.4% of the population suffers from prediabetes [2]. Prediabetes usually precedes diabetes and is more prevalent than diabetes [3]. Based on the National Health Survey 2010, the prevalence of diabetes was 11.3% [2]. Therefore, effective and early identification of subjects with diabetes and prediabetes is important to prevent complications or delay disease progression from prediabetes to diabetes. Singapore has the second-highest proportion of diabetes among developed nations, according to a 2015 International Diabetes Federation report [4]. About 440,000 Singapore residents who were 18 years and above had diabetes in 2014 [2] and the number is estimated to grow to 1,000,000 in 2050 [5]. The cost burden from diabetes, including medical expenses and productivity loss, was expected to rise from beyond $940 million in 2014 to $1.8 billion in 2050, a considerable and enormous drain on the healthcare system [6].

Traditionally, the gold standard for diagnosing diabetes and prediabetes has been based on the use of Fasting Plasma Glucose (FPG) and/or 2h plasma glucose after a 75-G Oral Glucose Tolerance Test (OGTT). Recently, an International Expert Committee (IEC), composed of members from the European Association for the Study of Diabetes, the International Diabetes Federation (IDF) and the American Diabetes Association (ADA) recommended values of HbA1c ≥ 6.5% (48 mmol/mol) as the cutoff point for establishing diabetes [7,8]. The use of HbA1c for the diagnosis of diabetes has

been accepted by many institutions and organizations, because of the many advantages such as the assay being quite well standardized, the analyte demonstrating low intra-individual variation and testing does not need fasting or constraint to certain times of the day. However, until recently, current clinical practice guidelines in Singapore only recommend screening with FPG, followed by an OGTT in those with FPG 6.1-6.9 mmol/L [9]. The use of HbA1c for the diagnosis of diabetes has not been accepted due to apprehensions around the influence of ethnicity, the presence of hemoglobin variants and other disorders that alter red cell turnover such as G6PD deficiency, which is not uncommon in Singapore.

Accumulating evidence substantiates the theory that race/ethnicity affects HbA1c [10-14]. While taking into account the factors that may impact glycemia, it is still probable that these disparities may be due to changes in glycemic control. The molecular mechanism causing the racial and ethnic differences is yet to be determined and no agreement has been achieved on whether different cutoffs should be used for different ethnicities. The HbA1c cutoffs for identifying diabetes and prediabetes in the Singaporean population were previously unclear. The objective of this study was to find the optimal HbA1c cutoff value and to appraise the utility of HbA1c as a screening tool for prediabetes and diabetes in Singapore, with ethnic Chinese (76.2% of the citizen population), Malays (15.0%), and ethnic Indians (7.4%) making up the majority of the population [15].

Methods

Study subjects

We obtained the National Healthcare Group Domain Specific Review Board (NHG DSRB) approval (Ref: 2017/00006) to conduct this study at Ng Teng Fong General Hospital, Singapore. This study was supported by JurongHealth Internal Research & Development Grant Award (Project Code Number: 16-54).

We designed a prospective study, whereby subjects were recruited from multiple community health screening events organized by the hospital with informed consent from Mar 2017-Mar 2018 (Figure 1). Eligible subjects were recruited after completing a questionnaire which established at least a slightly elevated risk of developing type 2 diabetes within 10 years based on a risk score of ≥7 [16]. Other inclusion criteria include sexes, age (20-80 years old) and ethnicity (Chinese, Malay or Indian). Laboratory tests performed were HbA1c and FPG which were collected from the same draw into a sodium fluoride and a K2EDTA tube and processed as soon as possible. All subjects had fasted a minimum of 8 hours prior to blood collection.

The exclusion criteria were as follows: those who were pregnant; ever diagnosed with diabetes; those with Chronic Kidney Disease (CKD); and those with hemoglobinopathies. The exclusion criteria of CKD and hemoglobinopathies were selected because of the physiological effects of reduced red blood cell lifespan which may lead to spurious HbA1c results.

In our prospective study, 227 subjects were recruited over 15 health screening events. Unfortunately, 8 subjects were excluded from the study due to unsuccessful blood draw and a further 5 subjects were excluded due to suspected hemoglobinopathies (using Bio-Rad Variant II TURBO, Bio-Rad Laboratories, Hercules, CA).

Definition of diabetes and prediabetes

In this study, the glycemic status of the study subjects was defined according to those recommended by World Health Organization in 2006 [17]. Normal FPG was defined as <6.1 mmol/L while prediabetes was defined as 6.1- 6.9 mmol/L. Diabetes was defined as FPG ≥7.0 mmol/L.

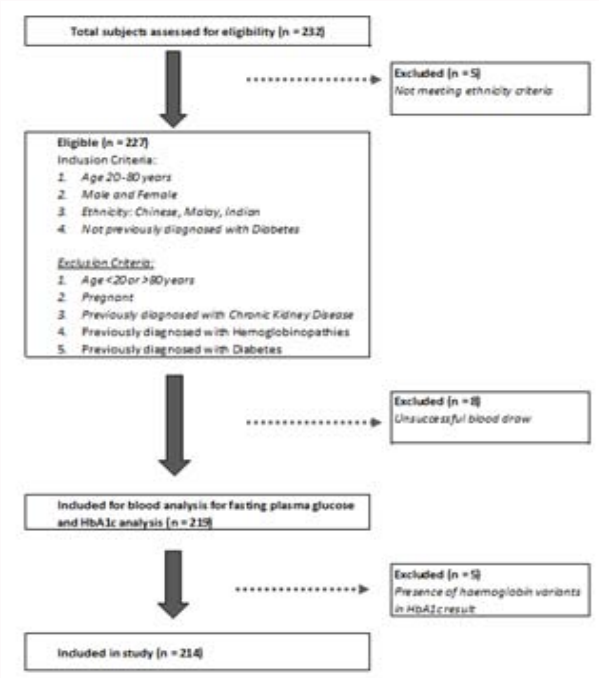

Figure 1: Flow diagram of participants' recruitment.

Laboratory analysis

All plasma glucose and HbA1c samples were evaluated in the same laboratory. The plasma glucose and HbA1c were measured on the Architect C16000 (Abbott Diagnostics, IL, USA) and Bio-Rad Variant II TURBO (Bio-Rad Laboratories, Hercules, CA) platforms using hexokinase and high performance liquid chromatography methods respectively. The HbA1c method used was National Glycohemoglobin Standardization Program-certified.

Statistical analysis

Receiver Operating Characteristic (ROC) curve was charted and the Area Under the Curve (AUC) of ROC was computed for HbA1c. In general, an AUC >0.9 indicates a high diagnostic value, 0.7<AUC≤0.9 indicates a moderate diagnostic value and 0.5<AUC≤ 0.7 indicates a low diagnostic value. The ideal cutoff value for HbA1c for detecting prediabetes was determined using the maximum of the Youden index [(sensitivity+specificity)-1]. We evaluated the sensitivity, specificity, Positive and Negative Predictive Values (PPV and NPV), and accuracy at different HbA1c thresholds. PPV and NPV were calculated based on the local population prevalence (5). The weighted kappa (κ) coefficients were used to test for agreement between HbA1c categorization and glucose-based diagnoses. κ coefficients between 0.8 and 1.0 are interpreted as denoting an almost perfect agreement, those between 0.6 and 0.8 are indicative of substantial agreement, and those between 0.4 and 0.6 are indicative of moderate agreement. Statistical analyses were performed using Microsoft Excel (2010).

Results

A total of 214 subjects were included in the final analysis. The subjects consist of 70 males and 144 females with ethnicity distribution of 176 Chinese, 14 Malay and 24 Indians. Table 1 shows

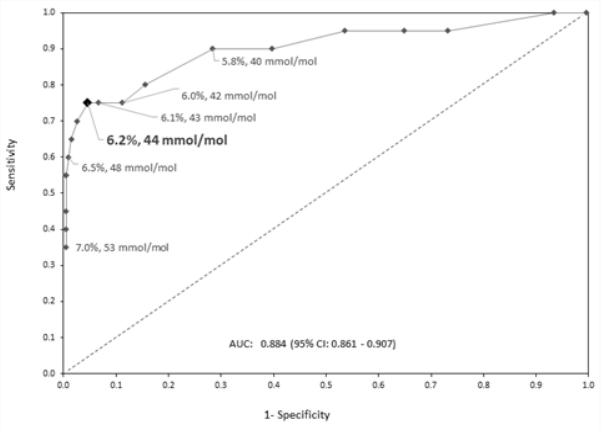

Figure 2: ROC curves of HbA1c to predict prediabetes and diabetes.

Table 1: Demographics of study participants.

	All	Normal	Prediabetes	Diabetes
Total Subject (n)	214	194	11	9
Age (Years)	-	-	-	-
Range	40 to 79	40 to 79	43 to 75	42 to 68
Mean±SD	57 ± 9	57 ± 9	58 ± 10	58 ± 8
Gender (n)	-	-	-	-
Male	70	63	5	2
Female	144	131	6	7
Ethnic Group (n)	-	-	-	-
Chinese	176	163	6	7
Malay	14	11	2	1
Indian	24	20	3	1
Blood Test (Mean±SD)	-	-	-	-
Fasting Glucose Levels (mmol/L)	5.3 ± 0.8	5.1 ± 0.4	6.4 ± 0.3	8.0 ± 1.1
HbA1c (%)	5.7 ± 0.5	5.5 ± 0.4	6.2 ± 0.6	7.2 ± 0.7
HbA1c (mmol/mol)	38 ± 6	37 ± 4	45 ± 6	56 ± 8

SD: Standard Deviation

the demographics characteristics of the subjects. In the present study, we identified a total of 194(90.7%) participants with normal glucose tolerance, 11 (5.1%) with prediabetes and 9(4.2%) with diabetes. Hba1c levels (%) were 5.5±0.4 (37 mmol/mol), 6.2±0.6 (42 mmol/mol), 7.2±0.7 (49 mmol/L) in individuals diagnosed as having normal glucose tolerance, prediabetes, and diabetes, respectively.

AUC of ROC analysis of HbA1c for the diagnosis of prediabetes and diabetes was 0.884(95% CI, 0.861-0.907) (Figure 2). The sensitivity decreased, whereas the specificity increased as the cutoff levels increased. The optimal HbA1c cutoff level as identified by the maximal Youden index were 6.2% (44 mmol/mol) for prediabetes (Table 2), which showed high sensitivity (75%) and specificity (95%), with a low proportion (5%) of false-negative results in disease identification.

When applying the ADA recommended HbA1c cutoff of ≥5.7% (39 mmol/mol) for the diagnosis of prediabetes in our study population, we obtained weighted κ coefficient of 0.19 (Table 3a). However, when we apply our ideal HbA1c cutoff based on our study to predict prediabetes and diabetes (6.2%, 44 mmol/mol) in our study population, we obtained weighted κ coefficient of 0.65, indicating a substantial agreement and a much better correlation (Table 3b).

Discussion

There are several limitations for using glucose for the screening and diagnosis of diabetes. In particular the need for the subject to be fasting at the time of the blood collection is a big hassle. In addition to intrinsic biological variability and the lack of sample stability, these factors impact the reproducibility in glucose testing [18]. On the other hand, HbA1c reflects chronic blood glucose values and is regularly used in checking glycemic control and guiding treatment. The decrease in microvascular complications with HbA1c and the absence of sample stability issues, together with some other pros, have led to the recommendation by some organizations that HbA1c be used for screening and diagnosis of diabetes [9]. The advantages include: (1) HbA1c does not require a fasting state before testing and samples may be taken any time of the day; (2) HbA1c better reflects longer term glycemia than plasma glucose and not influenced by acute factors such as stress and exercise; (3) the laboratory methods for HbA1c are now well standardized and consistent; (4) errors caused by nonglycemic factors affecting HbA1c, such as hemoglobinopathies, are uncommon [19].

An interesting finding from this study is the discordance between HbA1c and FPG in the detection of diabetes and prediabetes. In our study, if we use FPG ≥6.1 mmol/L for screening of prediabetes and diabetes in our study, 20 subjects will be subjected to further investigations. On the other hand, if we use HbA1c ≥6.2%, 24 subjects will be referred for further investigations. Therefore, overall, HbA1c identified more people at risk of diabetes than using FPG. This observation was consistent with other populations [20-23]. In our study, an HbA1c level of 6.2% (44 mmol/mol) had a very high specificity (95.4%) and low false-positive rate (4.6%) for the diagnosis of prediabetes and diabetes. However, we noted an HbA1c of 5.7% (39 mmol/mol) has low specificity (60.3%) when used as a threshold for the identification of prediabetes and diabetes in our population.

Lim *et al.,* showed that an HbA1c cutoff at 6.1% - 6.3% (43-45 mmol/mol) would have comparable sensitivity and specificity to the cutoff for FPG at 6.1 mmol/L that is currently recommended by Singapore health authorities as the first stage in screening for diabetes [24]. From our own data we propose a HbA1c cutoff of 6.2% (44 mmol/mol) with a high sensitivity of 75.0% and specificity of 95.4%. We agree with the views and findings of others that the threshold used for screening should be lower than that recommended for the diagnosis of diabetes. Lu *et al.,* evaluated HbA1c for screening and diagnosis of undiagnosed diabetes in an Australian study and proposed a cutoff of ≤5.5% (37 mmol/mol) to rule out diabetes and ≥7.0% (53 mmol/mol) to rule in diabetes [25]. Shimodaira *et al.,* proposed an HbA1c cutoff of 5.7% (39 mmol/mol) for the threshold for prediabetes in the Japanese population with a sensitivity of 60.6% and specificity of 72.1% [26]. In the Chinese population, an optimal HbA1c cutoff of 5.7% (38 mmol/mol) was recommended with a sensitivity of 59.4% and specificity of 73.9% [27], whereas in the Korean population, an optimal HbA1c cutoff of 5.7% (39 mmol/mol) had a sensitivity of 48.6% and specificity of 65.7% for the detection of prediabetes [28]. In the Chinese, Japanese and Korean studies, it appears that HbA1c is not the best diagnostic tool for detecting prediabetes. The high false-negative results would suggest that a high proportion of prediabetic individuals, who could benefit from lifestyle intervention, would be overlooked during screening. However, our results showed a significantly higher sensitivity and specificity which suggest that

Table 2: Youden index, sensitivity, specificity, PPV, NPV and accuracy for detecting prediabetes and diabetes.

HbA1c (%)	HbA1c (mmol/mol)	Youden Index	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
≥5.5	≥37	0.301	95	35.1	15.7	98.2	40.7
≥5.6	≥38	0.414	95	46.4	18.4	98.6	50.9
≥5.7	≥39	0.503	90	60.3	22.4	97.9	63.1
≥5.8	≥40	0.616	90	71.6	28.8	98.3	73.4
≥5.9	≥41	0.645	80	84.5	39.7	97.1	84.1
≥6.0	≥42	0.637	75	88.7	45.7	96.5	87.4
≥6.1	≥43	0.683	75	93.3	58.8	96.7	91.6
≥6.2	≥44	0.704	75	95.4	67.3	96.8	93.5
≥6.3	≥45	0.674	70	97.4	77.6	96.2	94.9
≥6.4	≥46	0.635	65	98.5	84.3	95.7	95.3
≥6.5	≥48	0.59	60	99	88.1	95.1	95.3
≥6.6	≥49	0.545	55	99.5	93.1	94.6	95.3
≥6.7	≥50	0.545	55	99.5	93.1	94.6	95.3
≥6.8	≥51	0.445	45	99.5	91.8	93.4	94.4
≥6.9	≥52	0.395	40	99.5	90.8	92.9	93.9
≥7.0	≥53	0.345	35	99.5	89.6	92.3	93.5
≥7.1	≥54	0.328	33.3	99.5	89.2	92.1	93
≥7.2	≥55	0.3	30	100	100	91.8	93.5

Table 3: Agreement between FPG and HbA1c in predicting prediabetes and diabetes.

(a) Weighted kappa (κ): 0.19 (95% CI: 0.10-0.28)

	Diagnosis based on Fasting Plasma Glucose	
Diagnosis based on HbA1c ≥5.7% (≥39 mmol/mol)	Normal	Prediabetes and Diabetes
Normal	117	2
Prediabetes and Diabetes	77	18

(b) Weighted kappa (κ): 0.65 (95% CI: 0.48-0.82)

	Diagnosis based on Fasting Plasma Glucose	
Diagnosis based on HbA1c ≥6.2% (≥44 mmol/mol)	Normal	Prediabetes and Diabetes
Normal	185	5
Prediabetes and Diabetes	9	15

HbA1c is an excellent screening tool for prediabetes and diabetes in the multiethnic Singaporean population.

The strength of this study is that the ethnicity composition of the study subjects fairly accurately reflects the actual Singaporean ethnic distribution. This allowed us to propose a single HbA1c cutoff for the screening of prediabetes. This study was performed on individuals without an established diagnosis of diabetes, allowing the results to be inferred to the general population. Unfortunately, we should mention that there are some limitations in the present study, such as inadequate sample size. Also, only a single point of measurement of FPG was taken, whereas the HbA1c signifies the average level of glycemia over several months. Failure to take into account the intra-individual variability of FPG may play a part in the discordance between HbA1c and FPG in the diagnosis of prediabetes and diabetes.

A systematic review concluded that HbA1c and FPG are both equally good as screening tools in detection of diabetes, but neither of the tests is useful in detecting prediabetes. Therefore, OGTT still has a role in the diagnosis of prediabetes [29]. By considering the use of HbA1c and harnessing the advantage of sampling at any time of the day, as an additional screening tool for the detection of diabetes, we can capture a much larger population who would otherwise not be screened due to inability to take time off work or inconvenienced by the fasting requirement of glucose testing. Also, there are several multiple independent and highly powered studies highlighting that non-fasting lipids are similar or better than fasting samples for predicting risk of cardiovascular disease [30]. These are in line with the effort of the Singapore Government in promoting public health screening to detect and manage chronic diseases such as diabetes and hyperlipidemia.

Recently, the Singapore Ministry of Health released new diabetes screening test guidelines in March 2019 which supports the use of HbA1c as an alternative initial screening test for diabetes. Based on analyses of the 2010 National Health Survey data, HbA1c results ≤6.0% (42 mmol/mol) correlated well with a diagnosis of no diabetes, while HbA1c results ≥7.0% (53 mmol/mol) correlated well with a diagnosis of diabetes. A screening HbA1c result of between 6.1-6.9% would be consistent with prediabetes and would necessitate further testing with either a FPG or a 2-hr OGTT [31].

We conclude that our study findings were consistent with the recommendations of the latest health screening guidelines for prediabetes and diabetes from the Ministry of Health. Despite the small sample size of our study, the proposed HbA1c cutoff at 6.2% has similar sensitivity (75.0%) and specificity (95.4%) in screening for prediabetes and diabetes compared to 6.1% which has a sensitivity of 75.0% and specificity of 93.3%. We have also established that HbA1c can be used as an alternative to FPG as a screening tool for prediabetes and diabetes in the multiethnic Singaporean population.

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