Original Article

Cutoff value of HbA1c for predicting diabetes and prediabetes in a Chinese high risk population aged over 45

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Objective: To evaluate the cutoff value of HbA1c for predicting diabetes and prediabetes in a Chinese high risk population aged over 45. **Methods:** A total of 619 people aged over 45 without diabetes were randomly recruited to complete the Finnish Diabetes Risk Score (FINDRISC) questionnaire. 208 high-risk individuals (defined by Diabetes Risk Score ≥9) had OGTT and HbA1c determined at the same time. **Results:** In a Chinese population aged over 45, the best cutoff values of HbA1c for detecting diabetes and prediabetes were 5.8% and 5.4% respectively. The area under the receiver operating characteristic (AUROC) curve of HbA1c for detecting diabetes was 0.85 (95% CI: 0.80-0.90) and prediabetes was 0.62 (95% CI: 0.54-0.70). The combined use of HbA1c and fasting blood glucose (FPG) had a larger AUROC than HbA1c alone (0.88, 95%CI: 0.83-0.92 in detecting diabetes vs 0.75, 95% CI: 0.67-0.82 in prediabetes), and had a higher sensitivity in predicting diabetes and higher specificity and positive predictive value (PPV) in predicting prediabetes. However, the AUROC between HbA1c alone and combined use in predicting diabetes was not significantly different (p=0.173). **Conclusions:** FINDRISC is a feasible tool to screen people who are at high risk of diabetes. The cutoff values of HbA1c to diagnose diabetes and prediabetes in a Chinese high risk population aged over 45 were 5.8% and 5.4%, respectively. The sensitivity and specificity of HbA1c for detecting diabetes and prediabetes were relatively low, so that the combined use of HbA1c and FPG may be more effective in prediction.

Key Words: cutoff, HbA1c, diabetes, prediabetes, risk

INTRODUCTION

As the lifestyle factors are changing in China, the latest survey of Chinese Diabetes Association showed that the prevalence of diabetes in adults increased from 2.6% to 9.7% over the past decade.[1] Considerable evidence has shown that middle aged people were prone to suffer from hypertension, obesity dyslipidemia and etc,[2,3] which are risk factors of diabetes. Moreover, in China, the prevalence of prediabetes is 15.5%, accounting for 148.2 million adults with prediabetes.[4] However, two-thirds of individuals with diabetes remained undiagnosed in Mainland China.[5] Therefore, to identify diabetes and prediabetes in high-risk subjects is most important for the health care system.

In 2010, an HbA1c value of 6.5% was adopted to diagnose diabetes[6] and the data to decide the criteria of HbA1c were from three cross sectional epidemiological studies,[7] not including the data of Chinese population. However, HbA1c may vary by ethnic group,[8-11] and results from studies on the effect of age and HbA1c have been conflicting.[12-14] Several investigations have studied the cutoff values of HbA1c for detecting diabetes in Chinese people,[15-17] but to date there is no data on cutoff point of HbA1c for a Chinese high risk population aged over 45. In this study, we used FINDRISC questionnaire to screen people with high risk of diabetes and then identified the best cutoff value of HbA1c for predicting diabetes and prediabetes in high-risk individuals who were over 45 years old.

SUBJECTS

This was a cross sectional epidemiological survey in Haizhu District in Guangzhou between May 2009 and June 2010. Residents in five communities were randomly chosen in the study. Exclusion criteria were known diabe-

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tes, cancer, hepatic failure, renal failure, psychiatric disturbance, and other systemic medical conditions. Excluding the missing data, a total of 619 Chinese people aged over 45 without previously diagnosed diabetes participated in the survey. All participants were firstly expected to complete FINDRISC questionnaire which is a one-page questionnaire containing eight questions, with categorized answers, about age, BMI and waist circumstance (WC), family history of diabetes, history of antihypertensive drug treatment and impaired glucose tolerance (IGT), physical activity, and daily consumption of fruits or vegetables.[18] Subjects with a FINDRISC Score ≥9 were defined as people who were at high risk of diabetes.[19] Furthermore, 208 high-risk subjects were allocated to receive a standard oral glucose tolerance test (OGTT), a physical examination including body height, weight, WC, hip circumstance (HC) and blood pressure, a collection of blood samples to determine the levels of fasting plasma glucose (FPG), two-hour postprandial plasma glucose (2h PG), glycated haemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Each participant gave written informed consent. The study had been approved by the local ethics committee (Zhujiang Hospital, Southern Medical University, Ethics Approval Number: 2007-NFMK-001).

MATERIALS AND METHODS

Measurements

Participants had a physical examination including measurement of body height, weight, WC, HC, and blood pressure. Body height and weight were measured with the participants minimally clothed, without shoes, in a standing position and BMI (kg/m^2) was calculated. WC was measured at midpoint between lower border of the rib cage and iliac crest at the end of a normal expiration. HC was measured at the horizontal of pubic symphysis. Blood pressure was measured twice by a doctor with a standard mercury sphygmomanometer on the non-dominant arm, with subjects seated after rest for at least 15 minutes. FPG was tested after 10 hours overnight fast and the blood sample was obtained 120 minutes after OGTT. Plasma glucose concentrations were determined by glucose oxidase method. TG, TC, HDL-C and LDL-C were determined enzymatically by an Abbott Aeroset biochemical analyzer. HbA1c was measured by high-performance liquid chromatography (HLC-723GHbG7; Tosoh Inc, Japan).

Definitions

The diagnosis of diabetes and impaired glucose regulation (IGR) were previously defined based on the 1999 World Health Organization (WHO) diagnostic criteria.[20] IGR included impaired fasting glucose (6.1 mmol/L≤FPG<7.0 mmol/L) as well as impaired glucose tolerance (7.8 mmol/L≤FPG<11.1 mmol/L). Individuals with IGR have been referred to as having prediabetes.[6] Diabetes and IGR were determined based on an OGTT.

Statistical analysis

The test of characteristics of the subjects were analyzed using SPSS software version 13.0 and the cutoff points of the indicators and area under receiver operating characteristic (AUROC) curve were calculated using MedCalc software version 9.6.2.0. Quantitative variables were expressed as means±standard deviation (SD). Categorical variables were expressed as percentages. One-way analysis of variance (ANOVA) was used to compare continuous variables. Bonferroni's correction was used for multiple comparisons. The combined use of HbA1c and FPG to detect diabetes and prediabetes was obtained by logistic models. Performance of HbA1c and the composite indicators were tested using receiver operating characteristic (ROC) curve analysis. Usefulness of a test was assessed by sensitivity, specificity, likelihood ratios (LRs), AUROC and predictive value (PV). The best cutoff point was determined as the value closest to the upper left-hand corner of the ROC curve, and was determined where the test characteristics were maximized. In a trade-off between sensitivity and specificity, sensitivity was prioritized over specificity as much as possible for the purpose of screening. Positive/negative PV (PPV/NPV) is defined as the proportion of those with a positive/negative test result who actually has/does not have disease. According to Hosmer and Lemeshow,[21] an AUROC value between 0.7 and 0.8 is considered "acceptable", and one between 0.8 and 0.9 "excellent" discrimination. A value of $p<0.05$ was considered statistically significant in all analyses.

RESULTS

Of the total 619 participants who were aged more than 45, 208 (33.6%) were at high risk of diabetes (86 men and 122 women). Of the 208 subjects, 69 (33.2%) had NGT (normal glucose tolerance), 84 (40.4%) had prediabetes, 55 (26.4%) had diabetes. Table 1 shows the clinical characteristics of the participants.

Subjects were divided into three groups on the basis of the results of OGTT. We found no differences in age, BMI, WC, HC, TG, HDL-C, systolic blood pressure (SBP) and diastolic blood pressure (DBP) among subjects with NGT, prediabetes and diabetes. Compared with subjects with diabetes, those with prediabetes had lower values of TC ($p=0.009$), LDL-C ($p=0.027$) and HbA1c ($p<0.001$). Compared with subjects with NGT, those with diabetes and prediabetes had higher value of HbA1c ($p<0.001$).

The AUROC curve shown in Figure 1-a and Figure 1-b represented the diagnostic accuracy of HbA1c, FPG, the combined use of HbA1c and FPG for diabetes and prediabetes. The best cutoff point of HbA1c for detecting diabetes and prediabetes in these high-risk subjects was 5.8% and 5.4%, respectively. The AUROC of HbA1c for detecting diabetes was 0.85 (95% CI: 0.80-0.90) with a sensitivity of 0.73 (95% CI: 0.59-0.84), a specificity of 0.88 (95% CI: 0.81-0.93) and for prediabetes was 0.62 (95% CI: 0.49-0.72) with a sensitivity of 0.61 (95% CI: 0.49-0.72), and a specificity of 0.58 (95% CI: 0.46-0.70). The combined use of HbA1c and FPG had larger AUROC than HbA1c alone (0.88, 95% CI: 0.83-0.92 in detecting diabetes vs 0.75, 95% CI: 0.67- 0.82 in prediabetes), and had higher sensitivity in predicting diabetes and higher specificity and PPV in prediabetes. However, the AUROC between HbA1c alone and combined use in predicting diabetes were not statistically different ($p=0.173$). The sensitivity of FPG alone was lowest among the three

methods, both in predicting diabetes and prediabetes (Table 2).

DISCUSSION

In the past 20 years, China has undergone rapid social and economic changes. The lifestyle and dietary habits of its people have also been changing, and the rates of diabetes, obesity, and other chronic conditions have increased dramatically over the past decades.[22] A national survey conducted in 1994 showed that the prevalence of diabetes and impaired glucose tolerance were 2.5% and 3.2%, respectively.[23] However, according to a study from June 2007 through May 2008, Yang et al found that 92.4 million adults 20 years of age or older (9.7% of adult population) have diabetes; 148.2 million adults (15.5%) have prediabetes. Further, the prevalence of diabetes and prediabetes increased with increasing age.[24] As society has aged, the proportion of the population in China aged 60 or above has exceeded 10% since 2000 and it is estimated that the population will reach 18% by 2025.[25] As a result, the prevalence of diabetes and prediabetes in older persons might increase dramatically. Nevertheless, it was still found that more than two in five cases with diabetes were undiagnosed.[26] Therefore, effective measurements should be taken for screening individuals who are at high risk of diabetes especially in middle aged and elderly persons. FINDRISC is a widely used, simple tool for identification of those at risk for diabetes and prediabetes. There were several projects already ongoing in different countries, using risk scores for identification of diabetic high-risk subjects.[27-32] With optimal cutoff level, the FINDRISC identified 66% men and 70% women of previously undiagnosed patients with type 2 diabetes.[18] Tankova et al found that, depending on the cutoff point chosen, the FINDRISC recognized undetected diabetes and prediabetes fairly well.[33] In our study, the high-risk subjects were based on Diabetes Risk Score ≥9.[19] Besides, HbA1c, which does not require patients to be fasting and reflects longer-term glycemia than does plasma glucose,[34] is more convenient for screening diabetes than plasma glucose. The aim of our study was to identify the optimal thresholds of HbA1c for detecting diabetes and prediabetes in middle aged and elderly individuals who may be at higher risk and to assess the performance of HbA1c in evaluating glucose tolerance.

Our results showed that with scoring 9 and above, the FINDRISC identified 40% subjects with prediabetes, and 26% with diabetes. The level of HbA1c increased significantly in the process of progression from NGT to prediabetes and diabetes. We found that compared with those with NGT, the value of HbA1c was higher in subjects with diabetes and prediabetes ($p<0.001$). Furthermore, compared with those with diabetes, the value of HbA1c in subjects with prediabetes was lower ($p<0.001$). The AUROC values of HbA1c for detecting diabetes and prediabetes were 0.85 (95% CI: 0.80-0.90) and 0.62 (95% CI: 0.54-0.70), respectively. The cutoff point of HbA1c for predicting diabetes was 5.8%, with a sensitivity of 0.73, and a specificity of 0.88. The optimal threshold of HbA1c for prediabetes was 5.4% with a sensitivity of 0.61, and a specificity of 0.58. However, the AUROC of HbA1c for detecting prediabetes was smaller than the "acceptable" discrimination and the sensitivity and the specificity of HbA1c for predicting diabetes and prediabetes were relatively low. As a result, the combined use of HbA1c and FPG was calculated in this study. The combined indicator had larger AUROC values than HbA1c alone (0.88, 95% CI: 0.83-0.92 in detecting diabetes vs 0.75, 95% CI: 0.67-0.82 in prediabetes). Furthermore, the combined use had higher sensitivity in predicting diabetes and higher specificity and PPV in prediabetes. Nevertheless, the AUROC between HbA1c alone and combined use in predicting diabetes were not statistically different ($p=0.173$), and the sensitivity of FPG alone was lowest among the three methods both in predicting diabetes and prediabetes.

Other investigations had reported similar results about

Table 1. Clinical characteristics of participants

Characteristics	NGT	Diabetes	Prediabetes
Total number (n)	69	55	84
Men/women (n)	30/39	26/29	30/54
Age (years)	67.0 (8.2)	69.8 (9.1)	70.1 (7.9)
FPG (mmol/L)	5.2 (0.5)	7.1 (1.9)§	5.7 (0.6)§¶
2h-PPG (mmol/L)	6.3 (1.0)	15.0 (4.0)§	9.0 (1.0)§¶
HbA1c (%)	5.4 (0.4)	6.5 (1.2)§	5.5 (0.4)¶
BMI (kg/m^2)	26.5 (2.75)	26.5 (3.17)	26.8 (3.47)
WC (cm)	89.5 (7.0)	90.0 (7.4)	89.7 (8.9)
HC (cm)	100 (6.4)	99.1 (6.1)	99.7 (7.0)
TC (mmol/L)	5.31 (1.51)	5.76 (1.21)	5.03 (1.43)†
TG (mmol/L)	1.96 (1.41)	2.39 (2.01)	2.36 (1.84)
LDL-C (mmol/L)	3.62 (1.01)	3.70 (1.00)	3.26 (0.89)‡
HDL-C (mmol/L)	1.43 (0.33)	1.37 (0.34)	1.40 (0.33)
SBP (mmHg)	139 (19.2)	140 (19.8)	140 (19.1)
DBP (mmHg)	80.2 (10.6)	78.4 (10.2)	81.8 (9.8)
Patients with a family history of diabetes-NO (%)	3 (4.8)	4 (7.3)	4 (4.8)
Patients had anti-hypertensive drugs-NO (%)	31 (49.2)	33 (60.0)	52 (61.9)
Patients participated in physical activities-NO (%)	33 (52.4)	50 (54.5)	53 (63.1)
Patients had vegetables-NO (%)	42 (66.7)	41 (74.5)	68 (81.0)

Values are mean(SD) unless stated otherwise. †$p=0.009$ versus diabetes, ‡$p=0.027$ versus diabetes, §$p<0.001$ versus NGT, ¶$p<0.001$ versus diabetes.

Table 2. Test characteristics (95% CIs) maximized under the best cut-off point in the entire population for predicting diabetes and prediabetes

	Sen	Spec	PPV	NPV	LR+	LR-	AUROC
Cut-off points for predicting diabetes: HbA1c 5.8%, FPG 6.4 mmol/L							
HbA1c	0.73 (0.59, 0.84)	0.88 (0.81, 0.93)	0.69 (0.56, 0.81)	0.89 (0.83, 0.94)	5.86 (4.9, 7.0)	0.31 (0.2, 0.6)	0.85 (0.80, 0.90)
FPG	0.58 (0.44, 0.71)	0.95 (0.89, 0.98)	0.80 (0.64, 0.91)	0.86 (0.79, 0.91)	10.6 (8.4, 13.2)	0.44 (0.2, 0.9)	0.84 (0.78, 0.88)[†]
HbA1c plus FPG	0.84 (0.71, 0.92)	0.82 (0.75, 0.88)	0.64 (0.52, 0.75)	0.93 (0.87, 0.97)	4.66 (4.1, 5.4)	0.20 (0.1, 0.4)	0.88 (0.83, 0.92)[‡]
Cut-off points for predicting prediabetes: HbA1c 5.4%, FPG 5.6 mmol/L							
HbA1c	0.61 (0.49, 0.72)	0.58 (0.46, 0.70)	0.61 (0.49, 0.72)	0.57 (0.45, 0.69)	1.44 (1.1, 1.9)	0.68 (0.5, 1.0)	0.62 (0.54, 0.70)
FPG	0.47 (0.36, 0.59)	0.86 (0.75, 0.93)	0.78 (0.64, 0.89)	0.60 (0.49, 0.69)	3.27 (2.5, 4.2)	0.62 (0.3, 1.1)	0.73 (0.65, 0.80)[§]
HbA1c plus FPG	0.61 (0.49, 0.72)	0.77 (0.65, 0.86)	0.74 (0.62, 0.85)	0.64 (0.53, 0.74)	2.61 (2.1, 3.3)	0.51 (0.3, 0.9)	0.75 (0.67, 0.82)[¶]

CI: confidence interval; FPG: fasting plasma glucose; LR+; positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; Sen: sensitivity; Spec: specificity.

[†]FPG vs HbA1c: p=0.681; [‡]HbA1c plus FPG vs HbA1c: p=0.173.

[§]FPG vs HbA1c: p=0.061; [¶]HbA1c plus FPG vs HbA1c: p=0.01.

HbA1c for detecting diabetes. The optimal threshold for HbA1c of 5.9% was found in a Canadian multiethnic population.[35] The National Health and Nutrition Examination Survey found that an HbA1c value of 6.5% was an optimal threshold for identifying diabetes in the US population.[36] A study from Japanese population showed that the HbA1c threshold of 6.1% was suitable for detecting undiagnosed diabetes.[11] Bao YQ et al concluded that an HbA1c threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults.[15] On the other hand, similar results of HbA1c for detecting prediabetes had been reported. The International Expert Committee noted that those with HbA1c levels ranging from 6.0% to 6.4% were at very high risk of developing diabetes.[37] American Diabetes Association in 2010 considered an HbA1c range of 5.7% to 6.4% as identifying individuals who were prediabetes.[38] Tankova et al demonstrated that the cutoff level of HbA1c for diagnosing prediabetes was 5.5% with a sensitivity of 86% and a specificity of 92%.[39] Data from Japan found that baseline HbA1c of 5.8% or greater imposed a 10-fold increase in diagnosed diabetes over next 7 years.[40] Yang et al found that the measurement of HbA1c may be efficient to diagnose prediabetes with the cutoff point of 5.9% in Chinese high risk people.[17]

Concerning the results, it should be considered that there were differences between the present study and previous investigations. Firstly, we focused on the high-risk Chinese individuals (determined by FINDRISC ≥9), but most previous studies, while finding the threshold of HbA1c for predicting diabetes and/or prediabetes in total population, had failed to focus on the people with high risk for diabetes. Secondly, compared with previous studies, the subjects in the study were above 45 years of age. Thirdly, the environment and lifestyle of people in Guangzhou is different from other populations, which may contribute to the distinctions. People in Guangzhou are thinner than those in Chinese northern cities and populations in other countries, which might result in lower value of HbA1c. In addition, the high-risk individuals were based on Diabetes Risk Score ≥9 in present study, which was different from some other studies.[28,30,32]

Limitations of the current study cannot be ignored. Inadequate sample size may have an effect on the outcome. The high-risk subjects in five communities is unlikely represent the Chinese population with high risk of diabetes, and the sensitivity and specificity of HbA1c to predict diabetes and prediabetes in this sample of subjects was relatively low and the combined use of HbA1c and FPG may be more effective for prediction to some extent. Moreover, it was a cross sectional study, so that similar epidemiological and clinical studies are needed to confirm and modify the results we found.

In conclusion, FINDRISC is a feasible, inexpensive, non-invasive tool to find asymptomatic high-risk subjects of diabetes. In a Chinese high risk population aged over 45, the optimal cutoff value of HbA1c for detecting diabetes was 5.8% with a sensitivity of 0.73, and a specificity of 0.88 and for prediabetes was 5.4% with a sensitivity of 0.61, and a specificity of 0.58. However, the sensitivity and specificity of HbA1c for detecting diabetes and prediabetes was relatively low, so that confirmation of the diagnosis by an additional plasma glucose measurement should be considered.

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AUTHOR DISCLOSURES

There are no conflicts of interests.

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Original Article

Cutoff value of HbA1c for predicting diabetes and prediabetes in a Chinese high risk population aged over 45

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糖化血红蛋白在中国45岁以上糖尿病高危人群糖尿病及糖尿病前期诊断的界点

目的：探讨糖化血红蛋白（HbA1c）在中国中老年糖尿病高危人群中是否存在诊断糖尿病及糖尿病前期的界点。**方法**：随机抽取广州市5个社区619名45岁或以上的中老年人填写芬兰糖尿病风险积分表（FINDRSC），积分≥9分定义为糖尿病高危人群。随后对筛查出的糖尿病高危人群（共208例）进行生化指标的检测，同时使用口服葡萄糖耐量试验（OGTT）及HbA1c诊断糖尿病及糖尿病前期，使用受试者工作特征（ROC）曲线下面积判断HbA1c或HbA1c联合空腹血浆血糖（FPG）在诊断糖尿病及糖尿病前期的诊断效能。**结果**：在这组糖尿病高危人群中，HbA1c诊断糖尿病及糖尿病前期的界值分别为5.8%及5.4%，其ROC曲线下面积分别为0.85（95% CI：0.80-0.90）及0.62（95% CI：0.54-0.70）；而HbA1c联合FPG诊断糖尿病及糖尿病前期的ROC曲线下面积均比前者大，且在诊断糖尿病中具有更高的灵敏度，而在诊断糖尿病前期中具有更高的特异度及阳性预测值。但是单用HbA1c或联合FPG诊断糖尿病的ROC曲线下面积之间差异无统计学意义（p=0.173）。**结论**：FINDRSC是筛查糖尿病高危人群的有效量表。在中国45岁或以上的中老年糖尿病高危人群中HbA1c诊断糖尿病及糖尿病前期的界值分别为5.8%及5.6%，但是其特异度及敏感度相对较低，因此需要联合FPG增加其预测疾病的可靠性。

关键词：诊断界值、糖化血红蛋白、糖尿病、糖尿病前期、风险