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Original Article

Use of glycated haemoglobin A_1c for diagnosing diabetes in Chinese subjects aged over 50 years-community based observation

Shuo Lin[1], Xiaofeng Li[2], Ping Li[3], Li Hu[4], Keyi Lin[1], Longyi Zeng[1]

Departments of [1]Endocrinology, [2]Pediatrics, [3]Gynaecology and Obstetrics, 3rd Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China; [4]Department of Endocrinology, The First Hospital of Changsha, China

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Abstract: Background: The performance of glycated haemoglobin A_1c (HbA_1c) for diagnosing diabetes in Chinese subjects remains uncertain. Our study aims to assess HbA_1c for the diagnosis of diabetes and identify the cut-point to be used in Chinese subjects aged over 50 years. Methods: From Oct 2010 to Jan 2011, we conducted a community-based cross-sectional survey in Shipai community, Guangzhou, China. A total of 1494 subjects over 50 years old were recruited. Each subject completed a uniform questionnaire and had a physical examination. Fasting blood samples were obtained to measure plasma glucose and HbA_1c. Diabetes is defined as fasting plasma glucose (FPG) of at least 7.0 mmol/L. One hundred and sixty-one subjects with diagnosed diabetes and 21 with missing data were excluded and data of 1312 subjects were analysed. Receiver operating characteristics (ROC) curve were plotted to assess the sensitivity and specificity of HbA_1c for diagnosing diabetes. Results: Among 1312 subjects, 53 subjects (4.0%) had diabetes, 88 subjects (6.7%) had IFG, 10.7% had hyperglycemia (diabetes plus IFG). According to the ROC curves, the area under the curve for HbA_1c in diagnosing diabetes was 0.945 (0.931-0.957). An HbA_1c threshold of 48 mmol/mol (6.5%) showed the highest combination of sensitivity (83.3%) and specificity (96.0%) for diagnosing diabetes. Conclusion: An HbA_1c threshold of 48 mmol/mol (6.5%) could be used for diagnosing diabetes in Chinese aged over 50 years. This threshold may be proper as a diagnostic criterion for diabetes in Chinese over 50 years old.

Keywords: Glycated haemoglobin, diabetes, diagnosis, impaired fasting glucose

Introduction

In China, more than 60% of diabetic patients are undiagnosed [1, 2]. More efficient methods to detecting diabetes need to be developed to improve the health care of diabetes. The widely used diagnostic tool for diabetes is fasting plasma glucose (FPG) or 2-h plasma glucose (2-hPG) during an oral glucose tolerance test (OGTT) by using 75 g anhydrous glucose [3]. The main limitations of these two methods are their poor reproducibility, difficulty in confirming a fasting status and special requirements for the OGTT [4].

Recently, several studies show that glycated haemoglobin A_1c (HbA_1c) may be useful for diagnosis of diabetes. American diabetes association (ADA), World Health Organization (WHO) and IDF subsequently adopted the use of the HbA_1c measurement as one of the diagnostic criteria [5-7]. However, the optimal HbA_1c threshold for detecting diabetes may vary by ethnic group and age [8-10]. The performance of HbA_1c in detecting diabetes and/or impaired fasting glucose (IFG) remains uncertain in Chinese subjects over 50 years old. The objective of this study was to evaluate HbA_1c in diagnosing diabetes and identified the optimal cut-point to be used in Chinese subjects aged over 50 years in a community-based setting.

Materials and methods

Study design and subjects

We conducted a community-based cross-sectional survey from Oct 2010 to Jan 2011 in

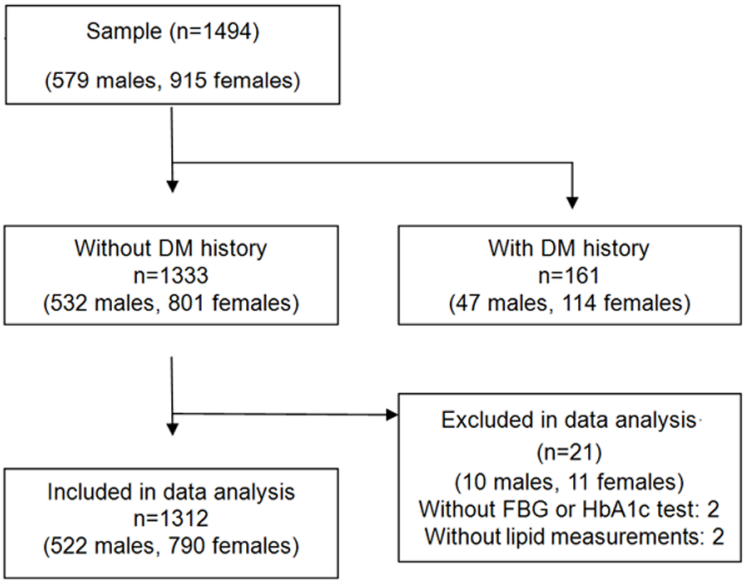

Figure 1. Flow diagram of recruitment of participants.

Shipai community, Guangzhou, Guangdong province, China. There were 2052 individuals aged over 50 years in this community. We investigated a total of 1494 subjects (72.8%). The survey was approved by the ethics committee of the 3rd affiliated hospital of Sun Yat-sen university. All subjects gave written informed consent prior to the survey.

Assessment

All subjects finished a questionnaire containing information about the medical history and treatment. Details of the study have been published elsewhere [11]. Each subject completed a physical examination including measurement of height, weight, waist circumference, and blood pressure. Fasting blood samples were obtained to measure blood lipids, plasma glucose and HbA$_1$c.

Detailed anthropometry (height, weight, and waist circumference) and blood pressure were taken using standard methods as previously reported [11]. We measured plasma glucose by the glucose oxidase method. We measured HbA$_1$c by using high performance liquid chromatography (D-10, BIO-RAD, America, reference range was 4.0-6.0%). The intra-assay and inter-assay coefficient of variation for HbA$_1$c was 0.46% and 0.53%, respectively. We measured blood lipids by using HITACHI 71-80 (Hitachi High-Tech Science Systems Corporation, Hitachinaka-shi, Japan).

Hypertension was diagnosed as systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or hypertension history diagnosed by a doctor or on anti-hypertensive treatment. The diagnostic criteria of diabetes and IFG were based on the 1999 WHO criteria [3]. Diabetes is defined as FPG of at least 7.0 mmol/L.

Statistical analysis

We performed statistical analysis by SPSS for windows 19.0. Continuous variables are presented as means (SD), except for skewed variables or medians (interquartile range). Categorical data were presented as number (percentage). We tested differences in continuous variables between groups by univariate analysis of variance (assuming a Gaussian distribution) or Kruskal-Wallis test (assuming a non-Gaussian distribution), and in categorical data by the chi-square test. We used Pearson correlation analysis to explore the association of HbA$_1$c with FPG; We plotted the receiver operating characteristic curve (ROC) to determine the optimal threshold for predicting diabetes or diabetes plus IFG. We considered a p value <0.05 as statistically significant for a two sided test.

Results

A total of 1494 subjects (72.8%) participated in the survey. After excluding 161 subjects (10.8%) with previously diagnosed diabetes and 21 with missing data (**Figure 1**), 1312 subjects had median age 60 years (interquartile range: 55-67 years), median FPG 5.0 mmol/L (interquartile range: 4.6-5.5 mmol/L), mean HbA$_1$c 5.8% (SD 0.76%), and were 60.2% female (**Table 1**). The characteristics of non-responsers (age and sex) were similar to the subjects investigated, which suggested that the investigated population were representative.

Among 1312 subjects, 53 subjects (4.0%) were diagnosed as diabetes, 88 subjects (6.7%)

Table 1. Characteristics of subjects according to levels of fasting plasma glucose

Characteristics	NFG	IFG	DM	Total
N (%)	1171 (89.3)	88 (6.7)	53 (4.0)	1312 (100.0)
Age (years)	60.0 (54.0-67.0)	62.0 (57.0-69.0)	60.0 (54.0-63.5)	60.0 (55.0-67.0)
Sex (female), % (n)	700 (59.8)	62 (70.5)	28 (52.8)	790 (60.2)
Body mass index (kg/m^2)	23.9 (21.7-26.1)	25.7 (23.8-28.1)**	26.1 (23.9-28.2)**	24.0 (21.9-26.4)
Waist circumference (cm)	86.0 (79.5-92.0)	89.8 (85.1-95.0)**	92.0 (85.8-99.0)**	86.5 (80.0-92.4)
Systolic blood pressure (mmHg)	132 (120-148)	142 (125-154)**	141 (125-153)	133 (120-148)
Diastolic blood pressure (mmHg)	80 (75-86)	83 (77-90)**	80 (75-88)	80 (75-87)
Total cholesterol (mmol/l)	5.80 (5.11-6.53)	6.04 (5.43-6.73)	6.03 (5.38-6.90)	5.83 (5.13-6.55)
Triglycerides (mmol/l)	1.82 (1.28-2.69)	2.20 (1.50-3.45)**	2.22 (1.71-3.95)**	1.85 (1.31-2.75)
HDL-c (mmol/l)	1.42 (1.22-1.67)	1.38 (1.19-1.56)	1.27 (1.11-1.64)	1.41 (1.21-1.66)
LDL-c (mmol/l)	3.64 (3.01-4.25)	3.88 (3.15-4.48)	3.65 (3.04-4.50)	3.66 (3.01-4.25)
Fasting plasma glucose (mmol/l)	4.9 (4.5-5.3)	6.5 (6.3-6.7)**	8.3 (7.6-11.4)**,##	5.0 (4.6-5.5)
HbA_1c (mmol/mol)	39 (37-42)	44 (41-48)**	58 (49-70)**,##	40 (5.2)
(%)	5.7 (5.5-6.0)	6.2 (5.9-6.5)**	7.5 (6.6-8.6)**,##	5.8 (0.76)

**compared with NFG group, P<0.01, ##: compared with IFG group, P<0.01. NFG: normal fasting plasma glucose, IFG: impaired fasting plasma glucose, DM: diabetes mellitus.

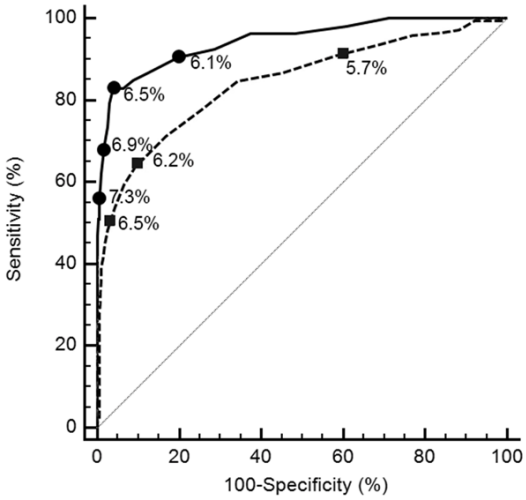

Figure 2. Receiver operating characteristic curves for glycated haemoglobin to diagnose diabetes (●), diabetes plus impaired fasting glucose (■). The area under the curve for HbA_1c in diagnosing diabetes and hyperglycemia (diabetes plus IFG) were 0.945 (95% CI 0.931-0.957) and 0.850 (95% CI 0.829-0.869) respectively. An HbA_1c threshold of 48 mmol/mol (6.5%) showed the highest combination of sensitivity (83.0%) and specificity (96.0%) for diagnosing diabetes. At an optimal cut-off point of ≥44 mmol/mol (6.2%), the sensitivity was 64.5% and specificity 90.5% for diagnosing hyperglycemia.

were diagnosed as IFG, 10.7% were identified as hyperglycemia (diabetes plus IFG). Mean HbA_1c in subjects with normal FPG (<6.1 mmol/L) was 5.7 (SD 0.4). **Table 1** shows the characteristics of subjects according to levels of FPG. Individuals with DM had highest level of FPG and HbA_1c than in individuals with IFG and normal FPG. The level of BMI, WC, triglyceride (TG) and proportions of BMI≥25 and hypertension were higher in individuals with IFG and DM than that in individuals with normal FPG. HbA_1c was significantly positively correlated with FPG (correlation coefficient was 0.785, P<0.001).

According to the receiver operating characteristics curve (**Figure 2**), the area under the curve for HbA_1c in diagnosing diabetes and hyperglycemia (diabetes plus IFG) were 0.945 (95% CI 0.931-0.957) and 0.850 (95% CI 0.829-0.869) respectively. An HbA_1c threshold of 48 mmol/mol (6.5%) showed the highest combination of sensitivity (83.0%) and specificity (96.0%) for diagnosing diabetes (with a highest Youden's index of 0.791). At an optimal cut-off point of ≥44 mmol/mol (6.2%), the sensitivity was 64.5% and specificity 90.5% for diagnosing hyperglycemia (with a highest Youden's index of 0.551). At an optimal cut-off point of ≥41 mmol/mol (5.9%), the sensitivity was 78.4% and specificity 63.1% for diagnosing IFG alone (ROC curve not shown). The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for identifying diabetes at HbA_1c thresholds of 1, 2, 3, and 4 standard deviations (0.4%) above the mean of normal FPG (5.7%) are shown in **Table 2**. As the number of standard deviations increased, sensitivity

Table 2. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for detecting diabetes with different HbA_1c thresholds. Values in parentheses are 95% confidence intervals

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
HbA_1c threshold (%)						
6.1 (1SD above normal mean)	90.6 (79.3-96.9)	80.3 (78.0-82.5)	16.2 (12.2-20.9)	99.5 (98.9-99.8)	4.6 (4.2-5.0)	0.1 (0.1-0.3)
6.3*	84.9 (72.4-93.3)	91.2 (89.5-92.7)	28.8 (21.9-36.6)	99.3 (98.6-99.7)	9.6 (8.6-10.8)	0.2 (0.1-0.3)
6.5 (2SD above normal mean)	83.0 (70.2-91.9)	96.0 (94.8-97.0)	46.8 (36.4-57.4)	99.3 (98.6-99.7)	20.9 (18.5-23.6)	0.2 (0.1-0.3)
6.9 (3SD above normal mean)	67.9 (53.7-80.1)	98.3 (97.5-99.0)	63.2 (49.2-75.7)	98.6 (97.8-99.2)	40.7 (33.8-49.0)	0.3 (0.2-0.6)
7.3 (4SD above normal mean)	56.6 (42.3-70.2)	99.4 (99.8-99.7)	78.9 (62.4-90.6)	98.2 (97.3-98.9)	89.1 (70.4-112.8)	0.4 (0.2-0.9)

*Threshold reported by Yuqian Bao et al. [9]. PPV: positive predictive value, NPV: negative predictive value, +LR: positive likelihood ratio, -LR: negative likelihood ratio.

Table 3. Distribution of participants with normal fasting glucose, IFG and diabetes stratified by different HbA_1c thresholds. Values are numbers (percentages)

HbA_1c mmol/mol, (%)	Fasting blood glucose		
	NFG (n, %)	IFG (n, %)	DM (n, %)
≥39 (5.7)	690 (58.9)	77 (87.5)	52 (98.1)
≥42 (6.0)	300 (25.6)	61 (69.3)	49 (92.5)
≥43 (6.1)	195 (16.7)	53 (60.2)	48 (90.6)
≥44 (6.2)	111 (9.5)	45 (51.1)	46 (86.8)
≥45 (6.3)	72 (6.1)	39 (44.3)	45 (84.9)
≥48 (6.5)	26 (2.2)	24 (27.3)	44 (83.0)

NFG: normal fasting plasma glucose, IFG: impaired fasting plasma glucose, DM: diabetes mellitus.

decreased and specificity increased. An HbA_1c threshold of 1 SD above the normal mean (43 mmol/mol, 6.1%) showed a very high sensitivity of 90.6% (74.7%-94.5%) and a high specificity of 80.3% (78.0%-82.5%) for detecting undiagnosed diabetes. A high sensitivity of 83.0% (70.2%-91.9%) and a very high specificity of 96.0% (94.8%-97.0%) were achieved at an HbA_1c threshold of 48 mmol/mol (6.5%) (2 SD above the normal mean), together with a low negative likelihood ratio of 0.2 (0.1-0.3), a high positive likelihood ratio of 46.8 (36.4-57.4), and a negative predictive value of 99.3% (98.6%-99.7%).

Distribution of individuals with normal FPG (NFG), IFG and diabetes stratified by different HbA_1c thresholds are shown in **Table 3**. Of the 94 participants with HbA_1c of 48 mmol/mol (6.5%) or above, 26 (2.2%) had normal FPG, 24 (27.3%) had IFG, and 44 (83.0%) were diagnosed with diabetes according to the 1999 WHO criteria. In contrast, of the 296 subjects with HbA_1c≥43 mmol/mol (6.1%), 195 (16.7%) had normal glucose tolerance, 53 (60.2%) had IFG, and 48 (90.6%) were diagnosed as having diabetes.

Discussion

In the present study, we demonstrate that an HbA_1c threshold of 48 mmol/mol (6.5%) is both sensitive and specific for detecting undiagnosed diabetes as defined by a FPG level ≥7.0 mmol/L in a Chinese community population aged over 50 years. This threshold is the same as that recommended by ADA, IDF and WHO [4-7].

The prevalence of diabetes has dramatically increased in recent years in China. However, by current screening or diagnostic tests, more than 60% of patients with diabetes may be undiagnosed in China [1, 2]. The diagnosis of diabetes is classically based on FPG or 2-hPG during OGTT. Both of these two methods are poor reproducible and need a fasting status. In addition, OGTT is time-consuming and requires special preparation. To simplify the test procedure and identify those at high microvascular disease risk, HbA_1c has been recommended as one criterion for diagnosing diabetes [4, 5, 9, 12-15].

In this study, an HbA_1c level of 48 mmol/mol (6.5%) showed an optimal combination of sensitivity (83.0%) and specificity (96.0%) for diagnosis of diabetes. This threshold was very close to the reported optimal HbA_1c threshold of 45 mmol/mol (6.3%) in Chinese subjects [9, 16], and 46 mmol/mol (6.4%) in Asian Indians [17], but higher than the results reported by Bennett CM *et al.* [14] in 1999-2004 National Health and Nutrition Examination Survey (NHANES) population (40 mmol/mol, 5.8%), Shimodaira M *et al.* [18] in Japanese subjects (42 mmol/mol,

6.0%). The optimal threshold in our study seem to be the highest one compared with those of other studies. The sensitivity of this threshold was higher to that reported by Yuqian Bao *et al.* [9] in 4886 Chinese adults (a sensitivity of 62.8% was reported), while the specifity was similar to that of the latter study (a specifity of 96.1% was reported). However, various sensitivities and specificities at different HbA_1c thresholds in diverse studies may due to different study subjects, ethnicity and assay methods [19-22]. Other factors such as aging [10], haemoglobin glycation and/or erythrocyte survival [19, 23] could affect the HbA_1c assay in addition to heritable factors [24]. HbA_1c levels are positively associated with age in nondiabetic populations in the Framingham Offspring Study (FOS) and National Health and Nutrition Examination Survey (NHANES) 2001-2004 [10]. Yang L *et al.* reported the cut-off points of HbA_1c for diagnosing diabetes in different age groups (18-39, 40-49, 50-59, 60-69 and ≥70 years) were 43 mmol/mol (6.1%), 45 mmol/mol (6.3%), 46 mmol/mol (6.4%), 48 mmol/mol (6.5%) and 46 mmol/mol (6.4%) in Chinese subjects, respectively [25]. These studies suggested HbA_1c threshold for diagnosing diabetes may varied in different age groups. In our study population with older age, higher level of FPG and HbA_1c, HbA_1c test could identify a high proportion of individuals with diabetes. This suggests HbA_1c is suitable for diagnosing undiagnosed diabetes in older high-risk individuals. Base on its strong association with micro-vascular complications [21], lower pre-analytical and biological variation, and no need for fasting [4], the utility of HbA_1c for diagnosing diabetes in this population should be recommended.

In this present study, we found that an HbA_1c threshold of 43 mmol/mol (6.1%) provided the optimal sensitivity (90.6%) and specifity (80.3%) for screen for diabetes. This cut point was similar to the cut point reported by Kumar PR *et al.* (43 mmol/mol, 6.1%) [15], and close to the cut point recommended by an international expert committee (42 mmol/mol, 6.0%) [4].

The strength of this study was that we evaluated HbA_1c for the diagnosis of diabetes and IFG in a Chinese community population. There were several limitations in our study. First, the subjects were diagnosed by FPG level instead of performing OGTT, which may underestimate the prevalence of undiagnosed diabetes. However, by FPG≥7.0 mmol/l could detect more than 50-70% patients with diabetes. Therefore, most of the diabetic patients would be detected by the screening algorithm we used. Second, about one quarter of subjects didn't participate in the survey, which may affect the HbA_1c threshold results. However, the clinical characteristics of non-responsed subjects were similar to that of the subjects investigated (data not shown). This may partly indicate that the subjects were representative sample of all subjects. Finally, our study only included subjects aged over 50 years in a Chinese community, which may restrict the application of study conclusion. Further investigations should be performed to prove our findings.

In summary, an HbA_1c threshold of 48 mmol/mol (6.5%) could be used for diagnosing diabetes in Chinese adults over 50 years old in community setting. This HbA_1c cut-point may be used as a diagnostic criterion for diabetes in Chinese subjects aged over 50 years when FPG and OGTT are not available.

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Disclosure of conflict of interest

None.

Address correspondence to: Longyi Zeng, Department of Endocrinology, The 3rd Affiliated Hospital Of Sun Yat-sen University, No.600, Tianhe Road, Guangzhou 510630, China. Tel: +86 13560044754; E-mail: longyi_zeng@163.com

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