BMJ

RESEARCH

Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey

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Cite this as: *BMJ* 2010;340:c2249
doi:10.1136/bmj.c2249

ABSTRACT

Objectives To evaluate haemoglobin A1c (HbA_{1c}) in diagnosing diabetes and identify the optimal HbA_{1c} threshold to be used in Chinese adults.

Design Multistage stratified cross sectional epidemiological survey.

Setting Shanghai, China, 2007-8.

Participants 4886 Chinese adults over 20 years of age with no history of diabetes.

Main outcome measures Performance of HbA_{1c} at increasing thresholds for diagnosing diabetes.

Results The area under the receiver operating characteristics curve for detecting undiagnosed diabetes was 0.856 (95% confidence interval 0.828 to 0.883) for HbA_{1c} alone and 0.920 (0.900 to 0.941) for fasting plasma glucose alone. Very high specificity (96.1%, 95% confidence interval 95.5% to 96.7%) was achieved at an HbA_{1c} threshold of 6.3% (2 SD above the normal mean). Moreover, the corresponding sensitivity was 62.8% (57.1% to 68.3%), which was equivalent to that of a fasting plasma glucose threshold of 7.0 mmol/l (57.5%, 51.7% to 63.1%) in detecting undiagnosed diabetes. In participants at high risk of diabetes, the HbA_{1c} threshold of 6.3% showed significantly higher sensitivity (66.9%, 61.0% to 72.5%) than both fasting plasma glucose ≥7.0 mmol/l (54.4%, 48.3% to 60.4%) and HbA_{1c} ≥6.5% (53.7%, 47.6% to 59.7%) ($P<0.01$).

Conclusions An HbA_{1c} threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults and had sensitivity similar to that of using a fasting plasma glucose threshold of 7.0 mmol/l. This optimal HbA_{1c} threshold may be suitable as a diagnostic criterion for diabetes in Chinese adults when fasting plasma glucose and oral glucose tolerance tests are not available.

INTRODUCTION

Diabetes is often not diagnosed until complications appear, and approximately 30% of people with diabetes may be undiagnosed.[1 2] Additionally, complications of diabetes have become a leading cause of impairment of human health.[3] More efficient approaches to diagnosing diabetes urgently need be developed to improve health care for patients with diabetes.

Existing diagnostic methods include plasma glucose specific tests (fasting plasma glucose or oral glucose tolerance test) and glycated haemoglobin A1c (HbA_{1c}), although the last method has not been recommended as a diagnostic tool mainly owing to the lack of standardised results.[4 5] The special requirements for the oral glucose tolerance test, or to obtain fasting and two hour postprandial plasma glucose, limit the clinical application of these methods. HbA_{1c} tests are convenient and easy to do without regard to the time elapsed since the previous meal.

Several methods have been used to measure HbA_{1c}, including low performance liquid chromatography, ion exchange high performance liquid chromatography, capillary electrophoresis, and immunoassay. Under the leadership of the National Glycohemoglobin Standardization Program, great progress has been made in standardising HbA_{1c} assays in many nations worldwide,[6 7] and high performance liquid chromatography is highly recommended. In China, hospitals in large and medium sized cities that participated in the Chinese Ministry of Health Quality Assessment Program for HbA_{1c} used this method. In recent years, HbA_{1c} has been widely used as a measure of glycaemic control in patients with diabetes after treatment, and efforts to further standardise its use have continued.[8 9]

Substantial evidence shows that HbA_{1c} may be a useful tool for screening for and diagnosis of diabetes.[10-14] An HbA_{1c} threshold of 6.5% was proposed for the diagnosis of diabetes on the basis of the data from the National Health and Nutrition Examination Survey.[10 11] However, findings from previous studies evaluating HbA_{1c} as a screening tool have suggested that the optimal threshold for detecting diabetes may vary by ethnic group.[11 12 15] Recently, an international expert committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation published a report on the role of the HbA_{1c} assay in the diagnosis of diabetes. It noted that an HbA_{1c} value of 6.5% is sufficiently sensitive and specific to identify people who are at risk of developing retinopathy and who should therefore be diagnosed as having diabetes.

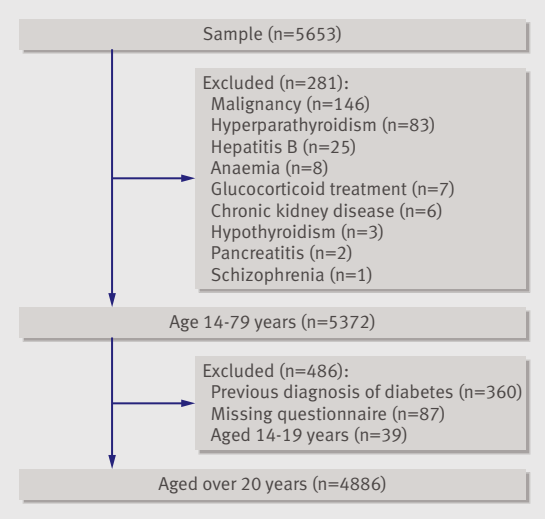

Fig 1 | Flow diagram of recruitment of participants

The committee examined data from three cross sectional epidemiological studies that included an Egyptian population, Pima Indians, and the US National Health and Nutrition Examination Survey population.[16] However, the performance of HbA_{1c} in detecting diabetes in the Chinese population remains unknown. The purpose of this study was to evaluate the efficiency of HbA_{1c} in diagnosing diabetes and to identify the optimal threshold in the adult Chinese population by using high performance liquid chromatography.

METHODS

Study design and population

This cross sectional epidemiological survey of diabetes and metabolic syndrome (Shanghai Diabetes Study II, SHDS II) in six communities in Shanghai between May 2007 and August 2008 followed a multistage stratified design. We divided each community into five groups according to age (20-29, 30-39, 40-49, 50-59, ≥60 years). The sampling proportion within each group was based on the age structure of the community. The average response rate was 95.9%. Exclusion criteria were cancer, severe psychiatric disturbance, chronic kidney disease, pregnancy, and glucocorticoid treatment. A total of 5372 Chinese people aged 14 to 79 years participated in the survey. All participants were expected to complete a uniform questionnaire containing questions about the histories of current and previous illness and medical treatment. Standard 75 g oral glucose tolerance tests were done in participants without known diabetes. We excluded 486 people, comprising 360 previously diagnosed as having diabetes, 87 with missing questionnaire data, and 39 aged under 20 years. We analysed data from 4886 participants aged over 20. Each participant gave written informed consent

Anthropometric and biochemical measurements

Participants arrived at the community service centre at 6 am after a 10 hour overnight fast. Each participant had a physical examination including measurement of height, weight, waist circumference, and blood pressure. We calculated body mass index as weight (kg) divided by squared height (m). We measured waist circumference at the horizontal plane between the inferior costal margin and the iliac crest on the mid-axillary line. Blood pressure was the average of three measurements made with a sphygmomanometer at two minute intervals.

After a fasting venous blood sample was drawn from the antecubital vein, each participant had a 75 g oral glucose tolerance test. We measured plasma glucose concentrations by the glucose oxidase method. We measured serum lipid profiles, including triglycerides, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol, by standard commercial methods on a parallel, multichannel analyser (Hitachi 7600-020, Tokyo, Japan). An experienced technician, who was blinded to the study, measured HbA_{1c} by high performance liquid chromatography (HLC-73G7, Tosoh, Japan). We measured HbA_{1c}, fasting plasma glucose, and two hour post-load plasma glucose within two hours of collection of blood. The Shanghai Diabetes Institute successfully participated in the HbA_{1c} Quality Assessment Program of the Chinese Ministry of Health between 2006 and 2008. The HbA_{1c} inter-assay and intra-assay coefficients of variation were <0.4%, and <0.6%.

Definitions

The oral glucose tolerance test is considered to be the gold standard for diagnosing diabetes.[17 18] The glycaemic thresholds for diagnosis of diabetes and impaired glucose regulation were based on the 1999 World Health Organization (WHO) criteria. Diabetes is defined as fasting plasma glucose of at least 7.0 mmol/l, two hour post-load plasma glucose of at least 11.1 mmol/l, or both.[4] Impaired glucose regulation is defined as impaired fasting glucose (fasting plasma glucose ≥6.1 mmol/l and <7.0 mmol/l and two hour post-load plasma glucose <7.8 mmol/l), impaired glucose tolerance (fasting plasma glucose <6.1 mmol/l and two hour post-load plasma glucose ≥7.8 mmol/l and <11.1 mmol/l), and impaired fasting glucose with impaired glucose tolerance (fasting plasma glucose ≥6.1 mmol/l and <7.0 mmol/l and two hour post-load plasma glucose ≥7.8 mmol/l and <11.1 mmol/l). Hyperglycaemic categories of diabetes are isolated high fasting plasma glucose concentrations (fasting plasma glucose ≥7.0 mmol/l and two hour post-load plasma glucose <11.1 mmol/l), isolated high two hour post-load plasma glucose concentrations (fasting plasma glucose <7.0 mmol/l and two hour post-load plasma glucose ≥11.1 mmol/l), and high fasting plasma glucose concentrations with high two hour post-load plasma glucose concentrations (fasting plasma glucose ≥7.0 mmol/l and two hour post-load plasma glucose ≥11.1 mmol/l).

Statistical analysis

We used SPSS version 11.5 for all statistical analyses. We presented continuous variables as means (SD),

Table 1 | Clinical characteristics of participants. Values are median (interquartile range) unless stated otherwise

Characteristics	Total (n=4886)	Men (n=1828)	Women (n=3058)
Age (years)	49.4 (37.9-57.7)	49.0 (37.4-59.0)	49.5 (38.2-56.9)
Body mass index (kg/m^2)	23.5 (21.4-25.9)	Mean 24.1 (SD 3.3)	23.2 (21.2-25.5)*
Waist circumference (cm)	79.0 (72.0-86.0)	84.0 (77.0-90.0)	76.0 (70.0-83.0)*
Systolic blood pressure (mm Hg)	120.0 (110.0-130.0)	120.0 (112.1-134.0)	120.0 (109.0-130.0)*
Diastolic blood pressure (mm Hg)	78.0 (70.0-82.0)	80.0 (71.7-88.0)	76.0 (70.0-80.0)*
Total cholesterol (mmol/l)	4.5 (4.0-5.2)	4.5 (3.9-5.1)	4.6 (4.0-5.3)*
Triglycerides (mmol/l)	1.3 (0.9-1.9)	1.5 (1.0-2.2)	1.2 (0.8-1.7)*
High density lipoprotein cholesterol (mmol/l)	1.3 (1.1-1.5)	1.2 (1.0-1.4)	1.4 (1.2-1.6)*
Low density lipoprotein cholesterol (mmol/l)	2.9 (2.4-3.4)	2.9 (2.4-3.4)	2.9 (2.4-3.4)
Fasting plasma glucose (mmol/l)	5.2 (4.8-5.6)	5.2 (4.7-5.6)	5.2 (4.8-5.6)
2 hour post-load plasma glucose (mmol/l)	6.0 (5.0-7.2)	5.9 (4.8-7.3)	6.0 (5.1-7.2)
HbA_{1c} (%)	5.6 (5.3-5.9)	5.6 (5.4-5.9)	5.6 (5.3-5.8)*
Normal glucose tolerance—No (%)	3748 (76.7)	1362 (74.5)	2386 (78.0)*
Impaired glucose regulation—No (%)	837 (17.1)	315 (17.2)	522 (17.1)
Undiagnosed diabetes—No (%)	301 (6.2)	151 (8.3)	150 (4.9)*
Fasting plasma glucose ≥7.0 mmol/l—No (%)	173 (58)	87 (58)	86 (58)
2 hour post-load plasma glucose ≥11.1 mmol/l and fasting plasma glucose <7.0 mmol/l—No (%)	128 (43)	64 (42)	64 (43)

*P<0.01 compared with men.

except for skewed variables, which we presented as medians (interquartile range). We expressed categorical variables as percentages. We used Pearson correlation analysis to investigate the association of HbA_{1c} with blood glucose concentrations (that is, fasting plasma glucose and two hour post-load plasma glucose). We used the method described by Hanley and McNeil to compare the area under the receiver operating characteristics curve for HbA_{1c} and fasting plasma glucose predicting undiagnosed diabetes.[19] We examined the sensitivity and specificity of HbA_{1c} with the receiver operating characteristics curve to identify participants as having undiagnosed diabetes. Thresholds were 1, 2, 3, and 4 standard deviations above the normal mean. We considered P values less than 0.05 to be statistically significant for a two sided test.

RESULTS

The final dataset included 4886 participants (1828 men and 3058 women) aged over 20 (median 49.4, interquartile range 37.9-57.7 years) from May 2007 to August 2008 (fig 1). Table 1 shows the clinical characteristics of the participants. We found no significant differences in age, low density lipoprotein cholesterol, fasting plasma glucose, and two hour post-load plasma glucose between men and women. Women had lower values of body mass index, waist circumference, blood pressure, triglycerides, and HbA_{1c} and higher levels of total cholesterol and high density lipoprotein cholesterol than did men (all P<0.01). The percentage of undiagnosed diabetes in women was significantly lower than that in men (P<0.01).

The dataset included data from 3748 people with normal glucose tolerance, 837 with impaired glucose regulation, and 301 with diabetes. Of the 837 participants with impaired glucose regulation, 199 (23.8%) had impaired fasting glucose, 534 (63.8%) had impaired glucose tolerance, and 104 (12.4%) had impaired fasting glucose with impaired glucose tolerance. Of the 301 participants with diabetes, 71 (24%) had isolated high fasting plasma glucose concentrations, 128 (43%) had isolated high two hour post-load plasma glucose concentrations, and 102 (34%) had high fasting plasma glucose concentrations with high two hour post-load plasma glucose concentrations. HbA_{1c} and either fasting plasma glucose or two hour post-load plasma glucose were significantly correlated, with correlation coefficients of 0.619 (P<0.001) and 0.622 (P<0.001) on the basis of Pearson correlation analysis.

The receiver operating characteristics curve shown in figure 2 represents the diagnostic accuracy of HbA_{1c} for undiagnosed diabetes. The area under the curve was 0.856 (95% confidence interval 0.828 to 0.883) for HbA_{1c} alone and 0.920 (0.900 to 0.941) for fasting plasma glucose alone. The two areas differed significantly from each other (P<0.001). Table 2 shows 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 glucose tolerance (5.5%). When the number of standard deviations increased, sensitivity decreased and specificity increased. An HbA_{1c} threshold of 1 SD above the normal mean (5.9%) showed a very high sensitivity of 77.7% (95% confidence interval 72.6% to 82.3%) and a moderate specificity of 78.2% (77.0% to 79.4%) for detecting undiagnosed diabetes. These findings coincided with the threshold selected by the closest distance to the left upper corner of the receiver operating characteristics curve, which indicated the best trade-off between sensitivity and specificity. A high specificity of 96.1% (95.5% to 96.7%) was

Table 2 | Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for detecting diabetes with fasting plasma glucose (FPG) in 1999 WHO criteria and HbA_{1c} thresholds (n=4886). Values in parentheses are 95% confidence intervals

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
HbA_{1c} threshold (%):						
5.9 (1 SD above normal mean)	77.7 (72.6 to 82.3)	78.2 (77.0 to 79.4)	19.0 (16.8 to 21.3)	98.2 (97.7 to 98.6)	3.6 (3.3 to 3.9)	0.3 (0.2 to 0.4)
6.3 (2 SD above normal mean)	62.8 (57.1 to 68.3)	96.1 (95.5 to 96.7)	51.5 (46.3 to 56.7)	97.5 (97.0 to 98.0)	16.2 (13.7 to 19.1)	0.4 (0.3 to 0.5)
6.7 (3 SD above normal mean)	37.9 (32.4 to 43.6)	99.1 (98.7 to 99.3)	72.6 (64.9 to 79.4)	96.1 (95.5 to 96.6)	40.4 (29.0 to 56.2)	0.6 (0.6 to 0.7)
7.1 (4 SD above normal mean)	26.3 (21.4 to 31.6)	99.8 (99.6 to 99.9)	87.8 (79.2 to 93.7)	95.4 (94.8 to 96.0)	109.7 (59.0 to 203.8)	0.7 (0.7 to 0.8)
6.5*	50.5 (44.7 to 56.3)	98.1 (97.6 to 98.4)	63.1 (56.6 to 69.2)	96.8 (96.2 to 97.3)	26.0 (20.6 to 32.9)	0.5 (0.5 to 0.6)
FPG ≥7.0 mmol/l	57.5 (51.7 to 63.1)	100.0 (99.9 to 100.0)	100.0 (97.9 to 100.0)	97.3 (96.8 to 97.7)	–	0.4 (0.4 to 0.5)

*Threshold recommended by American Diabetes Association/European Association for the Study of Diabetes/International Diabetes Federation.

achieved at an HbA_{1c} threshold of 6.3% (2 SD above the normal mean), together with a low negative likelihood ratio of 0.4 (0.3 to 0.5), a high positive likelihood ratio of 16.2 (13.7 to 19.1), and a negative predictive value of 97.5% (97.0% to 98.0%).

Subsequently, we compared the sensitivity of HbA_{1c} thresholds of 6.3% and 6.5% (as recommended by the international expert committee) with a fasting plasma glucose threshold of 7.0 mmol/l. The sensitivities of an HbA_{1c} threshold of 6.3% and this fasting plasma glucose concentration in detecting undiagnosed diabetes were 62.8% (57.1% to 68.3%) and 57.5% (51.7% to 63.1%) (P=0.183). However, the sensitivity of an HbA_{1c} threshold of 6.5% was 50.5% (44.7% to 56.3%), which was not significantly different from that of fasting plasma glucose (P=0.086). At an HbA_{1c} threshold of 6.5% (table 2), the positive and negative predictive values were 63.1% (56.6% to 69.2%) and 96.8% (96.2% to 97.3%) and the positive and negative likelihood ratios were 26.0 (20.6 to 32.9) and 0.5 (0.5 to 0.6). Interestingly, the sensitivity of an HbA_{1c} threshold of 6.3% was higher than that of an HbA_{1c} threshold of 6.5% (P=0.002).

We did a subgroup analysis of 3639 participants at high risk of diabetes (1436 men and 2203 women). The risk factors for diabetes included age over 45 and body mass index over 24.0.[5 20] The median age of this subgroup was 53.4 (interquartile range 47.0-60.3) years. Table 3 shows the sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio for identifying diabetes at different HbA_{1c} thresholds. At an HbA_{1c} threshold of 6.3%, the sensitivity was significantly higher than that of a fasting plasma glucose threshold of 7.0 mmol/l (66.9% (61.0% to 72.5%) *v* 54.4% (48.3% to 60.4%); P=0.003) with high specificity (94.8%, 94.0% to 95.6%). When we used a threshold of 6.5%, the sensitivity was significantly lower than that seen with a 6.3% threshold (53.7% (47.6% to 59.7%) *v* 66.9% (61.0% to 72.5%); P=0.002).

Of the 367 participants with HbA_{1c} of 6.3% or above (table 4), 74 had normal glucose tolerance, 104 had impaired glucose regulation, and 189 were designated as having diabetes when we applied the 1999 WHO criteria. In contrast, at the HbA_{1c} threshold of 6.5%, 33 had normal glucose tolerance, 56 had impaired glucose regulation, and 152 were designated as having diabetes.

Table 5 shows the number and clinical characteristics of patients identified as having diabetes on the basis of oral glucose tolerance test results with the 1999 WHO criteria and an HbA_{1c} threshold of 6.3%. One hundred and eighty-nine of the patients identified by HbA_{1c} overlapped with those diagnosed by using the WHO criteria. The anthropometric and biochemical measurements were comparable between the two groups.

DISCUSSION

In this community based study in 4886 Chinese adults, we found that an HbA_{1c} threshold of 6.3% had high specificity for detecting undiagnosed diabetes and equal sensitivity to that of a fasting plasma glucose threshold of 7.0 mmol/l. This threshold was more efficient in the people at high risk of diabetes.

Epidemiology of diabetes

Although the prevalence of diabetes mellitus has dramatically increased in recent years in China, the disease remains underdiagnosed. In the United States, for every two patients diagnosed as having diabetes in a hospital, at least one other patient in the hospital may have unrecognised diabetes and be at higher risk of poor health outcomes and high healthcare costs.[21] The epidemiological survey for diabetes in Shanghai, China, found that the annual incidence of diabetes was

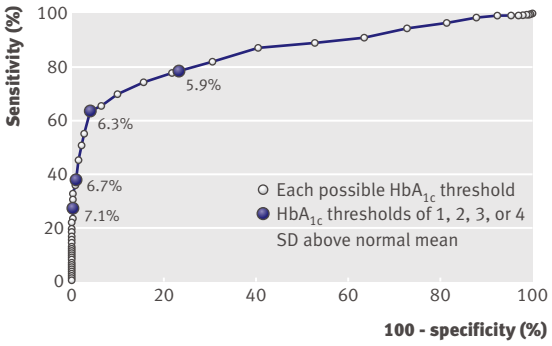

Fig 2 | Receiver operating characteristics curve of HbA_{1c} for detecting diabetes at each possible HbA_{1c} threshold. Area under curve=0.856 (95% CI 0.828 to 0.883)

Table 3 | Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for detecting diabetes with fasting plasma glucose (FPG) in 1999 WHO criteria and HbA_{1c} thresholds in patients at high risk of developing diabetes (n=3639). Values in parentheses are 95% confidence intervals

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
HbA_{1c} threshold (%):						
6.0	79.0 (73.7 to 83.7)	80.3 (78.9 to 81.6)	24.5 (21.7 to 27.5)	97.9 (97.3 to 98.4)	4.0 (3.7 to 4.4)	0.3 (0.2 to 0.3)
6.1	73.9 (68.3 to 79.0)	87.2 (86.0 to 88.3)	31.8 (28.1 to 35.5)	97.6 (97.0 to 98.2)	5.8 (5.1 to 6.5)	0.3 (0.3 to 0.4)
6.2	69.1 (63.3 to 74.6)	91.9 (90.9 to 92.8)	40.7 (36.2 to 45.3)	97.4 (96.7 to 97.9)	8.5 (7.4 to 9.8)	0.3 (0.3 to 0.4)
6.3	66.9 (61.0 to 72.5)	94.8 (94.0 to 95.6)	51.1 (45.8 to 56.4)	97.3 (96.6 to 97.8)	13.0 (11.0 to 15.3)	0.4 (0.3 to 0.4)
6.4	58.8 (52.7 to 64.7)	96.5 (95.8 to 97.1)	57.6 (51.5 to 63.4)	96.7 (96.0 to 97.3)	16.8 (13.7 to 20.6)	0.4 (0.4 to 0.5)
6.5*	53.7 (47.6 to 59.7)	97.4 (96.8 to 97.9)	62.7 (56.1 to 68.9)	96.3 (95.6 to 96.9)	20.8 (16.4 to 26.3)	0.5 (0.4 to 0.5)
FPG ≥7.0 mmol/l	54.4 (48.3 to 60.4)	100.0 (99.9 to 100.0)	100.0 (97.5 to 100.0)	96.5 (95.8 to 97.0)	–	0.5 (0.4 to 0.5)

*Threshold recommended by American Diabetes Association/European Association for the Study of Diabetes/International Diabetes Federation.

1.65% and the prevalence was 6.87%; more than 40% of people with diabetes were undiagnosed before the survey.[2] More efficient identification of people with diabetes is thus essential to allow provision of timely treatment and improve outcomes.

Advantages of HbA_{1c} in diagnosing diabetes

Historically, a lack of standardised HbA_{1c} measurements has meant that the American Diabetes Association has not recommended the use of HbA_{1c} as a diagnostic tool. However, recent improvements in standardised HbA_{1c} measurements worldwide, especially a new more specific reference measure developed in 2003,[22] have prompted re-evaluation of HbA_{1c} as a screening or diagnostic tool for diabetes.[1] Selvin et al found that the within-person coefficients of variation in two hour post-load plasma glucose, fasting plasma glucose, and HbA_{1c} were in descending frequency (16.7%>5.7%>3.6%).[23] These findings showed that HbA_{1c} was more reproducible and repeatable than fasting plasma glucose as a diagnostic tool for diabetes.[24]

A few practical considerations support the convenience of HbA_{1c} in diagnosing diabetes. Firstly, both fasting plasma glucose and oral glucose tolerance tests require the patient to fast for at least eight hours, which decreases the opportunities for diagnosing diabetes. However, HbA_{1c} testing can be done at any time without fasting or other preparation of the patient, which makes diagnosis on the same day possible. Secondly, both fasting plasma glucose and oral glucose tolerance tests may be affected by short term lifestyle changes, such as diet and amount of physical exercise before examination. In contrast, the HbA_{1c} value does not have such limitations as it reflects mean glycaemia over the preceding two to three months, which accurately reflects longer term glycaemia.

Recent studies have indicated that HbA_{1c} is similar or superior to fasting plasma glucose in screening for or diagnosis of diabetes compared with the gold standard, the oral glucose tolerance test.[13 15] In our study, the area under the receiver operating characteristics curve was 0.856 for HbA_{1c} for detecting undiagnosed diabetes, which corresponds to the findings of a study done in the Japanese population.[12] Another study found that HbA_{1c} measurement improved the detection of diabetes in people at high risk compared with a fasting plasma glucose threshold of 7.0 mmol/l.[25]

Ethnic differences in distribution of hyperglycaemic categories

Ethnic differences exist in the distribution of hyperglycaemic categories. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study showed that the proportions of patients with isolated high fasting plasma glucose concentrations, isolated high two hour post-load plasma glucose concentrations, and high fasting plasma glucose concentrations with high two hour post-load plasma glucose concentrations were 40%, 31%, and 29%.[26] Using only fasting plasma glucose concentrations, about two thirds of patients with diabetes could be detected.[27] However, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia study found corresponding proportions of 19%, 44%, and 37%. Therefore, only 56% of patients with diabetes could be detected with the fasting plasma glucose criterion alone, which left more Asian patients undiagnosed than was the case in the European population.[28] The 1994 China National Diabetes Mellitus Survey of Chinese adults showed that impaired glucose tolerance was the most common form of impaired glucose regulation and that high fasting plasma glucose concentrations with high two hour post-load plasma glucose concentrations was the most common subcategory of diabetes.[29] Our study confirmed the findings of the China National Diabetes Mellitus Survey, which suggested that a large number of people with diabetes

Table 4 | Distribution of participants with normal glucose tolerance, impaired glucose regulation, and diabetes stratified by HbA_{1c} thresholds of 6.3% and 6.5%. Values are numbers (percentages)

	75 g oral glucose tolerance test		
HbA_{1c} (%)	Normal glucose tolerance (n=3748)	Impaired glucose regulation (n=837)	Diabetes (n=301)
≥6.3*	74 (2.0)	104 (12.4)	189 (62.8)
≥6.5†	33 (0.9)	56 (6.7)	152 (50.5)

*Threshold found in this study.
†Threshold recommended by American Diabetes Association/European Association for the Study of Diabetes/International Diabetes Federation.

Table 5 | Clinical characteristics of participants identified as having diabetes by oral glucose tolerance test and HbA_{1c} threshold of 6.3%. Values are medians (interquartile ranges) unless stated otherwise

Characteristics	Diabetes identified by oral glucose tolerance test (n=301)	Diabetes identified by HbA_{1c} (n=367)
Mean (SD) age (years)	54.2 (11.9)	56.4 (10.4)
Mean (SD) body mass index (kg/m^2)	25.5 (3.7)	25.8 (3.5)
Mean (SD) waist circumference (cm)	86.4 (10.6)	86.9 (9.8)
Systolic blood pressure (mm Hg)	130.0 (120.0-140.0)	130.0 (120.0-140.0)
Diastolic blood pressure (mm Hg)	80.0 (74.0-90.0)	80.0 (74.0-90.0)
Total cholesterol (mmol/l)	5.0 (4.4-5.7)	5.2 (4.4-5.8)
Triglycerides (mmol/l)	1.8 (1.2-2.9)	1.9 (1.3-2.9)
High density lipoprotein cholesterol (mmol/l)	Mean 1.2 (SD 0.3)	1.2 (1.0-1.4)
Low density lipoprotein cholesterol (mmol/l)	3.1 (2.7-3.7)	Mean 3.3 (SD 1.0)
Fasting plasma glucose (mmol/l)	7.2 (6.2-8.1)	6.4 (5.7-7.4)
2 hour post-load plasma glucose (mmol/l)	12.7 (11.2-15.2)	10.3 (7.2-13.9)
HbA_{1c} (%)	6.5 (5.9-7.1)	6.6 (6.4-7.0)

(>40%) would be undiagnosed if only the fasting plasma glucose test was used. Accordingly, in the Chinese population, use of HbA_{1c} would be more suitable for diagnosing diabetes according to the distribution of types of hyperglycaemia.

HbA_{1c} threshold compared with other studies

Racial disparities in HbA_{1c} values exist,[30 31] and the optimal thresholds for detecting diabetes have been found to vary by ethnic group.[12 15] The 1999-2004 National Health and Nutrition Examination Survey found that an HbA_{1c} value of 6.5% or greater was an optimal threshold for identifying diabetes in the US population.[10] Data from the National Health and Nutrition Examination Survey III (1988-94) found indications of differences between ethnic groups in the sensitivity and specificity of HbA_{1c} (at 6.1%) for detecting undiagnosed diabetes. Sensitivity ranged from 58.6% in the non-Hispanic white population to 83.6% in the Mexican-American population; specificity ranged from 93.0% in the non-Hispanic black population to 98.3% in the non-Hispanic white population.[11] In a multiethnic population in Canada, the optimal threshold for HbA_{1c} of 5.9% was associated with a sensitivity of 75.0% (95% confidence interval 64.0% to 86.0%) and a specificity of 79.1% (76.4% to 81.8%).[32] A study of the Hong Kong Chinese population with known risk factors for glucose intolerance showed that an HbA_{1c} threshold of 6.1% gave an optimal sensitivity of 77.5% and specificity of 78.8% when two hour post-load plasma glucose of at least 11.1 mmol/l was used as the reference.[33] Similar results were found in the Japanese population, where the HbA_{1c} threshold of 6.1% was found to be suitable for detecting undiagnosed diabetes and predicting vascular complications.[12]

In our community based study, we found that an HbA_{1c} threshold of 5.9% provided the optimal sensitivity and specificity for screening for potential diabetes in the general Chinese population. Recently, an international expert committee reported that people with an HbA_{1c} value of at least 6% but less than 6.5% are likely to be at highest risk for progression to diabetes.[16] In our study, the proficiency of an HbA_{1c} threshold of 6.3% for detecting diabetes was equivalent to that of a fasting plasma glucose threshold of 7.0 mmol/l. However, in people at high risk of diabetes, the proficiency of an HbA_{1c} threshold of 6.3% in detecting diabetes was superior to that of both a fasting plasma glucose threshold of 7.0 mmol/l and an HbA_{1c} threshold of 6.5% (66.9% *v* 54.4% *v* 53.7%). On the basis of our results, an HbA_{1c} threshold of 6.3% may be acceptable as a diagnostic criterion for diabetes in the Chinese population, when fasting plasma glucose and oral glucose tolerance tests are not available.

Confounders and limitations of study

Some confounders and effect modifiers influence the clinical use of HbA_{1c} for screening for and diagnosis of diabetes. Firstly, the HbA_{1c} value reflects mean glycaemia over the preceding two to three months, so people with a history of diabetes of less than three months might not be identified by HbA_{1c} testing. However, this is extremely unlikely given that on average a seven year gap exists between the actual onset of diabetes and its diagnosis.[34] Secondly, conditions that shorten survival of erythrocytes, such as haemolytic anaemia, will decrease the concentration of HbA_{1c}. Conversely, conditions that prolong the age of erythrocytes, such as splenectomy and aplastic anaemia, will increase the concentration of HbA_{1c} independent of glycaemia. Haemoglobinopathies such as haemoglobin S (sickle cell) interfere with some assays. Thus, the use of HbA_{1c} may be inappropriate for such disorders.

Limitations of this study include an inadequate sample size. Additionally, as the high prevalence of impaired glucose tolerance has prognostic value regarding possible progression to diabetes and cardiovascular disease, the use of HbA_{1c} alone to diagnose diabetes could give a false sense of security. Thus, in patients with known risk factors for glucose intolerance, a 75 g oral glucose tolerance test, yearly HbA_{1c}

WHAT IS ALREADY KNOWN ON THIS TOPIC

HbA_{1c} might be a useful tool for screening for and diagnosis of diabetes

In June 2009, an international expert committee published a report recommending the use of an HbA_{1c} value of 6.5% or more as a diagnostic criterion for diabetes

As racial disparities in HbA_{1c} levels exist, the optimal threshold for diagnosing diabetes varies by ethnic group

WHAT THIS STUDY ADDS

In the Chinese population, an HbA_{1c} threshold of 6.3% may be acceptable as a diagnostic criterion for diabetes

In people at high risk of diabetes, an HbA_{1c} threshold of 6.3% was more efficient than a fasting plasma glucose threshold of 7.0 mmol/l

measurement, or both are needed to avoid missed diagnosis and opportunity for therapeutic intervention. Although either plasma glucose concentrations after fasting or two hour post-load plasma glucose after a 75 g oral glucose tolerance test could be used alone for diagnosing diabetes in epidemiological studies, according to 1999 WHO criteria,[4] additional testing is desirable to prove the reliability of the HbA_{1c} threshold in clinical studies. This study should be validated by similar epidemiological and clinical studies.

Financial implications

The cost in China of the HbA_{1c} test was similar to that of the oral glucose tolerance test. However, the first of these is more acceptable to patients than the second, because it causes less discomfort. Undiagnosed diabetes and its complications cause increased healthcare costs in America.[35] On the basis of our study, HbA_{1c} testing might help to reduce these costs by improving diagnosis of diabetes and enabling more timely therapeutic intervention in such patients.

Conclusions

In conclusion, this study found that an HbA_{1c} threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults and had sensitivity similar to that of using a fasting plasma glucose threshold of 7.0 mmol/l. These findings suggest that HbA_{1c}, with the optimal threshold of 6.3%, may be acceptable as a diagnostic criterion for diabetes in the Chinese population when fasting plasma glucose and oral glucose tolerance tests are not available.

Contributors: YB, XK, and WJ conceived and designed the study. XM and XH recruited samples. XM did the statistical analyses. JT measured HbA_{1c}. YB and XM wrote the first draft of the paper. YB, XM, CH, and WJ revised the paper and contributed to discussion. HL, MZ, and HW provided technical support. YB and XM contributed equally to this work and are the guarantors.
Funding: This work was funded by Shanghai United Developing Technology Project of Municipal Hospitals (SHDC12006101), Chinese National 973 Project (2007CB914702), Shanghai Key Laboratory of Diabetes Mellitus (08DZ2230200), Major Program of Shanghai Municipality for Basic Research (08dj1400601), and National Key Technology R&D Program of China (2009BAI80B01).
Competing interests: None declared.
Ethical approval: The local ethics committee approved the study, and all participants gave written informed consent.
Data sharing: No additional data available.

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Accepted: 6 April 2010