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

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ABSTRACT

Objectives To evaluate haemoglobin A1c (HbA1c) in diagnosing diabetes and identify the optimal HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c ≥6.5% (53.7%, 47.6% to 59.7%) (P<0.01).

Conclusions An HbA1c 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 HbA1c 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.12 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 (HbA1c), although the last method has not been recommended as a diagnostic tool mainly owing to the lack of standardised results.13 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. HbA1c tests are convenient and easy to do without regard to the time elapsed since the previous meal.

Several methods have been used to measure HbA1c, 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 HbA1c 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 HbA1c used this method. In recent years, HbA1c 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 HbA1c may be a useful tool for screening for and diagnosis of diabetes.10 14 An HbA1c 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 HbA1c as a screening tool have suggested that the optimal threshold for detecting diabetes may vary by ethnic group.11 12 13 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 HbA1c assay in the diagnosis of diabetes. It noted that an HbA1c 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.
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. However, the performance of HbA1c in detecting diabetes in the Chinese population remains unknown. The purpose of this study was to evaluate the efficiency of HbA1c 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 HbA1c by high performance liquid chromatography (HLC-73G7, Tosoh, Japan). We measured HbA1c, 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 HbA1c Quality Assessment Program of the Chinese Ministry of Health between 2006 and 2008. The HbA1c 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. 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. 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),
Normal glucose tolerance pressure, triglycerides, and HbA1c and higher levels of values of body mass index, waist circumference, blood glucose between men and women. Women had lower fasting plasma glucose, and two hour post-load plasma differences in age, low density lipoprotein cholesterol, characteristics of the participants. We found no significant August 2008 (fig 1). Table 1 shows the clinical charac-
quartile range 37.9-57.7 years) from May 2007 to
The final dataset included 4886 participants (1828 men
and 3058 women) aged over 20 (median 49.4, inter-
Age (years) 49.4 (37.9-57.7) 49.0 (37.4-59.0) 49.5 (38.2-56.9)
Body mass index (kg/m²) 23.5 (21.4-25.9) Mean 24.1 (SO 1.3) 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 (2.4-3.6) 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)
HbA1c (%) 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 HbA1c 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 HbA1c and fasting plasma glucose predicting undiagnosed diabetes.19 We examined the sensitivity and specificity of HbA1c 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, inter-
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 HbA1c, 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. HbA1c 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 HbA1c for undiagnosed diabetes. The area under the curve was 0.856 (95% confidence interval 0.828 to 0.883) for HbA1c 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 HbA1c 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 HbA1c 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
achieved at an HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c threshold of 6.3% was higher than that of an HbA1c 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 24.0.20 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 HbA1c thresholds. At an HbA1c 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 HbA1c of 6.3% or above (table 4), 74 had normal glucose tolerance, 104 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 HbA1c threshold of 6.3%. One hundred and eighty-nine of the patients identified by HbA1c 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 HbA1c 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 unrecognized 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...
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 HbA1c thresholds in patients at high risk of developing diabetes (n=3639). Values in parentheses are 95% confidence intervals

| HbA1c threshold (%) | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Positive likelihood ratio | Negative likelihood ratio |
|---------------------|-----------------|-----------------|-------------------------------|-------------------------------|-------------------------|--------------------------|
| 6.0                 | 79.0 (71.7 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      | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Positive likelihood ratio | Negative likelihood ratio |
|---------------------|-----------------|-----------------|-------------------------------|-------------------------------|-------------------------|--------------------------|
| 54.4 (48.3 to 60.4) | 100.0 (99.9 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.
†Threshold found in this study.

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 HbA1c in diagnosing diabetes

Historically, a lack of standardised HbA1c measurements has meant that the American Diabetes Association has not recommended the use of HbA1c as a diagnostic tool. However, recent improvements in standardised HbA1c measurements worldwide, especially a new more specific reference measure developed in 2003,22 have prompted re-evaluation of HbA1c 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 HbA1c were in descending frequency (16.7%>5.7%>3.6%).23 These findings showed that HbA1c was more reproducible and repeatable than fasting plasma glucose as a diagnostic tool for diabetes.24

A few practical considerations support the convenience of HbA1c 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, HbA1c 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 HbA1c 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 HbA1c 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.15 15 In our study, the area under the receiver operating characteristics curve was 0.856 for HbA1c for detecting undiagnosed diabetes, which corresponds to the findings of a study done in the Japanese population.12 Another study found that HbA1c 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...
Racial disparities in HbA1c values exist,\textsuperscript{30,31} and the HbA1c threshold compared with other studies in the Japanese population, use of HbA1c would be more suitable if a fasting plasma glucose test was used. Accordingly, in the Chinese population with known risk factors for glucose intolerance and a history of diabetes of less than three months, so people with known risk factors for 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 HbA1c

| Characteristics                                      | Diabetes identified by oral glucose tolerance test (n=301) | Diabetes identified by HbA1c (%) (n=367) |
|------------------------------------------------------|----------------------------------------------------------|----------------------------------------|
| Mean (SD) age (years)                                | 54.2 (11.9)                                              | 56.4 (10.4)                            |
| Mean (SD) body mass index (kg/m\textsuperscript{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)                        |
| HbA1c (%)                                            | 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 HbA1c would be more suitable for diagnosing diabetes according to the distribution of types of hyperglycaemia.

HbA1c threshold compared with other studies

Racial disparities in HbA1c values exist,\textsuperscript{30,31} and the optimal thresholds for detecting diabetes have been found to vary by ethnic group.\textsuperscript{12,15} The 1999-2004 National Health and Nutrition Examination Survey found that an HbA1c value of 6.5% or greater was an optimal threshold for identifying diabetes in the US population.\textsuperscript{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 HbA1c (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.\textsuperscript{11} In a multiethnic population in Canada, the optimal threshold for HbA1c 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%).\textsuperscript{32} A study of the Hong Kong Chinese population with known risk factors for glucose intolerance showed that an HbA1c 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.\textsuperscript{33} Similar results were found in the Japanese population, where the HbA1c threshold of 6.1% was found to be suitable for detecting undiagnosed diabetes and predicting vascular complications.\textsuperscript{12}

In our community based study, we found that an HbA1c 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 recommended that people with an HbA1c value of at least 6% but less than 6.5% are likely to be at highest risk for progression to diabetes.\textsuperscript{34} In our study, the proficiency of an HbA1c 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 HbA1c 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 HbA1c threshold of 6.5% (66.9% vs 54.4% vs 53.7%). On the basis of our results, an HbA1c 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 HbA1c for screening for and diagnosis of diabetes. Firstly, the HbA1c 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 HbA1c testing. However, this is extremely unlikely given that on average a seven year gap exists between the actual onset of diabetes and its diagnosis.\textsuperscript{34} Secondly, conditions that shorten survival of erythrocytes, such as haemolytic anaemia, will decrease the concentration of HbA1c. Conversely, conditions that prolong the age of erythrocytes, such as splenectomy and aplastic anaemia, will increase the concentration of HbA1c independent of glycaemia. Haemoglobinopathies such as haemoglobin S (sickle cell) interfere with some assays. Thus, the use of HbA1c 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 HbA1c 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 HbA1c
In the Chinese population, an HbA1c threshold of 6.3% may be acceptable as a diagnostic criterion for diabetes.

WHAT THIS STUDY ADDS

As racial disparities in HbA1c levels exist, the optimal threshold for diagnosing diabetes varies by ethnic group.

In people at high risk of diabetes, an HbA1c threshold of 6.3% was more efficient than a fasting plasma glucose threshold of 7.0 mmol/l.

Financial implications

The cost in China of the HbA1c 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. On the basis of our study, HbA1c 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 HbA1c 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 HbA1c, 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 HbA1c. 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.

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Competing interests: None declared.

Ethical approval: The local ethics committee approved the study, and all participants gave written informed consent.

WHAT IS ALREADY KNOWN ON THIS TOPIC

HbA1c 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 HbA1c value of 6.5% or more as a diagnostic criterion for diabetes.

Data sharing: No additional data available.

1. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson ML. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab 2008;93:2447-53.
2. Jia WP, Pang C, Chen L, Bao YQ, Liu JX, Lu HL, et al. Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. Diabetologia 2007;50:286-92.
3. World Health Organization. The world health report: primary health care—now more than ever. WHO, 2008.
4. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. WHO, 1999.
5. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(suppl 1):S5-20.
6. Little RR, Rohlffing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE, et al. The national glycohemoglobin standardization program: a five-year progress report. Clin Chem 2001;47:1985-92.
7. Little RR. Glycated hemoglobin standardization—national glycohemoglobin standardization program (NGSP) perspective. Clin Chem Lab Med 2003;41:1191-8.
8. Goldstein DE, Little RR, Lorenz RA, Malone JJ, Nathan D, Peterson CM, et al. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761-73.
9. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.
10. BueLL C, Kermah D, Davidson MB. Utility of A1c for diabetes screening in the 1999-2004 NHANES population. Diabetes Care 2007;30:2233-5.
11. Rohlffing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, et al. Use of GHB (HbA1c) in screening for undiagnosed diabetes in the US population. Diabetes Care 2000;23:187-91.
12. Nakagami T, Tominaga M, Nishimura R, Yoshikke N, Daimon M, Oizumi T, et al. Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan National Diabetes Survey. Diabetes Res Clin Pract 2007;76:251-6.
13. Wiener K, Roberts NB. The relative merits of haemoglobin A1c and fasting plasma glucose as first-line diagnostic tests for diabetes mellitus in non-pregnant subjects. Diabet Med 1998;15:558-63.
14. Barr RG, Nathan DM, Meigs JB, Singer DE. Tests of glycemia for the diagnosis of type 2 diabetes mellitus. Ann Intern Med 2002;137:263-72.
15. Bennett CM, Guo M, Dhamarge SC. HbA1c(c) as a screening tool for detection of type 2 diabetes: a systematic review. Diabet Med 2007;24:333-43.
16. International Expert Committee. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327-34.
17. Olabi B, Bhopal R. Diagnosis of diabetes using the oral glucose tolerance test. BMJ 2009;339:b4354.
18. WHO Expert Committee on Diabetes Mellitus. Second report. Technical report series no 646. WHO, 1980.
19. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-43.
20. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. Obes Rev 2002;3:147-56.
21. ACE/ADA Task Force on Inpatient Diabetes, American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycaemic control. Diabetes Care 2006;29:1955-62.
22. Miedema K. Towards worldwide standardisation of HbA1c determination. Diabetologia 2004;47:1143-8.
23. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med 2007;167:1545-51.
24. Lacher DA, Hughes JP, Carroll MD. Estimate of biological variation of glycated hemoglobin (HbA1c) in measures of glycemia and implications for the classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. WHO, 1999.
25. Perry RC, Shanikar RR, Fineberg N, McGill J, Baron AD. HbA1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). Diabetes Care 2001;24:465-71.
26. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 1998;317:371-5.

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27 DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397-405.

28 Qiao Q, Nakagami T, Tuomilehto J, Borch-Johnsen K, Balkau B, Iwamoto Y, et al. Comparison of the fasting and the 2-h glucose criteria for diabetes in different Asian cohorts. Diabetologia 2000;43:1470-5.

29 Yang Z, Yang WY, Li GW. National Diabetes Prevention and Control Cooperative Group. The distributive characteristics of impaired glucose metabolism subcategories in Chinese adult population. Zhonghua Yi Xue Za Zhi 2003;83:2128-31.

30 Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES, et al. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2753-7.

31 Viberti G, Lachin J, Holman R, Zinman B, Haffner S, Kravitz B, et al. A Diabetes Outcome Progression Trial (ADOPT): baseline characteristics of type 2 diabetic patients in North America and Europe. Diabet Med 2006;23:1289-94.

32 Anand SS, Razak F, Vuksan V, Gerstein HC, Malmberg K, Yi Q, et al. Diagnostic strategies to detect glucose intolerance in a multiethnic population. Diabetes Care 2003;26:290-6.

33 Ko GT, Chan JC, Yeung VT, Chow CC, Tsang LW, Li JK, et al. Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. Diabetes Care 1998;21:1221-5.

34 Harris MI. Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 1993;16:642-52.

35 Zhang Y, Dall TM, Mann SE, Chen Y, Martin J, Moore V, et al. The economic costs of undiagnosed diabetes. Popul Health Manag 2009;12:95-101.

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