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The diagnostic threshold of HbA1c and impact of its use on diabetes prevalence—A population-based survey of 6898 Han participants from southern China

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ABSTRACT

Objective. The objective of this study is to determine the diagnostic threshold of HbA1c for diabetes and the impact of using it on diabetes prevalence.

Methods. A population-based stratified study was conducted in 2010 among community-dwelling adults aged ≥35 years in southern China. Participants without previously-diagnosed diabetes (PDD) took oral glucose tolerance test (OGTT) and HbA1c assay. HbA1c diagnostic threshold was determined by receiver operating characteristic curve.

Results. A total of 6989 participants with mean age of 52 years were recruited. The area under curve of HbA1c was 0.903 (95% CI: 0.883–0.922), with optimal cut-off value at 6.25% (sensitivity 75.6% and specificity 91.9%). There were 449 (6.42%) patients with PDD and 422 (6.04%), 815 (11.66%) and 918 (13.13%) new cases diagnosed by OGTT, HbA1c ≥6.25% or either, respectively. When either HbA1c or OGTT was used, newly-diagnosed diabetes prevalence increased by 117.4%.

Conclusions. Diabetes is prevalent in southern China. Near half of the patients go undetected with current diagnostic criteria. HbA1c ≥6.25% may be the diagnostic threshold value but needs further verification. The introduction of HbA1c threshold into diabetes diagnosis in China will cause a substantial increase in diabetes prevalence and great challenge on the public healthcare system.

As estimated by International Diabetes Federation (IDF), there were 366 million people with diabetes worldwide in 2011 (IDF, 2012). Twelve percent of the world's total healthcare expenditures or 376 billion US dollars were spent on diabetes management in 2010 (Zhang et al., 2010). What is more important is under-diagnosis and delayed diagnosis of the disease. About one-third of cases are under-diagnosed worldwide. Even in well-developed countries, approximately 30% of diabetes cases are undiagnosed and about 25%–50% of people with newly-detected diabetes (NDD) already have established diabetic complications (Cowie et al., 2009). It is estimated that the average lag between onset and diagnosis of the disease is 7 years (Saudek et al., 2008). This delay in diagnosis and under-diagnosis hampers patients to benefit from early treatments that can prevent or delay the onset of costly and harmful complications. These realities highly emphasize the crucial needs to identify criteria that make the diagnosis of diabetes more efficiently and conveniently.

For decades, the diagnosis of diabetes has been mainly based on fasting plasma glucose (FPG) and/or 2-hour plasma glucose (2 h-PG) after 75-g glucose challenge. However, they had many shortcomings, including vulnerability to recent lifestyle change, high intra-individual variability (Selvin et al., 2007), technological challenge and time-consuming. HbA1c has several favorable properties, including greater convenience since fasting is not required, greater pre-analytical stability, less within-day and day-to-day variability, and its demonstrated correlation with chronic complications (Colagiuri et al., 2011). However,

Abbreviations: AUC, areas under the curve; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NDD, newly-detected diabetes; NPV, negative predictive value; OGTT, oral glucose tolerance test; PDD, previously-diagnosed diabetes; PPV, positive predictive value; ROC, receiver operating characteristic; SBP, systolic blood pressure; TC, total cholesterol; 2 h-PG, 2-hour plasma glucose; WHR, waist–hip ratio.

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lack of standardization of assay hindered it to become a diagnostic criterion for many years. With recent technical advances, HbA1c assay is now well standardized and reliable. Since 2009 several international diabetes associations (American Diabetes Association, 2010; International Expert Committee, 2009) have recommended the use of the HbA1c threshold value of 6.5% to diagnose diabetes. The recommendations also include that the HbA1c test should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP).

However, the diagnostic efficacy and the optimal threshold value of HbA1c remain unclear in Chinese diabetes population. Studies have demonstrated that HbA1c level may vary with patients' ethnicity, independent of glucose levels (Herman and Cohen, 2012; Selvin et al., 2011). Coupled with different diet styles of Chinese from western counterparts (He et al., 2009), it begs the question whether the American Diabetes Association (ADA) criterion of HBA1c at 6.5% can be applied to Chinese diabetes of Han nationality (the largest number in the world). This lack in epidemiological data and standardization of HbA1c assay in most Chinese hospitals makes HbA1c currently not an accepted diagnostic criterion in Chinese diabetes guideline. Furthermore, it is unclear to what extent the Chinese diabetes prevalence would change when HbA1c is accepted as a diagnostic criterion. Diabetes has a chronic course and requires expensive management. It is predictable that even a small increase in prevalence would cast a great challenge on the healthcare system.

Research design and methods

Study design and subjects

This population-based stratified cross-sectional survey was carried out in a southern town containing 17 villages, with a total population of 36,700. We used stratified sampling method to recruit a representative sample of subjects who were 35 years of age or older. The sampling process was stratified according to sex, age and economic development status (as assessed on the basis of the gross domestic product [GDP] for each village). Only subjects who had lived in their current residence for 5 years or longer were eligible to participate. A total of 7340 individuals were selected and invited to participate. Among them, 351 subjects were excluded because of acute illness, anemia (assessed by history), incomplete data or unwilling to participate, leaving 6989 subjects for analysis. The overall participating rate was 95.2%.

All participants provided written informed consent. The study is complied with the declaration of Helsinki. The study protocol was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University.

Anthropometric measurements

Anthropometric measurements including weight, height, waist circumference, hip circumference, blood pressure and heart rate were obtained according to standard technique by trained investigators. According to Chinese hypertension guideline (Liu, 2011), obesity was defined as body mass index (BMI) $\geq$28 kg/m^2. Abdominal obesity was defined as a waist circumference $\geq$90 cm in male or $\geq$85 cm in female. Hypertension was diagnosed as systolic blood pressure (SBP) $\geq$140 mm Hg and or diastolic blood pressure (DBP) $\geq$90 mm Hg or being on anti-hypertensive treatment.

Laboratory assay

After an overnight fast, all participants underwent FPG, HbA1c and lipid profile measurement. Participants without PDD underwent 75-g oral glucose tolerance test (OGTT) on the same day. HbA1c assay was performed with whole blood specimen. Other tests were performed with plasma. HbA1c was assayed by ion-exchange high-performance liquid chromatography (D-10, Bio-Rad Laboratories, Hercules, CA), which had been certified by NGSP and was traceable to the International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine reference method. Plasma glucose and lipid profiles were measured using a TBA-120 auto-analyzer (Toshiba Medical Systems, Japan).

Diabetes diagnosis

Currently, HbA1c is not accepted as a criterion for diabetes in China. As a result, all NDD was diagnosed based on ADA OGTT criteria (American Diabetes Association, 2012): FPG $\geq$7.0 mmol/l (126 mg/dl) or 2 h-PG $\geq$11.1 mmol/l (200 mg/dl) during an OGTT. Suspected subjects without hyperglycemic symptoms underwent another FPG and/or 2-h PG examination on a different day.

Statistical analysis

All statistical analyses were conducted using SPSS 13.0 statistical package (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean $\pm$ standard deviation when in normal distribution, or median (P2.5–P97.5) in skewed distribution. Categorical variables were expressed as numbers and percentages. The difference between non-diabetes group and diabetes group was test by *t*-test, nonparametric test, or Pearson chi-square test according to the variable type and data distribution. Receiver operating characteristic (ROC) curves were constructed to calculate sensitivity and specificity of HbA1c cutting points, using OGTT as the gold standard. For each HbA1c cutting point, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The point with maximum sensitivity and specificity was selected as the optimal cut-off value. A two-tailed p value $<$0.05 was considered statistically significant.

Results

Demographic and clinical features

Among the 6989 participants, 449 had PDD and 422 had NDD, with a mean age of 52 (ranging 36–80) years. The prevalence of diabetes was 12.46%.

The general data of the participants were presented in Table 1. Compared with non-diabetes group, patients in the diabetes group were

Table 1
Comparison of general data between non-diabetes group and diabetes group.

	Non-diabetes (n = 6118)	Diabetes[a] (n = 871)	p value
Age, years	51.0 (36.0–79.0)	59.0 (38.0–83.0)	0.000
Male, %	40.2	45.1	0.001
Diabetes family history, %	9.8	18.1	0.000
CHD, %	1.1	3.3	0.000
Smoking[b], %	25.2	27.8	0.102
Anthropometric index			
Height, cm	157.0 (143.0–173.5)	156.0 (140.8–172.0)	0.005
Weight, kg	60.0 (42.0–84.0)	65.0 (45.6–89.4)	0.000
BMI, kg/m^2	24.24 (18.29–32.02)	26.56 (19.77–34.31)	0.000
Obesity[c], %	15.4	33.3	0.000
Waist circumference, cm	82.0 (65.0–101.0)	88.0 (69.5–107.6)	0.000
Hip circumference, cm	94.0 (82.0–108.0)	96.0 (83.0–113.0)	0.000
WHR	0.87 (0.75–1.00)	0.91 (0.78–1.04)	0.000
Abdominal obesity, %	30.6	54.5	0.000
Hemodynamic index			
SBP, mm Hg	128.3 (102.4–174.3)	138.7 (107.9–185.8)	0.000
DBP, mm Hg	74.5 (57.0–98.0)	78.0 (59.9–101.9)	0.000
Hypertension, %	25.1	48.7	0.000
HR, bpm	80.0 (61.0–108.0)	82.0 (61.0–113.0)	0.000
Laboratory index			
TC, mmol/l	5.15 (3.46–7.32)	5.39 (3.10–8.16)	0.000
Triglyceride, mmol/l	1.21 (0.50–3.95)	1.68 (0.64–7.46)	0.000
HDL-C, mmol/l	1.43 (0.90–2.33)	1.30 (0.86–2.07)	0.000
LDL-C, mmol/l	3.06 (1.29–4.98)	3.15 (1.21–5.53)	0.078
HbA1c, %	5.70 (4.8–6.5)	6.80 (5.20–12.60)	0.000

Results are median (P2.5–P97.5) except for those specified. BMI, body mass index; CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; WHR, waist–hip ratio.

[a] All diabetes were diagnosed by OGTT criteria, with 449 cases of PDD and 422 cases of NDD.

[b] Smoking was defined as more than 400 cigarettes lifetime, or more than 1 cigarette/d in the last 6 months.

[c] Obesity was defined as BMI $\geq$ 28 kg/m^2.