Original Article

Glycated Haemoglobin in Diagnosis of Diabetes Mellitus and Pre-diabetes among Middle-aged and Elderly Population: Shanghai Changfeng Study*

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Abstract

Objective To investigate the optimal glycated haemoglobin (HbA1c) cut off points and evaluate the impact of HbA1c on diabetes and pre-diabetes in middle-aged and elderly population.

Methods Subjects were recruited from Shanghai Changfeng Study. A total of 1 973 community-based participants (age≥45) without known diabetes underwent oral glucose tolerance test (OGTT) by using a 75-g oral glucose load and HbA1c was measured by using high performance liquid chromatography (HPLC). Subjects were classified as normal glucose tolerance (NGT), pre-diabetes(impaired glucose regulation, IGR) and new diagnosed diabetes (NDD) per 1999 WHO criteria. Two tests are compared with receiver operating characteristic curve (ROC).

Results Among 1973 subjects, 271 (13.7%) were diagnosed as NDD and 474 (24.0%) as IGR by using OGTT. HbA1c was 5.7%±0.7% in this population. Use of 6.5% as the HbA1C cutoff point has sensitivity of 38.7% and specificity of 98.5%. We recommend 6.0% as a better cutoff value for diagnosis of diabetes in this population (AUC 0.829, 95% CI 0.798-0.860, $P<0.001$) with its sensitivity and specificity as 66.1% and 86.8%. For IGR, the results showed low sensitivity (44.9%) and specificity (66.7%) with an AUC of 0.571 for HbA1c when 5.8% was used as the cutoff point. Participants detected with HbA1c≥6.0% were associated with nearly the same metabolic characteristics, including body mass index (BMI), blood pressure, lipid profile and urine albumin-creatinine ratio (uACR) compared with diabetic subjects detected by OGTT.

Conclusion The optimum HbA1c cutoff point for diabetes in our study population was lower than ADA criteria, and HbA1c may not be used to identify IGR.

Key words: Glycated haemoglobin(HbA1c); Diabetes; Pre-diabetes; Impaired glucose regulation (IGR)

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INTRODUCTION

In 2010, American Diabetes Association (ADA) recommends using HbA1c≥6.5% for diagnosis of diabetes and using HbA1c 5.7%-6.4% for diagnosis of pre-diabetes (using the term 'category of increased risk for diabetes')[1]. More clinicians are in favor of using HbA1c as a diagnosis tool for the following reasons. First, HbA1c measurements can be conducted at any time and subjects do not need particular preparations. Second, HbA1c has a smaller intra-individual biological variability (within 2%) compared to that of plasma glucose[2]. HbA1c is not influenced by sudden glycaemic variations and reflects the mean plasma glucose levels over the last 2-3 months.

However, China Guideline to type 2 diabetes in 2010 did not recommend HbA1c for diagnosis of diabetes because of insufficient evidence-based data in Chinese population and non-standardized HbA1c measurement nationwide[3]. Results of three recent studies from different population groups in Shanghai[4], Beijing[5] and Qingdao[6], have found different cutoff points of HbA1c for diabetes. Moreover, most studies agreed to the use of HbA1c for diagnosis of diabetes but not for pre-diabetes[7-10]. Given the diversity of characteristics of Chinese population, more evidence and data are needed to evaluate HbA1c cutoff points in diagnosing abnormal glucose metabolism. The aim of this study was therefore to determine the optimal HbA1c cutoff points for detecting diabetes and pre-diabetes in middle-aged and elderly population in Shanghai and to validate whether the cutoff points were suitable by comparing the cardiovascular disease (CVD) risk in people classified as diabetes or pre-diabetes according to HbA1c cutoff points and OGTT test.

MATERIALS AND METHODS

Study Design and Population

Participants of our subjects were from Shanghai Changfeng Study (SCFS) from September 2010 to October 2011, which is a community-based prospective cohort study of chronic diseases among the middle-aged and elderly, as described elsewhere[11]. A total of 2 493 consecutive participants aged 45 years old and above were enrolled. We excluded 520 subjects, i.e., subjects who did not have HbA1c assessments and other key variables (e.g. age, blood glucose, height, weight) (*n*=84), subjects who had been diagnosed to have diabetes mellitus (*n*=393), subjects who had chronic renal failure on hemodialysis (*n*=2), anaemia (*n*=35), or subjects who were on glucocorticoid treatment (*n*=6). 1 973 participants remained eligible. The study had been approved by the Ethical Committee of Zhongshan Hospital, Fudan University. All the patients were consented upon entering the study.

Data Collection

Letters were sent to participants with instructions, asking them not to alter diet or physical activity for at least 3 days before test. A questionnaire was administered to evaluate their medical history and lifestyle.

Weight and height were measured while the participants were clothed in a light gown. Waist circumference was measured midway between the lowest rib margin and the iliac crest and hip circumference was measured at the widest level over the greater trochanters. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Resting blood pressure was measured three times with an electronic blood pressure monitor (OMRON Model HEM-752 FUZZY' Omron Co., Dalian, China), and then the average was calculated.

After an overnight fast, venous blood samples were collected at 0 and 120 min following 75-g oral glucose challenge for all participants. HbA1c were measured with high performance liquid chromatography (HPLC) (BIO-RAD II TURBO) and were standardized to the National Glycated Haemoglobin Standardization Program (NGSP). Plasma glucose levels were determined with a glucose oxidase method. Fasting blood glucose (FBG), postload blood glucose (PBG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c) and triglycerides (TG) were measured by a model 7600 automated bio-analyzer (Hitachi, Tokyo, Japan). Urinary albumin excretion rate was measured from an early morning urine sample, with the urinary albumin to creatinine ratio (uACR) detected by an immunonephelometric method.

Definition

According to WHO criteria, newly diagnosed diabetes (NDD) was defined as fasting plasma

glucose (FBG) with no previously confirmed or treated diabetes≥7.0 mmol/L and/or a 2-h plasma glucose level during an OGTT (OGTT 2hPBG) ≥11.1 mmol/L[12]. Pre-diabetes, referred to as impaired glucose regulation (IGR) was defined as FBG from 6.1 to less than 7.0 mmol/L and/or 2hPBG from 7.8 mmol/L to less than 11.1 mmol/L. IGR could be classified into three sub-groups: isolated IFG (i-IFG): with no previously confirmed and treated diabetes but with FBG from 6.1 to less than 7.0 mmol/L and 2-hour glucose less than 7.8 mmol/L; isolated IGT (i-IGT): with no previously confirmed or treated diabetes but with FBG less than 6.1 mmol/L and 2-hour glucose from 7.8 mmol/L to less than 11.1 mmol/L; IFG+IGT: with both IFG and IGT.

Statistical Analyses

All statistical analyses were performed by SPSS 16.0 for Windows (SPSS Inc, USA). P-P normal probability plots were used to test the normal distribution of variables. Normally distributed continuous variables were presented as mean±SD and the others as median [95% confidence interval (CI)]. All continuous variables but uACR were normally distributed. uACR were therefore log transformed. Differences among groups were tested by univariate analysis of variance (UNIANOVA) or one-way ANOVA, and post hoc comparisons were performed with LSD test. Chi-square statistical analysis was used to determine the difference in categorical variables. Receiver operating characteristic (ROC) curves were plotted and the area under the ROC curve (AUC) was calculated for HbA1c; an AUC value of <0.7 was considered sub-optimal. Additionally, Youden's index was calculated by the formula: [Youden's index= sensitivity+specificity-1]. The optimal cutoff point was the point on the ROC curve closest to the upper-left corner with maximum sensitivity and specificity, namely, the maximum Youden's index[13]. In all analyses, a two-sided *P*-value of <0.05 was considered to indicate statistical significance.

RESULTS

Population Characteristic

A total number of 1 132 (57.4%) women and 841 (42.6%) men had been evaluated. The mean HbA1c was 5.7% for this population. According to WHO criteria, 1 228 cases (62.2%) were classified as normal glucose tolerance (NGT), 474 cases (24.0%) were IGR and 271 (13.7%) were NDD. In IGR group, 37 cases (7.8%) were i-IFG, 399 cases (84.2%) were i-IGT and 38 cases (8.0%) were IFG+IGT. Table 1 describes

Table 1. Characteristics of Subjects Stratified by Glucose Status According to OGTT

	All	NGT	IGR	NDD	$P^{\#}$
n (%)	1973	1228(62.2%)	474(24.0%)	271(13.7%)	
Age (y)	61.3±10.0	59.8±9.6	63.3±10.3[a]	65.0±10.4[a,b]	<0.001
Male (*n*,%)	841(42.4%)	489(39.8%)	217(45.8%)[a]	135(49.8%)[a]	0.003
HbA1C%	5.7±0.7	5.5±0.3	5.7±0.4[a]	6.6±1.3[a,b]	<0.001
BMI (kg/m^2)	24.1±3.3	23.5±3.1	24.9±3.3[a]	25.6±3.6[a,b]	<0.001
Waist (cm)	83.5±9.7	81.2±9.0	86.1±9.3[a]	89.5±9.5[a,b]	<0.001
Hip (cm)	92.3±6.9	91.3±6.6	93.5±7.0[a]	94.8±7.2[a,b]	<0.001
WHR	0.904±0.074	0.889±0.073	0.919±0.068[a]	0.944±0.066[a,b]	<0.001
FBG (mmol/L)	5.3±1.1	4.9±0.4	5.3±0.6[a]	6.8±2.2[a,b]	<0.001
2hPBG (mmol/L)	7.7±3.6	5.9±1.2	8.9±1.3[a]	14.3±5.2[a,b]	<0.001
SBP (mmHg)	134.4±19.2	130.5±18.3	139.7±18.9[a]	142.6±18.7[a,b]	<0.001
DBP (mmHg)	76.3±10.2	75.1±10.0	78.2±10.4[a]	78.2±9.8[a]	<0.001
TC (mmol/L)	5.1±0.9	5.0±0.9	5.0±0.9	5.1±0.9	0.769
TG (mmol/L)	1.7±1.2	1.5±1.0	2.0±1.6[a]	2.1±1.2[a]	<0.001
HDL-C (mmol/L)	1.4±0.3	1.4±0.4	1.3±0.3[a]	1.2±0.3[a,b]	<0.001
LDL-C (mmol/L)	2.9±0.8	2.9±0.8	2.9±0.8	2.9±0.8	0.190
uACR$^{\diamond}$(μg/ng)	6.3(1.7-103.3)	5.8(1.6-82.9)	6.9(1.9-141.6)[a]	8.2(2.0-189.5)[a,b]	<0.001

***Note*.** Normally distributed continuous data are mean±SD. Non-normally distributed continuous data are median (95% CI). Categorical variables are percentage of subjects. $^{\diamond}$median (95% CI); $^{\#}$Differences within NGT, IGR and NDD groups. [a]Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: *P*<0.05 versus NGT; [b]Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: *P*<0.05 versus IGR. BMI: body mass index, WHR: waist-hip-ratio, FBG: Fasting blood glucose, 2h PBG: OGTT 2h blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: Total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, uACR: urine albumin-creatinine ratio.

the characteristics of this population stratified by their glycaemic states. As expected, age, HbA1c, BMI, WHR, systolic and diastolic blood pressure, blood glucose, TG and uACR increased with worsening of the glucose status, while HDL-C decreased. However, serum levels of TC and LDL-C were not statistically different among the three groups.

Based on ADA 2010 recommendation of HbA1c criteria, 130 cases (6.6%) had HbA1c≥6.5%, and 795 cases (40.3%) had HbA1c between 5.7% and 6.4%. This can be translated into a 1.68-fold increase in detection rate of people classified as having IGR, while using HbA1c≥6.5% decreased the detection rate of diabetes to nearly half of that using OGTT. Of the 130 cases with HbA1c≥6.5%, 4 (3.1%) cases were NGT, 21 (16.1%) were IGR, and 105 (80.8%) were NDD. Of the 795 cases with HbA1c between 5.7% and 6.4%, 443 (54.5%) were NGT, 237 (29.8%) were IGR, and 124 (15.6%) were NDD. Of the 1048 cases with HbA1c<5.7%, 790 (75.4%) were NGT, 216 (20.6%) were IGR, and 42 (4.0%) were NDD.

Of the 1 228 participants with NGT, 790 (64.3%) had HbA1C% <5.7%, 434 (35.3%) had HbA1C% between 5.7% and 6.4%, and 4 (0.3%) had HbA1C%≥6.5%. In IGR group (*n*=474), 216 (45.6%) had HbA1C% <5.7%, 237 (50%) had HbA1C% between 5.7% and 6.4%, and 21 (4.4%) had HbA1C%≥6.5%. In NDD (*n*=271) group, 42 (15.5%) had HbA1C% <5.7%, 124 (45.8%) had HbA1C% between 5.7% and 6.4%, and 105 (38.7%) had HbA1C%≥6.5%.

Diagnostic Properties of HbA1c

Figure 1 shows the ROC curve for HbA1c cutoff points evaluated against WHO criteria for participants with NDD and IGR. For IGR, a cutoff point of 5.8% had the optimum sensitivity (44.9%) and specificity (66.7%) with an AUC of 0.571. Table 2 showed the sensitivity, specificity, Youden's index, positive and negative predictive values, and positive and negative likelihood ratios for identifying diabetes at different HbA1c thresholds. Paired comparison on sensitivity showed significant difference between HbA1c cutoff points of 5.6%, 5.7%, 5.8%, 6.2%, 6.3%, 6.4%, 6.5%, and 6.0% (*P*<0.001, <0.001, 0.002, 0.008, <0.001, <0.001, <0.001, respectively), and there was no statistical significance between 5.9%, 6.1%, and 6.0% (*P*=0.137, 0.110, respectively). Paired comparison on specificity showed significant difference between 6.0% and the others (All *P*<0.001). For ADA HbA1c criterion 6.5%, we found sensitivity of 38.7% and specificity 98.5%. The optimal HbA1c cutoff point for NDD was 6.0% with sensitivity of 66.1%, specificity of 86.8% and an AUC of 0.829. The chance-corrected proportion agreement (kappa) for classification of diabetes between the criteria of the OGTT and HbA1c of 6.0% was 0.44.

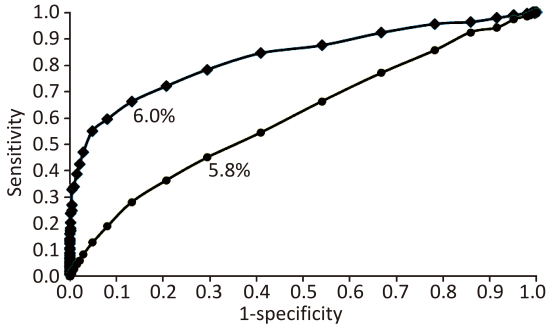

Figure 1. Receiver Operating Characteristic Curve of HbA1c for Diabetes and IGR. Area under curve is 0.829 (95% CI 0.798-0.860) for diabetes and 0.571 (95% CI 0.524-0.600) for IGR.

Of 130 participants with HbA1c≥6.5%, 105 (80.8%) had diabetes. The ADA cutoff point detected 48.0% of participants with NDD. Of 404 individuals with HbA1c level≥6.0%, 179 (44.3%) had newly diagnosed diabetes, and 133 (32.9%) had IGR. This cutoff point would detect 66.1% of patients with newly diagnosed diabetes and 28.1% of individuals with IGR.

Table 3 shows the number and clinical characteristics of participants identified as having diabetes based on OGTT criteria and the HbA1c threshold of 6.0%. The latter criteria detected more subjects. Although subjects with HbA1c≥6.0% had lower FBG and OGTT 2hPBG compared to those diagnosed according to WHO1999, other CVD risk factors including BMI, blood pressure and lipid profile were nearly the same, and there was no significant difference on uACR between these two groups.

Table 4 shows cardiovascular risk factors in different groups using WHO1999 and HbA1c criteria. As expected, individuals with NDD on OGTT had a number of significantly adverse cardiovascular risk factors compared to non-NDD among HbA1c≥6.0% and HbA1c<6.0% people. Non-NDD individuals with HbA1c≥6.0% already had higher BMI, WHR, SBP, uACR, and lower HDL-C compared to Non-NDD subjects with HbA1c<6.0%. In individuals with NDD on OGTT, subjects with HbA1c≥6.0% had worse hyperglycemic markers and lipid profile compared to

Table 2. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value for Detecting Diabetes Based on OGTT with HbA1c Thresholds

HbA1c (%)	Sensitivity (%)	Specificity (%)	Youden's Index	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio (%)	Negative Likelihood Ratio (%)
≥5.6	87.5 (83.0-90.9)	46.1 (43.7-48.4)	0.34	20.5 (18.3-22.9)	95.8 (94.2-97.0)	1.6 (1.5-1.7)	0.3 (0.2-0.4)
≥5.7	84.5 (79.7-88.3)	59.1 (56.8-61.4)	0.44	24.8 (22.1-27.6)	96.0 (94.6-97.0)	2.1 (1.9-2.2)	0.3 (0.2-0.4)
≥5.8	78.2 (72.9-2.7)	70.6 (68.4-72.7)	0.49	29.8 (26.5-33.2)	95.3 (94.0-96.4)	2.7 (2.4-2.9)	0.3 (0.2-0.4)
≥5.9	71.9 (66.3-77.0)	79.4 (77.4-81.2)	0.51	35.7 (31.8-39.8)	94.7 (93.4-95.7)	3.5 (3.1-3.9)	0.4 (0.3-0.4)
≥6.0	66.1 (60.2-71.4)	86.8 (85.1-88.3)	0.53	44.3 (39.5-49.2)	94.1 (92.9-95.2)	5.0 (4.3-5.8)	0.4 (0.3-0.5)
≥6.1	59.4 (53.5-65.1)	92.0 (90.6-93.2)	0.51	54.2 (48.5-59.8)	93.4 (92.1-94.5)	7.4 (6.2-9.0)	0.4 (0.4-0.5)
≥6.2	55.0 (49.0-60.8)	95.2 (94.1-96.1)	0.50	64.5 (58.1-0.4)	93.0 (91.7-94.1)	11.4 (9.0-14.5)	0.5 (0.4-0.5)
≥6.3	46.9 (41.0-52.8)	97.1 (96.2-97.8)	0.44	72.2 (65.1-78.3)	92.0 (90.6-93.2)	16.3 (12.0-2.1)	0.5 (0.5-0.6)
≥6.4	42.4 (36.7-48.4)	97.9 (97.1-98.5)	0.40	76.2 (68.8-82.3)	91.4 (90.1-92.6)	20.1 (14.1-28.5)	0.6 (0.5-0.7)
≥6.5	38.7 (33.1-44.7)	98.5 (97.8-99.0)	0.37	80.8 (73.2-86.6)	91.0 (89.6-92.2)	26.4 (17.4-40.0)	0.6 (0.6-0.7)

***Note*.** Values in parentheses are 95% confidence intervals.

Table 3. Clinical Characteristics of Participants Identified as Having Diabetes Based on OGTT and HbA1c

	NDD Defined by OGTT	NDD Defined by HbA1c≥6.0%	*P*
N	271	404	
Age (y)	65.0±10.4	63.8±10.1	0.128
Male (*n*,%)	135 (49.8%)	189 (46.8%)	0.485
HbA1C%	6.6±1.3	6.6±1.1	0.877
BMI (kg/m^2)	25.6±3.6	25.3±3.5	0.268
Waist (cm)	89.5±9.5	87.5±10.0	0.011
Hip (cm)	94.8±7.2	94.1±7.4	0.231
WHR	0.944±0.066	0.930±0.072	0.011
FBG (mmol/L)	6.8±2.2	6.2±1.8	0.001
2hPBG (mmol/L)	14.3±5.2	11.3±4.9	<0.001
SBP (mmHg)	142.6±18.7	140.0±19.0	0.052
DBP (mmHg)	78.2±9.8	77.1±10.2	0.166
TC (mmol/L)	5.1±0.9	5.2±1.0	0.470
TG (mmol/L)	2.1±1.2	2.0±1.1	0.134
HDL-C (mmol/L)	1.2±0.3	1.3±0.3	0.484
LDL-C (mmol/L)	2.9±0.8	3.0±0.9	0.231
uACR$^{\diamond}$(μg/ng)	8.2 (2.0-189.5)	7.4 (1.6-174.5)	0.155

***Note*.** Normally distributed continuous data are mean±SD. Non-normally distributed continuous data are median (95% CI). Categorical variables are percentage of subjects. $^{\diamond}$median (95% CI). BMI: body mass index, WHR: waist-hip-ratio, FBG: Fasting blood glucose, 2h PBG: OGTT 2h blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: Total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, uACR: urinary albumin-creatinine ratio.

Table 4. Cardiovascular Risk Factors in Different Groups Using WHO1999 and HbA1c Criteria

	Non NDD		NDD	
	(1) HbA1c<6.0%	(2) HbA1c≥6.0%	(3) HbA1c<6.0%	(4) HbA1c≥6.0%
n	1477	225	92	179
Age (y)	60.3±9.8	63.7±10.3*	67.1±10.8§‡	63.9±10.0$^{\#}$
Male (*n*,%)	609 (41.2%)	97 (43.1%)	43 (46.7%)	92 (51.4%)
HbA1C%	5.5±0.3	6.2±0.2*	5.6±0.2§,‡	7.1±1.4$^{\&,\#}$
BMI (kg/m^2)	23.8±3.2	24.9±3.4*	25.1±3.7§	25.9±3.5$^{\&}$
Waist (cm)	82.1±9.1	85.4±10.1*	88.3±10.0§,‡	90.1±9.2$^{\&}$
Hip (cm)	91.7±6.7	93.2±7.3*	93.9±6.9§	95.2±7.4$^{\&}$
WHR	0.895±0.073	0.916±0.075*	0.939±0.070§,‡	0.947±0.065$^{\&}$
FBG (mmol/L)	5.0±0.5	5.4±0.6*	5.8±1.5§,‡	7.3±2.3$^{\&,\#}$
2hPBG (mmol/L)	6.5±1.7	8.0±2.2*	12.3±6.0§,‡	15.3±4.4$^{\&,\#}$
SBP (mmHg)	132.4±18.8	137.9±19.4*	143.7±19.7§,‡	142.1±18.2$^{\&}$
DBP (mmHg)	76.0±10.2	76.0±9.9	77.4±8.5	78.7±10.4$^{\&}$
TC (mmol/L)	5.1±0.93	5.1±0.9	4.9±0.9	5.2±1.0$^{\#}$
TG (mmol/L)	1.6±1.3	1.8±1.0	2.0±1.2§	2.2±1.2$^{\&}$
HDL-C (mmol/L)	1.4±0.4	1.3±0.4*	1.3±0.4§	1.2±0.2$^{\#}$
LDL-C (mmol/L)	2.9±0.8	3.0±0.8	2.8±0.8‡	3.0±0.9$^{\&,\#}$
uACR$^{◇}$(μg/ng)	6.0 (1.7-83.2)	6.8 (1.3-188.1)*	8.3 (2.0-221.1)§	8.2 (2.1-131.5)$^{\&}$

Note. *Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: $P<0.05$ group (2) versus group (1). §Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: $P<0.05$ group (3) versus group(1). ‡Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: $P<0.05$ group (3) versus group(2). $^{\&}$Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: $P<0.05$ group (4) versus group(2). $^{\#}$Analysis of variance with LSD post-hoc test or Chi-square statistical analysis: $P<0.05$ group (4) versus group(3). Normally distributed continuous data are mean±SD. Non-normally distributed continuous data are median (95% CI). Categorical variables are percentage of subjects. $^{◇}$median (95% CI). BMI: body mass index, WHR: waist-hip-ratio, FBG: Fasting blood glucose, 2h PBG: OGTT 2h blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: Total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, uACR: urinary albumin-creatinine ratio.

those with HbA1c<6.0%. Except for blood glucose, SBP and WHR, there were no significant differences between non-NDD individuals with HbA1c≥6.0% and NDD subjects with HbA1c<6.0% in other cardiovascular risk factors including BMI and uACR. At the same time, non-NDD individuals with HbA1c≥6.0% had a worse lipid profile.

DISCUSSION

In the present study, we evaluated HbA1c as an alternative to OGTT for diagnosis of diabetes mellitus and pre-diabetes in order to find the optimal HbA1c cutoff points for diabetes and pre-diabetes in middle-aged and elderly participants enrolled. The results have shown that the optimal HbA1c cutoff value for diagnosis of DM was at 6.0% (AUC 0.829, 95% CI 0.798 to 0.860, $P<0.001$) with its sensitivity and specificity as 66.1% and 86.8%. Diabetes detected by HbA1c⩾6.0% was associated with nearly the same metabolic characteristics to diabetes detected by OGTT, including BMI, blood pressure, lipid profile and uACR, except for blood glucose. However, the use of the HbA1c levels had a clearly lower diagnostic validity for the IGR.

A cutoff point of HbA1c≥6.5% for the diagnosis of diabetes was recommended by 2010 ADA as optimal for detecting diabetic retinopathy[14]. However, we found in our study that HbA1c 6.5% has very low sensitivity of 38.6% and using ADA criteria also reduces detection rate of DM to nearly half. The cutoff point for screening new diagnosed diabetes with the highest sensitivity and specificity in our study was A1C level of 6.0%. There are considerable debates about the HbA1c cutoff points. Our results are consistent with other studies done in

China, in which the values are lower than the ADA recommended HbA1c levels for diabetes: ≥6.3% in Shanghai[4], ≥6.0% in Beijing[5], and ≥5.6% in Qingdao[6]. These may due to the different demographic and biochemical characteristics of thestudies. Compared with the population with a cutoff point of 6.3% in Shanghai, our study participants were older, had a higher BMI, HbA1c and blood glucose level, and had a greater proportion of participants with newly diagnosed diabetes. These differences may explain why we had a lower cutoff point compared with them. The HbA1c level and proportion of newly diagnosed diabetes were almost the same in our study and in Qingdao study. Our laboratory analysis method for HbA1c was High Performance Liquid Chromatography (HPLC). The one used in the Qingdao study was an immunoturbidimetry method. The A1C concentration in Qingdao study was calculated by using the formula: [calculated A1C (%)=0.81×A1C(test result)+2.39]. The diversity could be partially due to the different detection methods uesd. Results of other studies from different ethnic groups, such as Dutch population[8] and US population[9], also have found different cutoff points of HbA1c for diabetes, i.e., 5.8% and 5.7%, respectively. Other studies found that the distribution of HbA1c varied with races[15]. This suggests that the worldwide variability on different ethnic groups could further add to the difficulties of identical standard HbA1c cutoff point for diabetes worldwide[10].

The use of HbA1c as a diagnostic test in IGR is debatable. People detected by ADA HbA1c criteria were 1.68 folds compared to those diagnosed by WHO criteria. Of 795 individuals with HbA1c between 5.7% and 6.4%, 237 (29.8%) were IGR. This range detected only 50% of participants with IGR. This relatively large degree of discordance suggests using recommended HbA1c cutoff point would lead to a change in those people classified as having IGR. In our study, the AUC for HbA1c cutoff point (6.0%) for DM >0.7, and on the other hand, HbA1c (5.8%) had a sub-optimal AUC (0.571). We found low sensitivity and specificity of the HbA1c cutoff point (5.8%) for IGR using OGTT criteria. The low sensitivity (44.9%) of the HbA1c cutoff point (5.8%) would lose a great proportion of IGR participants who could get benefit from lifestyle intervention. The results suggested that HbA1c was applicable for detecting diabetes, but not for IGR, and this finding is consistent with other studies using HbA1c to detect IGR[8,5,16-17]. A systemic review also suggested that the sensitivity of HbA1c for detecting impaired glycaemic states was generally low across the studies[18].

ADA recommendations of HbA1c for the diagnosis of diabetes are based on the relations of HbA1c with microvascular disease, especially retinopathy[1]. As we know, cardiovascular diseases are the leading cause of death in diabetic patients. It is important that HbA1c cutoff point could be a better hyperglycemic index associated with both CVD risk factors and microvascular diseases. Our study showed that there were no significant differences in major CVD risk factors and uACR between subjects with HbA1c≥6.0% and diabetic subjects diagnosed according to WHO1999. We noted that non-NDD participants with HbA1c≥6.0% had significantly worse cardiovascular risk profiles compared to non-NDD participants with HbA1c<6.0%, including higher BMI, WHR, SBP, uACR, and lower HDL-C. Interestingly, there were no significant differences between non-NDD individuals with HbA1c≥6.0% and NDD subjects with HbA1c<6.0% in some cardiovascular risk factors including BMI and uACR. Meanwhile, non-NDD individuals with HbA1c≥6.0% had a worse lipid profile. uACR, to some extent, could indicate microvascular diseases. Thus, the cutoff point of HbA1c≥6.0% may be reasonable for diabetes in this population.

A standardized and accurate diagnosis criterion for diabetes plays an extremely important role in clearly detecting and treating the disease. Although the HbA1c test has been standardized in this study, there might be concerns about its relatively expensive cost and lack of standardization nationwide. The identification of individuals with abnormal glucose metabolism is important because early interventions could prevent or delay hyperglycemia related complications. Larger Chinese prospective studies to determine whether the HbA1c cutoff point is appropriate for not only detection of diabetes and IGR but also cardiovascular disease events and mortality are therefore warranted.

We recognize several limitations of this study. First, all participants only had one OGTT test and HbA1c measurement. Second, as our participants were middle-aged and elderly subjects, the results could not be applied to younger population. Third, Shanghai Changfeng Study is a cluster sample population study. Finally, only half of the originally invited subjects participated the study.

In summary, within this middle-aged and elderly population, we found the optimum HbA1c cutoff point≥6.0% for diabetes which was lower than of the cutoff point in ADA criteria, and HbA1c may not be able to identify IGR. Population specific optimum cutoff points may therefore necessitate further and more comprehensive studies.

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CONFLICT OF INTEREST

No authors have any financial/conflict interest to disclose.

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