Glycated Hemoglobin A1c, Fasting Plasma Glucose, and Two-Hour Postchallenge Plasma Glucose Levels in Relation to Carotid Intima-Media Thickness in Chinese with Normal Glucose Tolerance

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Context: The association between hyperglycemic markers and cardiovascular risk is not consistent in nondiabetic subjects. Even less are the data regarding the associations in subjects with normal glucose tolerance (NGT).

Objective: Our objective was to assess the association of glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and 2-h postchallenge glucose with carotid intima-media thickness (CIMT) in subjects with NGT.

Design, participants and measurements: This cross-sectional study included 1627 participants with NGT and aged 40 yr and above, who were randomly recruited from Songnan Community, Baoshan District, Shanghai. All participants received a 75-g oral glucose tolerance test, blood HbA1c assay, and CIMT measurements.

Results: Using multivariable linear regression, after adjustment for age, sex, smoking and drinking status, body mass index, blood pressure, and serum lipids, the increasing trend of CIMT was found in HbA1c quartiles (P = 0.016) rather than in FPG and postchallenge glucose quartiles. Furthermore, in a fully adjusted logistic model including FPG and postchallenge glucose as covariates, participants in the highest quartile of HbA1c, as compared with those in the lowest quartile, still conferred a 68% increased odds of elevated CIMT (≥0.70 mm).

Conclusions: In the population of NGT, HbA1c is significantly associated with CIMT independent of conventional cardiovascular risk factors, FPG, and postchallenge glucose. The results implied that HbA1c could be more informative of cardiovascular risk as compared with FPG and postchallenge glucose in subjects with NGT. (J Clin Endocrinol Metab 96: E1461–E1465, 2011)

Recently, the American Diabetes Association (ADA) International Expert Committee proposed that glycated hemoglobin A1c (HbA1c) should be used as a diagnostic index for diabetes based on a hyperglycemia-related microvascular complication, retinopathy (1). On the other hand, it is well known that in diabetic patients, macrovascular complications are the leading cause of mortality and morbidity (2). Diabetic patients experienced a 2- to 4-fold increase of cardiovascular diseases (CVD) risk compared with those without diabetes (3). Given the greater...
Clinical and biochemical measurements

Study population and design

A cross-sectional survey was performed during 2008–2009 in a population from Songnan community located in Baoshan District, Shanghai. First, all the residents aged 40 yr or above were invited to receive a fasting blood test. Based on the results of fasting glucose level and history of diabetes, participants were categorized into three groups: NGT, impaired glucose regulation, and diabetes. According to a ratio of 1:4:1:2:1, we randomly selected participants from these groups to receive a more comprehensive survey including a standard 75-g OGTT, blood and urine collection, an anthropometric measurement, and a questionnaire survey. A total of 10,185 residents participated in the survey in 2008, and 4012 were included in the survey in 2009. After excluding participants who had incomplete information of FPG and postchallenge glucose levels (n = 107) and HbA1c (n = 38) and those with impaired glucose regulation (n = 958) or with a history of diabetes (n = 813) or with newly diagnosed diabetes (n = 469), the sample in the analysis included 1627 subjects. Written consent was obtained from all participants, and ethics approval was obtained from the Institutional Review Board of Ruijin Hospital.

Clinical and biochemical measurements

The detailed information about medical history and lifestyles including smoking and drinking status were obtained using a standard questionnaire by the trained physicians. Current smoking status was defined as yes if the subject smoked at least one cigarette per day or seven cigarettes per week in the past 6 months. Current drinking status was defined as yes if the subject consumed alcohol at least once a week in the past 6 months. Anthropometric measurements included body weight, body height, and waist circumference (WC). Body mass index (BMI) was calculated using the formula of weight/height² (kilograms per square meter). Blood pressure was measured on the non-dominant arm in a seated position after a 10-min rest, using an electronic blood pressure monitor (OMRON Model HEM-752 FUZZY® Omron Co., Dalian, China). Three measurements were taken at 1-min intervals, and the average was used for analysis. All participants were informed to fast for at least 10 h before blood samples were collected. Two-point (0 and 2 h) OGTT with a 75-g glucose load was performed. FPG, postchallenge glucose, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), and triglycerides (TG) were measured using an automated biochemical instrument (Bayer Biochemical autoanalyzer ADVIA 1650, Bayer, Leverkusen, Germany). HbA1c was measured by HPLC (Bio-Rad Co., Hercules, CA).

CIMT on the far wall of the right and left common carotid arteries, 1.5 cm proximal to the bifurcation, was measured by a trained sonographer using a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Genova, Italy) with a linear 7.5-MHz transducer. The transducer was manipulated so that the lumen diameter was maximized in the longitudinal plane. CIMT was measured online at the end of diastole as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first and second lines represent the lumen-intimal interface and the collagen-contained upper layer of tunica adventitia, respectively. The greater value of the right and left common CIMT was used for analysis.

Definitions

NGT was defined as FPG higher than 5.6 mmol/liter and postchallenge glucose below 7.8 mmol/liter and without type 2 diabetes history according to the 2003 American Diabetes Association (ADA) criteria (6). The upper quartile of CIMT (≥0.7 mm) was defined as elevated CIMT.

Statistics analysis

All statistical analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC). Data are presented as means ± sd or medians (interquartile ranges). Differences in quartiles of HbA1c were tested by one-way ANOVA. The χ² test was adopted to compare categorical variables. Linear regressions were performed to evaluate the associations between CIMT and quartiles of glycemic markers with or without adjustments. Confounders adjusted in linear regressions included age, sex, smoking and drinking status, BMI, blood pressure, and serum lipids. We also implemented four logistic regression models to assess the relationship between HbA1c categories and elevated CIMT. In model 1, no covariates were adjusted; in model 2, age, sex, and smoking and drinking status were adjusted; in model 3, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), WC, BMI, SBP, FPG, postchallenge glucose, TG, TC, LDL, and CIMT (all P < 0.05). Compared with the participants in the highest quartile of HbA1c, those in the lowest, the second, and the third quartiles had significantly lower levels of CIMT (0.58 ± 0.11, 0.60 ±
TABLE 1. Clinical characteristics of the study population according to HbA1c quartiles

<table>
<thead>
<tr>
<th>HbA1c quartiles (%)</th>
<th>n</th>
<th>Age (yr)</th>
<th>Male [n (%)]</th>
<th>Current smoker [n (%)]</th>
<th>Current drinker [n (%)]</th>
<th>WC (cm)</th>
<th>BMI (kg/m²)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>FPG (mmol/liter)</th>
<th>TG (mmol/liter)</th>
<th>HDL-c (mmol/liter)</th>
<th>LDL-c (mmol/liter)</th>
<th>TC (mmol/liter)</th>
<th>HDL-c, LDL-c, TG, FPG, and postchallenge glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5–5.6%</td>
<td>290</td>
<td>55.8 ± 8.8a</td>
<td>124 (42.8)</td>
<td>72 (29.5)</td>
<td>63 (23.7)</td>
<td>82.4 ± 8.9b</td>
<td>23.8 ± 3.1c</td>
<td>127 ± 18c</td>
<td>77 ± 10</td>
<td>4.70 ± 0.39c</td>
<td>1.13 (0.81–1.68)</td>
<td>1.37 ± 0.32</td>
<td>2.21 ± 0.65b</td>
<td>0.58 ± 0.11c</td>
<td>5.7–6.1%</td>
</tr>
<tr>
<td>5.7–5.8%</td>
<td>474</td>
<td>58.0 ± 9.3b</td>
<td>169 (35.7)</td>
<td>112 (27.1)</td>
<td>74 (16.9)</td>
<td>84.8 ± 9.1</td>
<td>24.5 ± 3.2</td>
<td>132 ± 21</td>
<td>77 ± 10</td>
<td>5.06 ± 0.89</td>
<td>1.30 (0.94–1.84)</td>
<td>1.38 ± 0.31</td>
<td>2.31 ± 0.64</td>
<td>0.60 ± 0.14b</td>
<td>5.9–6.1%</td>
</tr>
<tr>
<td>5.9–6.1%</td>
<td>370</td>
<td>58.9 ± 9.1b</td>
<td>135 (36.5)</td>
<td>84 (27.4)</td>
<td>64 (18.3)</td>
<td>83.7 ± 8.9b</td>
<td>24.3 ± 3.3c</td>
<td>131 ± 20</td>
<td>77 ± 10</td>
<td>5.12 ± 0.92</td>
<td>1.20 (0.88–1.69)</td>
<td>1.40 ± 0.32</td>
<td>2.38 ± 0.64</td>
<td>0.60 ± 0.15b</td>
<td>&gt;6.1%</td>
</tr>
<tr>
<td>&gt;6.1%</td>
<td>493</td>
<td>61.0 ± 9.6</td>
<td>177 (35.9)</td>
<td>100 (24.5)</td>
<td>85 (18.6)</td>
<td>86.1 ± 9.8</td>
<td>24.9 ± 3.7</td>
<td>134 ± 21</td>
<td>77 ± 10</td>
<td>5.15 ± 0.96</td>
<td>1.21 (0.89–1.78)</td>
<td>1.41 ± 0.33</td>
<td>2.40 ± 0.66</td>
<td>0.63 ± 0.13</td>
<td>0.14, and 0.60 ± 0.15 vs. 0.63 ± 0.13 mm, all P &lt; 0.01, Table 1).</td>
</tr>
</tbody>
</table>

Association between elevated CIMT, FPG, postchallenge glucose, and HbA1c

We further analyzed the association with logistic regressions in four different models (Table 2). HbA1c quartiles were associated with elevated CIMT in an adjusted model, including age, sex, smoking and drinking status, BMI, SBP, DBP, TC, HDL-c, LDL-c, and TG. The participants with HbA1c higher than 6.1% still had 63% higher odds of elevated CIMT as compared with those with HbA1c below 5.7% after adjustments, although the association was somehow less marked. The association between CIMT and HbA1c was still significantly present.

TABLE 2. Odds ratios of elevated CIMT according to HbA1c quartiles

<table>
<thead>
<tr>
<th>HbA1c quartiles (%)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>&lt;5.7 (reference)</td>
<td>1.00</td>
<td>&lt;0.0001</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5.7–5.8</td>
<td>1.16 (0.78–1.74)</td>
<td>0.21</td>
<td>1.06 (0.66–1.73)</td>
<td>0.40</td>
</tr>
<tr>
<td>5.9–6.1</td>
<td>1.31 (0.89–1.91)</td>
<td>0.79</td>
<td>1.14 (0.72–1.81)</td>
<td>0.71</td>
</tr>
<tr>
<td>&gt;6.1</td>
<td>2.15 (1.52–3.05)</td>
<td>&lt;0.0001</td>
<td>1.70 (1.10–2.61)</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

P values were calculated from the logistic regression models. The elevated CIMT was defined as at least 0.70 mm. CI, Confidence interval; OR, odds ratio. Model 1 is unadjusted; model 2 is adjusted for age, sex, and smoking and drinking status; model 3 is adjusted for age, sex, smoking and drinking status, BMI, SBP, DBP, TC, HDL-c, LDL-c, and TG; model 4 is adjusted for age, sex, smoking and drinking status, BMI, SBP, DBP, TC, HDL-c, LDL-c, TG, FPG, and postchallenge glucose.
after a further adjustment for FPG and postchallenge glucose.

Discussion

In this community-based study, we reported that higher HbA1c in a population with NGT was significantly associated with elevated CIMT independent of age, sex, BMI, smoking, and drinking status, blood pressure, and serum lipid levels and even FPG and postchallenge glucose. However, FPG was not associated with CIMT, and the association between postchallenge glucose and CIMT disappeared after adjustment for conventional cardiovascular risk factors.

The relationship between hyperglycemia and cardiovascular risk in diabetic patients has been well established. However, studies regarding the relationship between cardiovascular risk and various hyperglycemic markers in population without diabetes were not conclusive (7, 8). Although HbA1c is believed to relate to microvascular complication, the association of HbA1c with macrovascular complication is not consistent, particularly in those with NGT (5, 7–9). Khaw et al. (10) and Selvin et al. (11) reported that elevated HbA1c levels were an independent risk factor for coronary heart disease in subjects without diabetes. In an elderly nondiabetic population, Doruk et al. (9) found no significant association between HbA1c and CIMT. However, the majority of previous studies were conducted in subjects without clinically evident diabetes (9–11), which meant that those studies inevitably included participants with prediabetes. In contrast, our study was conducted in a population with NGT. Thus, the association between HbA1c and CIMT in our present study was not confounded by diabetes and impaired glucose tolerance.

Some studies have argued that plasma glucose levels may be log-linearly associated with risk of vascular disease across the spectrum (12, 13). Nevertheless, Reykjavik’s study has shown that in subjects with fasting glucose less than 7.0 mmol/liter (14), no significant association was observed between fasting glucose and coronary heart diseases. In the present study, we adopted CIMT as an early marker of CVD, similar to Reykjavik’s study; we did not find any correlation between FPG and CIMT. In contrast, an independent association between CIMT and HbA1c was detected, which was in line with the results from the Atherosclerosis Risk in Communities study (8).

Although postprandial hyperglycemia is confirmed to be related to the development of CVD in diabetic patients (15), OGTT is not convenient in routine clinical practice. Moreover, Selvin et al. (16) found that 2-h postchallenge glucose had substantially more variability compared with either FPG or HbA1c (16). Therefore, the nonsignificant association between postchallenge glucose and CIMT in the present study might be attributable to high variability in postchallenge glucose. In the present study, postchallenge glucose was initially associated with CIMT in an unadjusted model. After adjustment for conventional cardiovascular risk factors including age, blood pressure, and lipids levels, the association between postchallenge glucose and CIMT disappeared. Thus, we assumed that those conventional cardiovascular risk factors might also contribute to the association with CIMT in NGT subjects.

Intensive glucose control showed beneficial effects on prevention of microvascular diseases (17); however, several large intervention studies did not show that intensive glucose control reduced cardiovascular events in patients with previously diagnosed diabetes (18–20). However, in newly diagnosed type 2 diabetes, the United Kingdom Prospective Diabetes Study showed a borderline improvement in myocardial infarction risk (P = 0.052) in individuals randomized to tight glucose control, which was taken by some investigators as evidence of a beneficial effect of glucose control on macrovascular outcomes (17). Moreover, the post hoc analyses of Veterans Affairs Diabetes Trial showed that subjects with type 2 diabetes for less than 12 yr could receive benefits from intensive glucose control (20). In contrast, those with a longer duration of diabetes could not receive benefits or even were adversely affected. These results highlight the importance of aggressive treatment of diabetes as early as possible, preferably at the time of diagnosis. Therefore, the hyperglycemic markers closely associated with CVD risk factors in subjects with NGT should be more investigated. Our results provide evidence that in subjects with NGT, HbA1c might be a better hyperglycemic index associated with CVD risk factors.

Some limitations of our present study are of concern. First, our study included only middle-aged and elderly subjects with NGT, and the results may not be applied to a general population with different age composition. Second, we adopted a single HbA1c value for analysis. Previous studies showed that HbA1c was less varied in subjects with NGT (17), and it was impractical to implement multiple HbA1c measurements in large epidemiological studies.

In conclusion, our study has demonstrated that HbA1c is associated with CIMT, an early marker of atherosclerosis, independent of conventional CVD risk factors, FPG, and postchallenge glucose, which adds evidence to the notion that HbA1c might be superior to FPG and postchallenge glucose in relation to cardiovascular risk in subjects with NGT.
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