Glycated Hemoglobin is Associated with the Complexity of Coronary Artery Disease, Even in Non-Diabetic Adults

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Aim: Glycated hemoglobin (HbA1c) is associated with an increased risk of cardiovascular disease and death from any cause. The aim of this study was to examine the relationship between HbA1c value and coronary artery lesion complexity.

Methods: The subjects were 638 consecutive patients who underwent their first coronary angiography and had their HbA1c levels measured from December 2008 to August 2011. Sixty-one hemodialysis patients were excluded and 577 were analyzed. The complexity of the coronary artery lesions was evaluated using the SYNTAX score (SXscore). The subjects were divided into quartiles according to either the HbA1c or the fasting plasma glucose (FPG) values. Logistic regression analysis (with forced entry methods) was used to predict the prevalence of an intermediate or high SXscore.

Results: Both the higher HbA1c quartiles (Q1 to Q4) and higher FPG quartiles were significantly associated with a higher SXscore (p for trend <0.0001 and 0.026, respectively). The association between higher HbA1c quartiles and a higher SXscore was even observed in non-diabetic subjects (n=433, Q1: 3.0±6.8, Q2: 6.9±15.6, Q3: 7.6±11.8, Q4: 7.4±13.4 p for trend=0.004). In addition, a higher HbA1c quartile independently predicted patients with intermediate or high SXscores (SXscore ≥23) after adjusting for age, sex, hypertension, dyslipidemia, creatinine and FPG values (Odds ratio: Q1: 1.00 reference, Q2: 3.24, Q3: 3.03, Q4: 8.04).

Conclusion: HbA1c is significantly associated with the complexity of coronary lesions. This association is even observed in non-diabetic adults. A higher HbA1c value is an independent predictor of the prevalence of complex coronary lesions.


Key words; SYNTAX score, Diabetes mellitus, Stable coronary artery disease, Glucose

Introduction

Fasting glucose is a well-accepted parameter for diagnosing diabetes¹, ². Based on the established association between glycated hemoglobin (HbA1c) and microvascular disease, the American Diabetes Association (ADA) and Japan Diabetes Society recommend using HbA1c as a criterion for diagnosing diabetes³, ⁴. HbA1c can be assessed in the non-fasted state and has higher reproducibility than fasting glucose; therefore, HbA1c offers several diagnostic advantages compared to fasting glucose and should be considered an established marker of long-term glycemic control in patients with diabetes mellitus¹, ³, ⁵, ⁷. In addition, an elevated HbA1c value is associated with the risk of polyvascular disease and future microvascular and macrovascular disease⁸, ⁹. Furthermore, a previous study reported that an elevated HbA1c level is predictive of the prevalence of cardiovascular disease and mortality in patients without diabetes mellitus, independent of the fasting glucose value¹⁰. However, no previous reports have examined the association between HbA1c and coronary artery lesion morphology (lesion complexity), especially in non-diabetic patients.

The SYNTAX score (SXscore) is a score which is used to predict clinical outcomes in patients with sin-
Glycated Hemoglobin and the SYNTAX Score

The glomerular filtration rate (GFR) was calculated using the level-modified Modification of Diet in Renal Disease formula, as modified for Japanese populations: estimated glomerular filtration rate (eGFR) = 0.741 × 175 × age in years − 0.203 × serum creatinine − 1.154. The female sex adjustment (eGFR female = eGFR × 0.742) was applied when appropriate.

Coronary artery stenosis was defined as stenosis with a diameter of ≥ 50%.

SYNTAX Score and Angiographic Analysis

According to the baseline diagnostic angiogram, each coronary lesion creating a stenosis obstructing ≥ 50% of the diameter in vessels ≥ 1.5 mm was scored separately, and these scores were added together to produce the overall Sxscore, which was calculated using the Sxscore algorithm. This algorithm is available on the SYNTAX website. The patients’ Sxscores were independently assessed by two experienced interventional cardiologists who were blinded to the carotid-US data. These cardiologists had previously calculated Sxscores for more than 100 patients before assisting in our study. The κ value for Sxscore interobserver variability was 0.75, and the κ value for intraobserver variability was 0.86. In cases of disagreements about the Sxscore, the average reported value from the two readers was used as the final value.

Aim

The aim of this study was to assess the predictive impact of HbA1c and fasting glucose for coronary lesion complexity, as evaluated by the Sxscore.

Methods

Study Patients

We considered 638 consecutive patients who were admitted to Toho University Ohashi Medical Center and the National Center for Global Health and Medicine from December 2008 to August 2011, who underwent their first coronary angiography and whose HbA1c levels were measured. Sixty-one hemodialysis patients were excluded and 577 were analyzed. The study patients were divided into quartiles (Q1 to Q4) according to their HbA1c and fasting plasma glucose (FPG) values. Our study complied with the Declaration of Helsinki, and written informed consent was obtained from all of the patients.

Procedures and Definitions

Blood samples were obtained after an overnight fast (12 hours) and tested with an automatic clinical chemistry analyzer (LABOSPECT 008; Hitachi, Tokyo, Japan). Blood glucose, serum triglycerides, total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol concentrations were measured using enzymatic methods. HbA1c was assessed using high-performance liquid chromatography. HbA1c was calculated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value using the following formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (Japan Diabetes Society) (%) + 0.25%.

Diabetes mellitus was defined as a fasting plasma glucose ≥ 126 mg/dL, HbA1c (NGSP) ≥ 6.5% or the use of insulin or oral hypoglycemic agents. Hypertension (HT) was defined as having systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or as receiving current treatment for HT. We defined dyslipidemia as having low density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, high density lipoprotein (HDL) cholesterol < 40 mg/dL, or serum triglyceride ≥ 150 mg/dL or as receiving current treatment for dyslipidemia. The glomerular filtration rate (GFR) was calculated using the level-modified Modification of Diet in Renal Disease formula, as modified for Japanese populations: estimated glomerular filtration rate (eGFR) = 0.741 × 175 × age in years−0.203 × serum creatinine−1.154. The female sex adjustment (eGFR female = eGFR × 0.742) was applied when appropriate.

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Statistical Analysis

The continuous variables are presented as the means ± SDs. The categorical variables are presented as

Table 1. Angiographic characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>577</td>
</tr>
<tr>
<td>Coronary angiography for</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>321 (55.6)</td>
</tr>
<tr>
<td>Valvular disease (%)</td>
<td>164 (28.4)</td>
</tr>
<tr>
<td>Aortic disease (%)</td>
<td>45 (7.8)</td>
</tr>
<tr>
<td>Cardiomyopathy (%)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Cardiac tumor</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Others</td>
<td>29 (5.0)</td>
</tr>
<tr>
<td>Patients with any coronary lesions (%)</td>
<td>249 (43.2)</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td></td>
</tr>
<tr>
<td>Low (0-22) (%)</td>
<td>500 (86.7)</td>
</tr>
<tr>
<td>Intermediate (23-32) (%)</td>
<td>41 (7.1)</td>
</tr>
<tr>
<td>High (33 or more) (%)</td>
<td>36 (6.2)</td>
</tr>
</tbody>
</table>

The reasons for coronary angiography and details of coronary artery lesions are shown.
the higher HbA1c category was significantly associated with a higher proportion of male sex and HT, higher FPG, LDL cholesterol and triglyceride and lower HDL cholesterol.

Higher HbA1c values were significantly associated with higher SXscores (Q1: SXscore 4.0±10.5, Q2: 7.6±14.2, Q3: 7.1±12.1, Q4: 12.7±14.8, p for trend <0.0001) (Fig. 1). Similarly, higher FPG quartiles showed a higher prevalence of male sex and hypertension. Higher HbA1c quartiles also showed significantly higher FPG, LDL, triglyceride values and lower HDL values.

![Fig. 1. SYNTAX scores of the patients, stratified according to the HbA1c quartiles.](image)

Higher HbA1c quartiles had a significantly higher SXscore. P for trend <0.0001

**Table 2. Patient characteristics stratified according to HbA1c quartiles**

<table>
<thead>
<tr>
<th>Glycated Hemoglobin Category (NGSP %)</th>
<th>Any (n=577)</th>
<th>Q1 (&lt;5.5) (n=151)</th>
<th>Q2 (5.6-5.8) (n=136)</th>
<th>Q3 (5.9-6.3) (n=148)</th>
<th>Q4 (≥6.4) (n=142)</th>
<th>p value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>68.9±11.7</td>
<td>67.3±12.5</td>
<td>70.7±10.8</td>
<td>68.7±12.2</td>
<td>69.1±11.1</td>
<td>.408</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>63.4</td>
<td>57.0</td>
<td>57.4</td>
<td>70.9</td>
<td>68.3</td>
<td>.019</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>58.4</td>
<td>53.0</td>
<td>52.2</td>
<td>63.5</td>
<td>64.8</td>
<td>.047</td>
</tr>
<tr>
<td><strong>Fasting glucose (mg/dL)</strong></td>
<td>111.6±34.2</td>
<td>97.7±19.7</td>
<td>102.1±19.1</td>
<td>104.8±20.6</td>
<td>142.6±48.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>186.7±36.6</td>
<td>189.2±28.1</td>
<td>188.4±39.6</td>
<td>180.1±36.2</td>
<td>189.4±41.8</td>
<td>.541</td>
</tr>
<tr>
<td>LDL</td>
<td>109.6±32.8</td>
<td>98.9±29.5</td>
<td>107.2±30.7</td>
<td>106.4±29.7</td>
<td>119.8±36.5</td>
<td>.002</td>
</tr>
<tr>
<td>HDL</td>
<td>52.9±15.0</td>
<td>56.3±15.1</td>
<td>55.3±16.8</td>
<td>52.2±14.4</td>
<td>50.1±13.6</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Triglyceride (mg/dL)</strong></td>
<td>127.1±69.7</td>
<td>120.3±69.7</td>
<td>113.3±59.3</td>
<td>135.0±76.3</td>
<td>139.6±69.1</td>
<td>.003</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73 m²)</strong></td>
<td>80.9±24.4</td>
<td>82.9±22.5</td>
<td>81.2±26.9</td>
<td>79.7±24.7</td>
<td>79.7±23.5</td>
<td>.242</td>
</tr>
<tr>
<td><strong>SYNTAX score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-22) (%)</td>
<td>86.7</td>
<td>96.7</td>
<td>89.0</td>
<td>88.5</td>
<td>71.8</td>
<td></td>
</tr>
<tr>
<td>Intermediate (23-32) (%)</td>
<td>7.1</td>
<td>1.3</td>
<td>5.1</td>
<td>6.8</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>High (33 or more) (%)</td>
<td>6.2</td>
<td>2.0</td>
<td>5.9</td>
<td>4.7</td>
<td>12.7</td>
<td></td>
</tr>
</tbody>
</table>

Higher HbA1c quartiles showed a higher prevalence of male sex and hypertension. Higher HbA1c quartiles also showed significantly higher FPG, LDL, triglyceride values and lower HDL values.

Counts or proportions (percentages). A one-way analysis of variance model and Kruskal-Wallis test were used to analyze in multigroups. To obtain the regression coefficient, simple regression analysis was used. Logistic regression analysis (with forced entry methods) was used to predict the prevalence of an intermediate or high SXscore. Adjustments were made for age, sex, hypertension, dyslipidemia, and creatinine in Model 1. Model 2 was adjusted for the variables in model 1 plus fasting glucose. A p-value <0.05 was considered to be significant. SPSS ver.17 (SPSS Japan Inc., Tokyo, Japan) was used for the analyses.

**Results**

Coronary angiography was performed to evaluate the ischemic heart disease characteristics (55.6%) and preoperative evaluation of coronary artery disease for valvular disease (28.4%) or aortic disease (7.8%). The proportion of patients with any coronary artery disease was 43.2%. Consistent with the SYNTAX trial, the low, intermediate and high SXscores were defined as 0 to 22, 23 to 32 and 33 or more, respectively. The proportions of patients with low, intermediate and high SXscores were 86.7%, 7.1% and 6.2%, respectively (Table 1). The patient characteristics for each of the HbA1c quartiles are shown in Table 2. There were no significant differences in age, total cholesterol and eGFR among these 4 groups. In contrast,
Glycated Hemoglobin and the SYNTAX Score

Quartiles remained significantly associated with the SXscore, but the FPG quartiles ceased to be associated with the SXscore (HbA1c Q1: 15.3 ± 16.7, Q2: 17.9 ± 14.1, Q3: 17.6 ± 14.8, Q4: 21.2 ± 14.2, \( p \) for trend = 0.048, Fig. 3). When patients with diabetes mellitus (\( n = 144 \)) were excluded, 433 non-diabetic patients exhibited significantly higher SXscores (Q1: 5.9 ± 10.9, Q2: 7.1 ± 13.6, Q3: 8.6 ± 14.7, Q4: 9.0 ± 13.1, \( p \) for trend = 0.026) (Fig. 2). The regression coefficient between HbA1c and the SXscore was 2.031 (\( p < 0.0001 \)). In contrast, the regression coefficient between FPG and the SXscore was 0.034 (\( p = 0.030 \)). When the study population was limited to patients with one or more coronary artery lesions, the HbA1c quartiles remained significantly associated with the SXscore, but the FPG quartiles ceased to be associated with the SXscore (HbA1c Q1: 15.3 ± 16.7, Q2: 17.9 ± 14.1, Q3: 17.6 ± 14.8, Q4: 21.2 ± 14.2, \( p \) for trend = 0.048, Fig. 3) (FPG Q1: 15.8 ± 12.2, Q2: 19.5 ± 13.6, \( p \) for trend = 0.026). When the study population was limited to patients with a coronary artery disease, FPG quartiles did not correlate with the SXscore.

Fig. 2. SYNTAX scores of the patients, stratified according to the FPG quartiles.
Higher FPG quartiles presented significantly higher SXscores. \( p \) for trend = 0.026

Fig. 3. SYNTAX scores of the patients with one or more coronary artery lesions, stratified according to the HbA1c quartiles.
Higher HbA1c quartiles still showed a significantly higher SXscore even when the study population was limited to patients with a coronary artery disease. \( p \) for trend = 0.048

Fig. 4. SYNTAX scores of the patients with one or more coronary artery lesions, stratified according to the FPG quartiles.
When the study population was limited to patients with a coronary artery disease, FPG quartiles did not correlate with the SXscore.

Fig. 5. SYNTAX scores of non-diabetic patients, stratified according to the HbA1c quartiles.
Higher HbA1c quartiles showed a significantly higher SXscore even in the non-diabetic subset. \( p \) for trend = 0.004
prandial spikes in the blood glucose level, and have high intraindividual reproducibility. In particular, postprandial hyperglycemia has been strongly related to diabetic complications; however, patients with postprandial hyperglycemia do not always present with a high FPG value. In these patients, FPG underestimates the severity of the glycometabolic disorder. This phenomenon may contribute to the superiority of HbA1c over fasting glucose for long-term macrovascular risk stratification.

Previous studies have reported an association between elevated cardiovascular risk and elevated HbA1c values in non-diabetic patients; however, some studies have demonstrated unfavorable effects from lowering the HbA1c values of diabetic patients with the goal of improving cardiovascular outcomes. Although the effects of the fasting glucose level on the development of cardiovascular disease are still unclear, the beneficial effects of glucose control on microvascular disease have been well established; therefore, the effect of intensive glucose control is still controversial. According to single regression analysis, regression coefficients between the SXscore and HbA1c or FPG were 2.031 and 0.034, respectively. Our study therefore demonstrated the superiority of HbA1c over fasting glucose as a predictor of the prevalence of complex coronary artery lesions. In addition, our data suggest that HbA1c values, even in the normal range, can predict the prevalence of complex coronary artery disease. In particular, the patients in the lowest HbA1c quartile had a distinctly lower risk of complex coronary artery disease. For patients without hypoglycemia, further study to evaluate the benefit of intensive treatment of glycometabolic disorder to obtain a lower HbA1c value is warranted.

A previous report found that the SXscore predicted major adverse cardiovascular and cerebrovascular event (MACCE) outcomes in patients who underwent coronary revascularization and its prognostic value was supported by the results of this study. In the present study, we analyzed the relationship between SXscore and HbA1c values. We found that higher HbA1c quartiles were associated with higher SXscores even in non-diabetic patients. In addition, higher HbA1c categories were able to independently predict patients with intermediate or high SXscores after adjustment for age, sex, hypertension, dyslipidemia and creatinine. This finding supports the usefulness of HbA1c measurement.

Discussion

The principal findings of our study indicate that HbA1c values are associated with coronary lesion complexity and that this association is also observed in non-diabetic patients. Previous studies reported the relationship between cardiovascular events and HbA1c values; however, they did not investigate coronary lesion morphology. In addition, we found that HbA1c is an independent predictor of the prevalence of complex coronary artery lesions (SXscore ≥23). In this analysis we used two models. In Model 1, we excluded FPG because the correlation with HbA1c was extremely high (r=0.593, p<0.0001). In both models, the predictive values of HbA1c are presented and this result strengthens the usefulness of HbA1c measurement.

HbA1c values reflect the previous several months of endogenous exposure to glucose, including postprandial spikes in the blood glucose level, and have high intraindividual reproducibility. In particular, postprandial hyperglycemia has been strongly related to diabetic complications; however, patients with postprandial hyperglycemia do not always present with a high FPG value. In these patients, FPG underestimates the severity of the glycometabolic disorder. This phenomenon may contribute to the superiority of HbA1c over fasting glucose for long-term macrovascular risk stratification.

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Table 3. Adjusted Odds Ratios for Prediction of Intermediate or High SYNTAX Score Patients, According to the HbA1c Quartiles

<table>
<thead>
<tr>
<th>HbA1c Quartiles (NGSP %)</th>
<th>Adjusted Odds Ratio (95%CI)</th>
<th>p value</th>
<th>Adjusted Odds Ratio (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (&lt;5.5%)</td>
<td>1.00 (reference)</td>
<td></td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Q2 (5.6-5.8%)</td>
<td>3.22 (1.12-9.22)</td>
<td>.030</td>
<td>3.24 (1.13-9.31)</td>
<td>.029</td>
</tr>
<tr>
<td>Q3 (5.9-6.3%)</td>
<td>3.14 (1.11-8.86)</td>
<td>.030</td>
<td>3.03 (1.07-8.58)</td>
<td>.037</td>
</tr>
<tr>
<td>Q4 (≥6.4%)</td>
<td>9.46 (3.54-25.29)</td>
<td>&lt;.0001</td>
<td>8.04 (2.80-23.03)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, sex, hypertension, dyslipidemia and creatinine.
Model 2 was adjusted for the variables in model 1 plus fasting glucose.

were identified within the sample. The association between higher HbA1c quartiles and higher SXscores was observed even in non-diabetic patients (HbA1c Q1: 3.0 ± 6.8, Q2: 6.9 ± 15.6, Q3: 7.6 ± 11.8, Q4: 7.4 ± 13.4, p for trend=0.004, Fig.5). In addition, the higher HbA1c categories were able to independently predict patients with intermediate or high SXscores (SXscore ≥23) after adjustment for age, sex, hypertension, dyslipidemia and creatinine (Model 1: Q1 odds ratio: 1.00 reference, Q2 odds ratio: 3.22, 95%CI: 1.12 to 9.22, Q3 odds ratio: 3.14, 95%CI: 1.11 to 8.86, Q4 odds ratio: 9.46, 95%CI: 3.54 to 25.29). After adjustment for Model 1 plus FPG (Model 2), the higher HbA1c quartiles still showed independent predictive value for the intermediate or high SXscore (Q1 odds ratio: 1.00 reference, Q2 odds ratio: 3.24, 95%CI: 1.13 to 9.31, Q3 odds ratio: 3.03, 95%CI: 1.07 to 8.58, Q4 odds ratio: 8.04, 95%CI: 2.80 to 23.03) (Table 3).
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Disclosures
None.

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Study Limitations
This study has some limitations. First, because the patients enrolled in our study were candidates for coronary angiography, the results may have been subject to selection bias; therefore, our findings may not be applicable to the general population. Second, the patients presented with relatively low SYNTAX scores, and over 50% of the patients presented with an SYNTAX score of 0. Third, the entire study population was Japanese. Fourth, we do not have enough data about smoking and alcohol use. These factors were therefore not adjusted. The relationship between the smoking status and the prevalence of coronary artery disease has been reported in Japan, and a higher prevalence of smoking was observed in the male sex. In our results, higher HbA1c quartiles showed a higher proportion of male sex. In contrast, cigarette smoking might be a stronger risk factor for coronary artery disease in female than male sex. These findings might affect the odds ratios. Fifth, this is a cross-sectional study. We could not present the duration of diabetes, and there are no data about the duration or effectiveness of diabetic therapy; these factors might affect our results. Therefore, to investigate the effect of glycemic disorder on coronary lesion complexity, a randomized controlled trial is needed.

Clinical Implications
Cardiologists have to recognize the risks of glycemic disorder, even in the non-diabetic range. Aggressive interventions in early-stage glycemic disorders may improve the risks of cardiovascular disease as it has a so-called “legacy effect”.

Funding
None.
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