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Hemoglobin glycation index predicts cardiovascular disease in people with type 2 diabetes mellitus: A 10-year longitudinal cohort study

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ABSTRACT

Background and aims: Previous studies have suggested that the hemoglobin glycation index (HGI) can be used as a predictor of diabetes-related complications. We examined the prognostic significance of a high HGI for cardiovascular disease (CVD) in an ongoing hospital-based cohort.
Methods: From March 2003 to December 2004, 1302 consecutive patients with type 2 diabetes and without a prior history of CVD were enrolled. CVD was defined as the occurrence of coronary artery disease or ischemic stroke. The HGI was calculated as the measured glycated hemoglobin (HbA1c) minus predicted HbA1c. Predicted HbA1c were calculated for 1302 participants by inserting fasting blood glucose (FBG) into the equation, Predicted HbA1c level = 0.02106 × FBG [mg/dL] + 4.973. Cox proportional hazards models were used to identify the associations between the HGI and CVD after adjusting for confounding variables.
Results: During 11.1 years of follow-up, 225 participants (17.2%) were newly diagnosed with CVD. The baseline HGI was significantly higher in subjects with incident CVD than in those without CVD, although the baseline FBG levels did not differ according to the occurrence of CVD. Compared with patients without CVD, those with CVD were older, had a longer duration of diabetes and hypertension, and used more insulin at baseline. A Cox hazard regression analysis revealed that the development of CVD was significantly associated with baseline HGI (hazard ratio [HR], 1.94; 95% confidence interval [CI], 1.31–2.87; $p < 0.001$, comparing the highest and lowest quartiles of HGI). This relationship was unchanged after additional adjustment for baseline HbA1c level (HR, 1.74; 95% CI, 1.08–2.81). The HRs of HbA1c in relation to outcomes were similar to or lower than those seen for HGI. After adjustment for HGI, the effect of the highest HbA1c on incident CVD disappeared.
Conclusions: High HGI was independently associated with incident CVD in patients with type 2 diabetes. Patients with high HGI at baseline had a higher inherent risk for CVD.

1. Introduction

Numerous studies have shown that variation in glycated hemoglobin A1c (HbA1c) in human populations cannot be fully explained by interindividual variation in mean blood glucose (MBG).[1–7] More recent studies that have compared HbA1c levels by ethnicity have consistently demonstrated higher HbA1c levels in East Asian and African-American individuals compared with Caucasians.[8,9] Clinical studies have convincingly demonstrated that some individuals and ethnic groups have persistently lower or higher than expected HbA1c levels compared with others with similar blood glucose levels. Interindividual variations in HbA1c caused by factors other than MBG, including genetic factors and differences in hemoglobin glycation rates, erythrocyte life-span, or mean erythrocyte age, have been reported in individuals with type 2 diabetes and in those without diabetes.[10,11]

Discordances between HbA1c and other measures of glycemic control are common in clinical practice. The hemoglobin glycation index (HGI) was developed to quantify interindividual variations in HbA1c caused by factors other than blood glucose concentration.[2–4] HGI is calculated as the difference between the observed HbA1c value and the predicted HbA1c derived by inserting the individual fasting blood glucose (FBG) into a population regression equation expressing the linear association between HbA1c and plasma glucose levels. It has been reported that in patients with type 1 diabetes, a higher HGI corresponds with a greater risk of retinopathy and nephropathy.[5] It was also reported that a high HGI was significantly associated with inflammatory markers such as white blood cell counts and C-reactive protein levels in individuals without diabetes.[12] Higher HGI levels have been proposed

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to identify a phenotype of glucose metabolism characterized by an increased susceptibility to protein glycation and tissue accumulation of advanced glycation end products (AGEs).[13] A higher degree of nonenzymatic glycation of intracellular proteins may play a pathogenic role in the complications of diabetes. Indeed, a recent study showed that a high HGI was independently associated with an increased risk of CVD in treatment-naïve individuals with prediabetes or diabetes.[14] Therefore, we conducted a prospective hospital-based cohort study involving >1000 patients with type 2 diabetes to examine the prognostic significance of a high HGI for CVD during a median 11.1 years of follow-up.

2. Methods

2.1. Study population

From January 2003 to December 2004, 1302 individuals with type 2 diabetes aged 25–75 years were consecutively recruited and received follow-up until January 2013 to May 2015 at the university-affiliated Diabetes Center of St. Vincent's Hospital in South Korea.[15,16] Patients were excluded if they were older than 75 years, were mentally ill, had type 1 diabetes or gestational diabetes, were receiving steroid therapy, or had any severe illness such as malignancy, severe infection, liver cirrhosis, or heart failure. Patients with a history of CAD or stroke at baseline were excluded. CAD and stroke were defined using the same definitions as described in the study outcomes. Subjects with type 2 diabetes who had impaired renal function [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] were also excluded. This prospective cohort study was approved by the Catholic Medical Center Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants provided signed written informed consent.

2.2. Study outcomes

The primary end point of this study was newly diagnosed CVD, which was defined as coronary artery disease (CAD) or ischemic stroke.[17] CAD was defined as either a diagnosis of angina pectoris, an incident of myocardial infarction, or a requirement for coronary revascularization (coronary bypass surgery or coronary angioplasty). Manifestations of stroke included transient ischemic attack (TIA) or cerebral infarction. Follow-up visits were performed every 3–4 months, and we verified the onset of CVD from hospital records. Diagnosis of CVD was confirmed by specialists including a cardiologist, a neurologist, and a neurosurgeon. A physician evaluated whether the subjects had experienced CVD events based on the above-listed criteria or information from medical records if the subject attended another hospital for CVD events. Specialists including cardiologists, neurologists, or neurosurgeons confirmed the clinical diagnosis of CVD based on verified medical records or clinical manifestations.

2.3. HGI calculation

All blood samples were taken in the morning following a minimum 8-h fast. The FBG and lipid profile were assessed using an automated enzymatic method (Hitachi 736–40; Hitachi, Tokyo, Japan). The HbA1c levels were determined using high-performance liquid chromatography, with a reference range of 4.4% to 6.4% (Bio-Rad, Montreal, Quebec, Canada). HGI was defined as the difference between the measured HbA1c level and that predicted from FBG levels, calculated using a HbA1c–FBG regression equation based on data obtained from all the study subjects ($N = 1302$). The correlation between HbA1c and FBG was examined using linear regression analysis, and established the following equation (Fig. 1): Predicted HbA1c level = 0.02106 × FBG [mg/dL] + 4.973 ($r = 0.67$; $p < 0.001$).

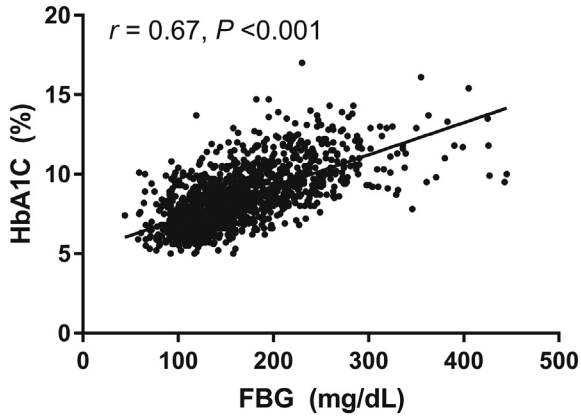

Fig. 1. Regression of FBG on HbA1c. The line represents the simple linear regression line of the equation: Predicted HbA1c level = 0.02106 × FBG [mg/dL] + 4.973 ($r = 0.67$; $P < 0.001$).

2.4. Statistical analysis

All data are reported as the mean ± SD or number (percentage). Student's *t*-test or chi-squared test, when appropriate, was used to compare the baseline characteristics of the study participants, who were grouped according to their development of CVD during follow-up. Baseline characteristics were compared between the quartiles of HGI using analysis of variance (ANOVA) or chi-square tests as indicated. We applied multivariate Cox proportional hazards models to test the associations between the HGI and incident CVD after adjusting for the following covariates: age, sex, duration of diabetes, presence of hypertension, body mass index, eGFR, albuminuria, smoking, insulin treatment, and use of sulfonylurea and aspirin. The proportional hazards assumption was confirmed using log-minus log-survival plots. Hazard ratios (HRs) were calculated and the results are reported as HRs and 95% confidence interval (CI). All data were analyzed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA), and a p value <0.05 was considered to indicate significance.

3. Results

3.1. General characteristics

In the cohort of 1302 patients, 757 participants (58.1%) were women, and the cohort mean age and diabetes duration were 55.5 ± 10.9 and 6.5 ± 6.6 years, respectively. During 11.1 years of follow-up, 225 participants (17.2%) were newly diagnosed with CVD; 137 (10.5%) because of CAD events, 101 (7.8%) because of stroke (including TIA), and 12 (0.9%) were diagnosed with both CAD and stroke. During the follow-up period, 70 participants (5.4%) died (20 because of a CVD event).

The baseline HGI was significantly higher in participants with incident CVD than in those without CVD (Table 1), although the baseline FBG levels did not differ according to the occurrence of CVD. The patients who developed CVD were older, more likely to be female, had a longer duration of diabetes, more frequently used insulin, and had a higher frequency of hypertension. The mean eGFR was lower and the proportion of patients with urine albuminuria ≥100 mg/g creatinine was higher in the group with incident CVD (Table 1).

3.2. Characteristics according to the baseline HGI quartiles

The characteristics of the study population, grouped according to quartiles of HGI, are shown in Table 2. Those participants in the higher quartiles of HGI were older, more likely to be female, had a longer duration of diabetes, and more frequently used insulin. The mean values of

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