Association Between Coronary Artery Calcification and the Hemoglobin Glycation Index: The Kangbuk Samsung Health Study

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Context: The hemoglobin glycation index (HGI) is known to be correlated with the risk for cardiovascular disease.

Objective: To analyze the association between incident coronary artery calcification (CAC) and the changes in HGI among participants without diabetes, over 4 years.

Design, Setting, Participants, and Outcome Measures: A retrospective study of 2052 nondiabetic participants in whom the coronary artery calcium score was measured repeatedly over 4 years, as part of a health checkup program in Kangbuk Samsung Hospital in Korea, and who had no CAC at baseline. The HGI was defined as the difference between the measured and predicted hemoglobin A1c (HbA1c) levels.

Results: A total of 201 participants developed CAC after 4 years, and the mean baseline HGI was significantly higher in those patients. The incidence of CAC gradually increased from the first to the fourth quartile groups of baseline HGI. The odds ratio (OR) for incident CAC was the highest among the four groups divided by the quartiles of the baseline HGI and was significant after adjustment for confounding variables (vs first quartile group: OR, 1.632; 95% confidence interval, 1.024 to 2.601). The incidence of and risk for CAC development were significantly higher than in other groups compared with the low-to-low group after adjustment for confounding factors; however, when baseline HbA1c level was included in the model, only participants with a low-to-high HGI over 4 years showed a significantly increased OR for CAC development compared with the low-to-low group (OR, 1.722; 95% confidence interval, 1.046 to 2.833).

Conclusions: The participants with a high baseline HGI and consistently high HGI showed a higher risk for incident CAC than those with a low baseline HGI. An increased HGI over 4 years significantly increased the risk for CAC regardless of the baseline HbA1c levels. (***J Clin Endocrinol Metab*** **102: 4634–4641, 2017)**

Recent studies have suggested the deleterious effects of glycemic variance on the vascular complications of diabetes (1, 2). Studies that have focused on continuous glucose monitoring systems show that glucose fluctuation, in addition to hemoglobin A1c (HbA1c) levels or actual glucose levels, is associated with poor cardiovascular outcomes in patients with type 2 diabetes because of the effects of advanced glycation end products (AGEs), increased oxidative stress, or inflammation (3–5).

The measurement of HbA1c levels is considered the gold standard in the evaluation of glycemic control in patients with diabetes and is known to be significantly correlated to the mean blood glucose (MBG) concentration of the past 2 months (6, 7). However, numerous

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Abbreviations: AGE, advanced glycation end product; CAC, coronary artery calcification; CACS, coronary artery calcium score; CVD, cardiovascular disease; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HGI, hemoglobin glycation index; MBG, mean blood glucose; OR, odds ratio.

studies have shown considerable variation in the relationship between HbA1c and MBG in specific conditions, such as in the case of hemoglobinopathy, pregnancy, and renal or hepatic function (8). The hemoglobin glycation index (HGI) was introduced in 2002 by Hempe *et al.* (9) to overcome that HbA1c is not necessarily correlated with MBG. The HGI is calculated by subtracting the predicted HbA1c level from the measured HbA1c level. The predicted HbA1c is calculated on the basis of the observed MBG by using a linear regression equation between blood glucose and HbA1c levels. Individuals with a high/low HGI have HbA1c levels that are higher/lower than those expected from their blood glucose levels; these could be considered signatures of individuals (9, 10).

Recently conducted studies suggested that in patients with type 1 and type 2 diabetes, a higher HGI corresponded to a higher risk for vascular complications compared with patients who have a lower HGI (10, 11). In a subanalysis of Actions to Control Cardiovascular Risk in Diabetes, patients with low and moderate HGIs at baseline showed improved cardiovascular outcomes in the intensive treatment arm compared with those with high HGIs; this suggests that calculating the HGI at baseline can identify the subpopulations with harms or benefits from intensive glycemic control (11). Furthermore, of the patients who participated in the Diabetes Control and Complications Trial, those with a high HGI at the baseline showed a threefold increase in the risk for retinopathy and a sixfold increase in the risk for nephropathy compared with those with a low HGI (10). In addition, a recently conducted study showed that a high HGI was independently associated with an increased risk for cardiovascular disease (CVD) in treatment-naive participants with prediabetes or diabetes (12). These results suggest that the HGI is a predictor of future CVD. However, none of the aforementioned studies analyzed the association between the timely changes in the HGI and CVD outcomes.

The coronary artery calcium score (CACS) is a noninvasive and safe method for the assessment of the coronary atherosclerotic burden and has been shown to have an excellent correlation with future CVD events in numerous cohort studies (13). In this study, we evaluated the association between the interval changes of HGI and the development of coronary artery calcification (CAC) in a 4-year follow-up conducted in a population of 2052 individuals without diabetes.

Materials and Methods

Study population

This retrospective longitudinal study was a part of the Kangbuk Samsung Health Study, which included participants from a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The purpose of the medical health checkup program is to promote the health of employees through regular health checkups and to enhance the early detection of diseases. Most of the examinees are employees and their family members, belonging to various industrial companies from around the country. The medical examinations are largely paid for by employers, and a considerable proportion of the examinees undergo examinations annually or biannually.

The initial study population comprised 2618 individuals who participated in the medical checkup program between January 2010 and December 2010 and whose CACS was measured at baseline. They underwent a repeat checkup and their CACS was measured again between January 2014 and December 2014. Of these participants, 156 were excluded because of the presence of diabetes in 2010, a history of ischemic stroke in 8, a history of coronary artery disease in 15, and missing data in 33. After exclusions, there were 2411 participants for whom data on the CACS (two scores measured over a 4-year period) were present. Of these, 335 participants had a CACS > 0 at baseline. To exclude the influence of antidiabetic medications or insulin, we excluded an additional 24 participants who revealed that they were taking antidiabetic medications in 2014. After the further exclusion of 335 participants who had a CACS > 0 at baseline and were taking antidiabetic medications in 2014, the final analysis included 2052 participants. The substudy that was analyzed after further exclusion of 1057 participants with prediabetes in 2010 was performed among 995 participants.

The institutional review board of the Kangbuk Samsung Hospital approved this study. The requirement for informed consent was waived because we used unidentifiable data that were routinely collected during the health screening process.

Anthropometric measurement and laboratory assessment

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire, and physical measurements and serum biochemical parameters were obtained by trained staff during the health examinations. Participants were asked to wear light clothing and no shoes before their body weight was measured to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index was calculated as the weight in kilograms divided by the height in meters squared. Trained nurses measured the sitting blood pressure with standard mercury sphygmomanometers. A smoker was defined as a participant who replied "yes" to the question "Have you smoked more than 5 packs of cigarettes in your life?" on the self-questionnaire. An alcohol drinker was defined as a participant who consumed alcohol more than twice a week. Regular exercise was defined as the performance of vigorous exercise more than once a week.

All the participants were examined after an overnight fast. The hexokinase method was used to measure fasting blood glucose (FBG) concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). An enzymatic calorimetric test was used to measure the total cholesterol and triglyceride concentrations. The selective inhibition method was used to measure the level of high-density lipoprotein cholesterol, and a homogeneous

enzymatic calorimetric test was used to measure the level of low-density lipoprotein cholesterol. Serum insulin levels were measured by using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics).

The presence of diabetes mellitus was determined according to the results of the self-questionnaire, and FBG and HbA1c levels were determined as suggested by the American Diabetes Association (14). In brief, diabetes was defined as an FBG level ≥ 126 mg/dL or an HbA1c level ≥ 6.5%, having a self-reported history of diabetes, or the current use of antidiabetic medication. Prediabetes was defined as an FBG level ≥ 100 mg/dL or HbA1c level ≥ 5.7% (14).

HbA1c levels were measured by using the immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland), with a reference value of 4.4% to 6.4%. The method was aligned with the standards of the Diabetes Control and Complications Trial and National Glycohemoglobin Standardization Program (15). The intra-assay coefficient of variation was 2.3%, and the interassay coefficient of variation was 2.4%; both values were within the acceptable limits defined by the National Glycohemoglobin Standardization Program (16).

Calculation of HGI and its interval changes over 4 years

To estimate the interindividual variance in HbA1c levels, the HGI was calculated by using HbA1c and FBG levels (9). The linear relationship between HbA1c and FBG was estimated from the linear regression analysis of the study participants' HbA1c and FBG levels in 2010 and 2014 (Supplemental Fig. 1):

$$2010: \text{HbA1c} = 0.009 \times \text{FBG} + 4.749,\ R^2 = 0.088$$
$$2014: \text{HbA1c} = 0.017 \times \text{FBG} + 3.896,\ R^2 = 0.294.$$

The predicted HbA1c levels were calculated from these equations by using each participant's FBG value. The HGI was defined as the difference between the measured HbA1c and the predicted HbA1c: HGI = measured HbA1c – predicted HbA1c. The correlation coefficient between the HGI values in 2010 and 2014 was found to be 0.559 (r = 0.559; $P < 0.01$) (Supplemental Fig. 2).

The participants were divided into two groups according to median of HGI: "low" if the HGI was lower than the median and "high" if the HGI was greater than or equal to the median. The median cutoffs of HGI in 2010 and 2014 were −0.0135 and 0.0440. The participants were divided into four groups according to the changes in the HGI over four 4 years: low to low, low to high, high to low, and high to low.

Measurement of CACS

Coronary calcium scoring was performed by using 64-slice spiral multidetector computed tomography (GE Healthcare, Tokyo, Japan), and HEARTBEAT-CS was the software used to measure CACS (Philips, Cleveland, OH). The 64-slice computed tomography was performed by using the following protocol: 0.625-mm slice thickness, 120 kVP, 800 effective mAs, and 400-millisecond rotational speed. The severity of CAC was assessed by using the Agatston score (17). The total CACS was determined by the sum of the individual scores for the four major epicardial coronary arteries: the left main, left anterior descending, left circumflex, and right coronary arteries.

The development of incident CAC was defined by changes in the CACS > 0 over 4 years.

Statistical analysis

Data were presented as mean ± standard deviation and numbers with percentages. The Student *t* test was used to compare the baseline characteristics of the study participants, divided by the incidence of CAC development over 4 years. The one-way analysis of variance test was performed to compare the differences between the groups divided by the baseline quartiles of HGI and divided by the changes in the HGI over 4 years. Pearson correlation analyses were used to analyze the correlations between FBG and HbA1c at different time points. The Pearson χ^2 test was used to compare the categorical variables between the groups, divided by the development of CAC over 4 years, and to compare the proportion of participants with incident CAC among the groups, divided by the baseline quartiles of HGI or changes in the HGI over 4 years.

Logistic regression analysis was performed to evaluate the odds ratio (OR) of CAC development according to the four groups of the baseline quartiles of the HGI and according to the four groups divided by the changes in the HGI over 4 years, after adjustment for the confounding variables. A stepwise regression model was used for the analyses.

PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL), was used for the statistical analyses. All the reported *P* values were two tailed, and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The general characteristics of the study population are shown in Table 1. The mean age of the population was 40 years, and 91% of the participants were men, pointing to a relatively extreme deviation in terms of sex.

Comparison of the metabolic parameters according to the development of CAC over 4 years

Of the 2052 participants who did not have CAC at the baseline, 201 (9.8%) developed CAC over the course of 4 years (Table 1). The participants who developed CAC were older, were likelier to be obese and male, had higher FBG levels and blood pressure, and showed worse lipid profiles than those who did not develop CAC over 4 years. The mean baseline HGI was higher in the participants who developed CAC after 4 years. More smokers were present in the CAC group than in the non-CAC group (Table 1).

Comparison of metabolic parameters and incidence of CAC between groups, divided by HGI at baseline

When the participants were divided into four groups according to the baseline quartiles of the HGI, as the mean HGI increased from first to fourth quartiles, the participants were found to be older and more likely to be obese (Table 2). The mean values of HbA1c, total

Table 1. Comparison of Metabolic Parameters Between Those Who Developed and Those Who Did Not Develop CAC

Variable	All Participants (n = 2052)	Participants Who Did Not Develop CAC (n = 1851 [90.2%])	Participants Who Developed CAC (n = 201 [9.8%])	*P* Value
Age (y)	40.2 ± 5.5	39.9 ± 5.4	42.5 ± 5.5	<0.01
Men, n (%)	1867 (91.0)	1672 (90.3)	195 (97.0)	<0.01
BMI (kg/m^2)	24.6 ± 3.0	24.5 ± 3.0	25.6 ± 2.8	<0.01
SBP (mm Hg)	118.2 ± 11.8	117.8 ± 11.6	121.8 ± 13.0	<0.01
DBP (mm Hg)	75.6 ± 8.8	75.3 ± 8.7	78.8 ± 9.3	<0.01
FBG (mg/dL)	94.6 ± 8.4	94.3 ± 8.2	97.2 ± 9.5	<0.01
HbA1c (%)	5.60 ± 0.3	5.59 ± 0.3	5.68 ± 0.2	<0.01
TC (mg/dL)	206.2 ± 35.9	204.6 ± 35.4	220.5 ± 37.1	<0.01
TG (mg/dL)	145.1 ± 96.7	142.3 ± 95.8	171.2 ± 101.4	<0.01
HDL-C (mg/dL)	52.4 ± 12.5	52.6 ± 12.6	50.0 ± 10.9	<0.01
LDL-C (mg/dL)	128.7 ± 32.5	127.4 ± 32.0	140.9 ± 34.7	<0.01
Fasting insulin (μIU/mL)	5.9 ± 3.5	5.8 ± 3.5	6.6 ± 4.0	<0.01
Mean baseline HGI	−0.04 ± 0.2	−0.11 ± 0.2	0.06 ± 0.2	<0.01
Changes in HGI over 4 y	0.05 ± 0.2	0.05 ± 0.2	0.03 ± 0.2	0.129
Smoker, n (%)[a]	1,142 (55.7)	1009 (54.5)	133 (66.2)	<0.01
Alcohol consumption, n [b]	879 (42.8)	782 (42.2)	97 (48.3)	0.06
Regular exercise, n (%)[c]	526 (25.6)	473 (25.6)	53 (26.4)	0.43

Unless otherwise noted, values are the mean ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

[a]Those who have smoked >5 packs of cigarettes in their life.

[b]Those who consume alcohol more than two times a week.

[c]Those who perform vigorous exercise more than once every week.

cholesterol, and low-density lipoprotein cholesterol significantly increased and high-density lipoprotein cholesterol significantly decreased from the first to the fourth quartiles of the baseline HGI.

The proportion of participants with incident CAC after 4 years significantly increased as the baseline HGI increased from the first to the fourth quartile groups (Table 2, Supplemental Fig. 3).

Table 2. Comparison of Metabolic Parameters Between the Groups, Divided by Baseline Quartiles of HGI

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value
Age (y)	39.2 ± 5.4	39.8 ± 5.6	40.6 ± 5.5	41.2 ± 5.2	<0.01
Men, n (%)	482 (94.1)	477 (92.8)	458 (89.3)	450 (87.7)	<0.01
BMI (kg/m^2)	24.2 ± 2.8	24.5 ± 2.7	24.7 ± 3.0	25.2 ± 3.2	<0.01
SBP (mm Hg)	118.7 ± 12.1	118.6 ± 11.4	117.6 ± 12.4	117.7 ± 11.5	0.282
DBP (mm Hg)	75.5 ± 8.9	76.0 ± 8.5	75.4 ± 9.1	75.5 ± 8.8	0.759
FBG (mg/dL)	94.8 ± 7.7	94.7 ± 8.1	94.2 ± 8.1	94.8 ± 9.5	0.621
HbA1c (%)	5.30 ± 0.1	5.52 ± 0.1	5.66 ± 0.1	5.91 ± 0.2	<0.01
TC (mg/dL)	195.7 ± 33.6	205.9 ± 34.0	209.7 ± 36.1	213.4 ± 37.3	<0.01
TG (mg/dL)	138.9 ± 114.6	141.1 ± 86.1	149.7 ± 96.6	150.7 ± 86.8	0.117
HDL-C (mg/dL)	52.9 ± 12.5	53.0 ± 12.7	52.6 ± 13.1	50.9 ± 11.3	0.018
LDL-C (mg/dL)	119.5 ± 30.0	128.6 ± 30.8	131.0 ± 32.9	135.6 ± 34.1	<0.01
Fasting insulin (μIU/mL)	5.5 ± 3.2	5.8 ± 3.4	5.9 ± 3.4	6.4 ± 4.0	0.001
Mean baseline HGI	−0.30 ± 0.1	−0.09 ± 0.04	0.07 ± 0.04	0.31 ± 0.1	<0.01
Changes in HGI over 4 y	0.15 ± 0.2	0.09 ± 0.2	0.03 ± 0.2	−0.07 ± 0.2	<0.01
Smoker, n (%)[a]	278 (54.3)	281 (54.7)	295 (57.5)	288 (56.1)	0.718
Alcohol consumption, n [b]	243 (47.5)	225 (43.8)	213 (41.5)	198 (38.6)	0.032
Regular exercise, n (%)[c]	150 (29.3)	136 (26.5)	123 (24.0)	117 (22.8)	0.083
Proportion of participants with incident CAC, n (%)	32 (6.3)	45 (8.8)	57 (11.1)	67 (13.1)	<0.01

Unless otherwise noted, values are the mean ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

[a]Those who have smoked >5 packs of cigarettes in their life.

[b]Those who consume alcohol more than two times a week.

[c]Those who perform vigorous exercise more than once every week.

Comparison of metabolic parameters and incidence of CAC between groups, divided by changes in HGI over 4 years

The participants were divided into four groups according to the changes in the HGI (lower or higher than the median) over 4 years (Table 3). The status of 717 (34.9%), 309 (15.1%), 308 (15.0%), and 718 (35%) participants changed from low to low, from low to high, from high to low, and from high to high, divided by the median of the HGI in each year, over 4 years. The participants in the high-to-high group were found to be the oldest at baseline among the four groups. All the parameters were the worst in the high-to-high group and the best in the low-to-low group, including FBG and HbA1c levels. The mean fasting insulin levels were also the highest in the high-to-high group compared with the other groups.

The incidence of CAC after 4 years was the highest in the high-to-high group (12.3%) compared with the other groups and the lowest in the low-to-low group (Table 3, Supplemental Fig. 4).

Risk for incident CAC after 4 years according to baseline HGI quartiles

The ORs for CAC development after 4 years of follow-up, according to baseline quartiles of HGI, were analyzed by using logistic regression analyses (Table 4). The OR for CAC development significantly increased (by up to 2.3 times) from the first to the fourth quartile group of baseline HGI before adjustment (model 1 in Table 4). The fourth quartile group of baseline HGI showed a sustained increased risk for incident CAC compared with the first quartile group, even after adjustment for multiple factors, including metabolic and lifestyle-related factors (model 4 in Table 4). However, when baseline HbA1c level was included in the model, the significance in the fourth quartile disappeared (model 5 in Table 4).

When similar analyses were performed in 995 participants without any glucose abnormalities at baseline, only the fourth quartile group of the baseline HGI showed a sustained increased risk for incident CAC compared with the first quartile group from model 1 to model 4 (Supplemental Table 1). When the baseline HbA1c level was included in the model, the significance in the fourth quartile disappeared, similar to the analysis performed in total study population (model 5 in Supplemental Table 1).

Risk for incident CAC according to changes in HGI over 4 years

When the participants were divided into four groups based on the changes in the HGI over 4 years, with the median HGI at that time point being assigned as the cutoff, the ORs for incident CAC were found to have

Table 3. Comparison of Baseline Metabolic Parameters Between the Groups, Divided by Changes in HGI Over 4 Years

Variable	Low to Low (n = 717 [34.9%])	Low to High (n = 309 [15.1%])	High to Low (n = 308 [15.0%])	High to High (n = 718 [35%])	*P* Value
Age (y)	39.4 ± 5.3	39.7 ± 5.8	40.7 ± 5.9	40.9 ± 5.1	<0.01
Men, n (%)	682 (95.1)	277 (89.6)	278 (90.3)	630 (87.7)	<0.01
BMI (kg/m^2)	24.3 ± 2.7	24.5 ± 2.9	24.7 ± 3.1	25.0 ± 3.1	<0.01
SBP (mm Hg)	119.2 ± 12.0	117.3 ± 11.0	118.1 ± 11.8	117. 5 ± 12.0	0.019
DBP (mm Hg)	76.1 ± 8.9	74.9 ± 8.1	76.2 ± 9.0	75.1 ± 8.9	0.054
FBG (mg/dL)	94.5 ± 7.8	95.2 ± 8.0	94.2 ± 8.7	94. 7 ± 8.9	0.480
HbA1c (%)	5.38 ± 0.2	5.48 ± 0.1	5.73 ± 0.2	5.81 ± 0.2	<0.01
TC (mg/dL)	198.9 ± 34.2	205.2 ± 33.7	209.4 ± 37.0	212.4 ± 36.6	<0.01
TG (mg/dL)	140.3 ± 102.4	139.4 ± 98.8	136.1 ± 78.0	156.3 ± 96.5	0.002
HDL-C (mg/dL)	53.0 ± 12.3	52.9 ± 13.4	53.7 ± 13.3	50.9 ± 11.7	0.001
LDL-C (mg/dL)	122.3 ± 30.0	128.2 ± 32.1	130.9 ± 33.3	134.3 ± 33.6	<0.01
Fasting insulin (μIU/mL)	5.6 ± 3.0	5.9 ± 3.9	5.8 ± 3.4	6.3 ± 3.9	0.002
Mean baseline HGI	−0.22 ± 0.1	−0.13 ± 0.1	0.13 ± 0.1	0.21 ± 0.2	<0.01
Changes in HGI over 4 y	0.04 ± 0.2	0.32 ± 0.2	−0.23 ± 0.2	0.07 ± 0.2	<0.01
Smoker, n (%)[a]	399 (55.6)	160 (51.8)	171 (55.5)	412 (57.4)	0.432
Alcohol consumption, n [b]	347 (48.4)	121 (39.2)	142 (46.1)	269 (37.5)	<0.01
Regular exercise, n (%)[c]	197 (27.5)	89 (28.8)	76 (24.7)	164 (22.8)	0.112
Proportion of participants with incident CAC, n (%)	45 (6.3)	32 (10.4)	36 (11.7)	88 (12.3)	<0.01

Unless otherwise noted, values are the mean ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

[a]Those who have smoked >5 packs of cigarettes in their life.

[b]Those who consume alcohol more than two times a week.

[c]Those who perform vigorous exercise more than once every week.

Table 4. Risk for Incident CAC According to Quartiles of Baseline HGI

	OR (95% CI)				
HGI Quartile	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
First	1.000	1.000	1.000	1.000	1.000
Second	1.439 (0.899–2.304)	1.403 (0.871–2.257)	1.277 (0.786–2.073)	1.282 (0.789–2.082)	1.264 (0.705–2.265)
Third	1.875 (1.194–2.945)	1.770 (1.120–2.797)	1.542 (0.963–2.469)	1.531 (0.955–2.455)	1.494 (0.715–3.121)
Fourth	2.253 (1.451–3.500)	2.075 (1.326–3.248)	1.634 (1.026–2.600)	1.632 (1.024–2.601)	1.566 (0.540–4.543)

CI, confidence interval. Model 1: no adjustment; model 2: adjusted for age and sex; model 3: adjusted for the factors in model 2 plus FBG, insulin, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and body mass index; model 4: adjusted for the factors in model 3 plus smoking, alcohol consumption, and exercise status; model 5: adjusted for the factors in model 4 plus baseline HbA1c levels.

increased twofold in the high-to-low and high-to-high groups and increased 1.7-fold in the low-to-high group compared with the low-to-low group before adjustment (model 1 in Table 5). These significantly increased ORs were sustained even after adjustment for multiple factors, including metabolic and lifestyle-related factors (model 4 in Table 5). Interestingly, when the baseline HbA1c level was included in the model, all the significance disappeared, except in the low-to-high group (model 5 in Table 5).

When similar analyses were performed in 995 participants without any glucose abnormalities at baseline, the significantly increased OR for incident CAC after adjustment for multiple factors was sustained only in the high-to-high group compared with the low-to-low group (Supplemental Table 2). However, when the baseline HbA1c level was included in the model, the significance disappeared (model 5 in Supplemental Table 2).

Discussion

This study evaluated the relationship between changes in the HGI over 4 years and the development of CAC in Korean adults without diabetes. We found that a high HGI at baseline significantly increased the incidence of and risk for CAC development over a course of 4 years. In addition, the incidence of CAC after 4 years was higher in participants with a high baseline HGI or a high HGI 4 years later. Interestingly, the risk for CAC was consistently higher only in participants with a low HGI at the baseline and a high HGI after 4 years compared with those with a consistently low HGI over 4 years, when the baseline HbA1c level was included in the model; this suggests that an elevated HGI, over 4 years, strongly affects CAC development, regardless of the baseline HbA1c level.

Numerous studies have reported a significant association between high HGIs and the increased risk for CVD (10–12). The Actions to Control Cardiovascular Risk in Diabetes study, conducted among 10,251 participants, found that HGIs calculated at the baseline could identify subpopulations with harms or benefits from intensive glycemic control (11). In that analysis, patients were divided into three groups according to baseline HGI levels derived from 1000 randomly extracted participants. Intensive treatment was associated with improved primary outcomes in the low and moderate HGI subgroups, but not in the high HGI groups, suggesting the need to take into account the HGI besides the HbA1c level, which is not a "one-size-fits-all" indicator of the risk for diabetes-related complications. In another subanalysis of participants from the Diabetes Control and Complications Trial, a threefold increase in the risk for retinopathy and sixfold increase in the risk for nephropathy was reported in patients with type 1 diabetes who had high HGIs compared with those who had low HGIs (10). In a study recently conducted among 1248 treatment-naive Korean participants with prediabetes or diabetes, the highest HGI

Table 5. Risk for Incident CAC According to Interval Changes in HGI Over 4 Years

	OR (95% CI)				
HGI Divided by Median	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Low to low	1.000	1.000	1.000	1.000	1.000
Low to high	1.725 (1.074–2.772)	1.806 (1.116–2.921)	1.750 (1.072–2.857)	1.748 (1.070–2.857)	1.722 (1.046–2.833)
High to low	1.976 (1.247–3.132)	1.851 (1.158–2.958)	1.698 (1.050–2.747)	1.693 (1.046–2.739)	1.583 (0.868–2.885)
High to high	2.086 (1.433–3.036)	2.015 (1.376–2.950)	1.693 (1.140–2.515)	1.680 (1.129–2.500)	1.547 (0.852–2.807)

CI, confidence interval. Model 1: no adjustment; model 2: adjusted for age and sex; model 3: adjusted for the factors in model 2 plus FBG, insulin, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and body mass index; model 4: adjusted for the factors in model 3 plus smoking, alcohol consumption, and exercise status; model 5: adjusted for the factors in model 4 plus baseline HbA1c levels.

tertile was independently associated with a composite CVD after adjustment for other CVD risk factors (12). These results are in line with our study, except that our study evaluated the association between the interval changes in the HGI over 4 years and the development of subclinical atherosclerosis in participants without diabetes.

Our study assessed the influence of changes in the HGI over 4 years on the development of subclinical atherosclerosis. Although HbA1c reflects the variations in the blood glucose levels in the past 2 to 3 months and is known to be stable, HbA1c levels also vary widely. The authors of previously conducted studies suggested that HbA1c levels could reflect both differences in the blood glucose levels over time and the individual effects of additional biological factors that influence nonenzymatic protein glycation (10, 18). The hypothesis is that individuals with a high HGI have a propensity to glycate other proteins and, thus, the HGI can help identify a phenotype of glucose metabolism that is characterized by individual differences in the susceptibility to hemoglobin glycation. Those authors also suggested that the HGI could be a marker of the inherent risk for vascular complications in patients with diabetes. There were subject-to-subject differences in the HGI, and there was less intraindividual variability within the same individual (9, 10). It is assumed that HGI could be considered as a fixed phenotype that reflects the glycation tendency of an individual and subsequently be related to the probability of vascular complications.

In the current study, we analyzed the HGI twice in a span of 4 years in the same population. The correlation coefficient between the HGI values in 2010 and 2014 was 0.559 in the simple correlation analysis. This coefficient value was numerically high, but we cannot conclude that the HGI value is an "inherent" or a "fixed" phenotype because the correlation between the repeated values in a 4-year interval is far from complete. Because no studies to date have evaluated repeated HGI values at different time points, we cannot verify our findings. Therefore, we assume that although the HGI could reflect a certain inherent glycation ability, HGI levels might have changed over time in some cases because only 70% of our study population remained in the same half divided by the median of the HGI after 4 years.

In our study, the incidence of and the risk for CAC development linearly increased as the baseline HGI levels increased from the first to the fourth quartile. If the HGI is an inherent phenotype of glycation, those with high HGI values at baseline would have a higher inherent risk for CVD and thus an increased risk for CAC development; this is in line with the findings of previously conducted studies (10–12). However, these significant increases in the risk for CAC development disappeared after adjustment for the baseline HbA1c levels because those with high HGI values had high baseline HbA1c levels. This might suggest the importance of HbA1c levels rather than HGI values on the development of CVD, as reported by a study that negated the importance of HGI (19).

We analyzed the risk for CAC development in the four groups divided by the HGI values at baseline and 4 years later. Those who had low HGI values at both times showed the lowest incidence and the risk for CAC development compared with those in the low-to-high, high-to-low, or high-to-high groups over 4 years. As expected, these significant differences disappeared when the baseline HbA1c level was included in the model, except for those with low HGI values at the baseline who moved to the high HGI group after 4 years. These findings are of interest because HGI values are not a fixed phenotype but can be changed over time. Furthermore, in addition to HGI values at certain time points predicting the development of subclinical atherosclerosis, changes in the HGI could influence vascular health, too.

Our study has some limitations. First, because our study population comprised participants without diabetes, the results have to be interpreted with caution in individuals with diabetes or those who are being treated. Second, our study used only FBG, not MBG, to estimate the correlation with HbA1c, as in a previous study (10). Because only FBG was included in the linear regression model, the level of postprandial glucose could have affected the HGI level. Third, because we did not measure any other glycation product, such as AGEs, the role of HGI could be considered only as a hypothesis. If AGEs could be measured and could analyze the correlation with the HGI, we could suggest whether HGI actually reflects the glycation phenotype. Last, when the analyses were performed in participants without any glucose abnormalities at baseline, the results were not reproduced, suggesting that the influence of HGI on incident CAC was not so strong in normoglycemic population. However, the incidence of CAC in the study participants with completely normal baseline glucose levels after 4 years was only 6.8%, which was roughly half the incidence in the total study population (in which those with prediabetes at baseline were included). Therefore, the weak correlation between HGI and CAC development in this subgroup could be due to the low incidence of CAC in this group. Despite these limitations, our study findings are a valuable addition to the field of diabetic complications.

In conclusion, we report the association between changes in HGI values over 4 years and CAC development in adults without diabetes. The risk for CAC development was high in the participants with a high baseline HGI, which was attenuated after adjustment for

baseline HbA1c levels. However, the risk for CAC development was consistently high in the participants who had low HGI values and in whom the HGI values increased over 4 years, regardless of baseline HbA1c levels. Our findings suggest that HGI values could change in one third of the general population, and these changes could affect the development of subclinical atherosclerosis. Further research on the relationship between HGI values and AGEs could uncover the exact mechanisms of the deleterious effects of high HGI values and timely increases in the HGI values on the development of atherosclerosis.

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