Glucose Variability and Risk of Hepatocellular Carcinoma in Patients with Diabetes: A Nationwide Population-Based Study

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ABSTRACT

Background: Although diabetes is a well-known risk factor for hepatocellular carcinoma, exactly which metabolic parameters of diabetes are associated with hepatocellular carcinoma remain unexplored. In this study, we investigated the relationship between glucose variability (GV) and hepatocellular carcinoma in patients with diabetes through a nationwide population-based study.

Methods: A population-based cohort study including 674,178 diabetic subjects participating in more than three health examinations within 5 years from the index year (2009 and 2010) were followed until the end of 2017. The coefficient of variation, SD, variability independent of the mean, and average real variability were calculated as GV indices.

Results: During a median follow-up of 6.7 years, there were 5,494 cases of hepatocellular carcinoma. When groups were classified according to glucose level, the highest risk for hepatocellular carcinoma was observed when the basal blood glucose level was 180 mg/dL or greater [adjusted HR (aHR), 1.19; 95% confidence interval (CI), 1.08–1.31]. We observed increasing trends for the relationship between GV and hepatocellular carcinoma in multivariable Cox proportional analyses. The risk of hepatocellular carcinoma increased by 27% (aHR, 1.27; 95% CI, 1.17–1.38) for the highest quartile of GV relative to the lowest quartile. These findings were consistent regardless of the presence of chronic viral hepatitis or cirrhosis, alcohol consumption, or body mass index.

Conclusions: GV was an independent predictor of hepatocellular carcinoma, even after adjusting for confounding factors. There was a linear relationship between increase in GV and prevalence of hepatocellular carcinoma.

Impact: Visit-to-visit GV might be helpful for identifying patients with diabetes at high risk of hepatocellular carcinoma.

Introduction

After the introduction of universal vaccination programs and the development of effective antiviral agents, the influence of hepatitis B virus and hepatitis C virus, previously the main causes of hepatocellular carcinoma, has gradually decreased. However, the incidence of hepatocellular carcinoma has increased from 1999 to 2011. Hepatocellular carcinoma is the second largest cause of cancer mortality in Republic of Korea (South), resulting in significant healthcare-related economic burden in our country (1, 2). With increasing prevalence of obesity and diabetes, interest in metabolic risk factors for hepatocellular carcinoma is also increasing these days. For example, the prevalence of nonalcoholic fatty liver disease increased from 18.6% in 1998–2001 to 21.5% in 2016–2017 in Korea (3).

Diabetes mellitus is another significant risk factor for the development of hepatocellular carcinoma (4). Several studies have reported that diabetes increases the risk of hepatocellular carcinoma by about 2.4–4 times (4–6). The most common pathophysiologies are obesity, impaired insulin sensitivity, and nonalcoholic fatty liver disease (NAFLD) (7, 8). Moreover, patients with diabetes are more likely to develop severe forms of NAFLD, such as nonalcoholic steatohepatitis and cirrhosis, leading to hepatocellular carcinoma (9). However, there have been no studies exploring exactly which metabolic parameters can be used to estimate the risk of hepatocellular carcinoma in patients with diabetes. If high-risk patients can be identified among diabetics, the incidence of hepatocellular carcinoma could be lowered by surveillance.

Recently, glucose variability (GV) has attracted attention as a prognostic tool in patients with diabetes, alongside traditional tools, such as glycated hemoglobin (HbA1c) and postprandial glucose (10). GV is considered to indicate quality of glycemic control, and increases progressively from prediabetes through advanced type 2 diabetes mellitus (11). Day-to-day (short term) GV is an indicator of glucose fluctuation and is reported to be associated with micro- and macrovascular complications, such as retinopathy, microalbuminuria, and acute myocardial infarction, independent of mean glucose level (12–14). In addition, visit-to-visit (long term) GV is also

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associated with all-cause mortality, stroke, and dementia in the general population (15–18).

However, to our knowledge, no studies have investigated the role of GV in the development of hepatocellular carcinoma. In relation to liver disease, few studies have suggested that GV gradually progresses in accordance with the progression of hepatic fibrosis, suggesting a link between GV and hepatocellular carcinoma (19). A Taiwanese study involving 4,805 patients with type 2 diabetes mellitus showed that annual GV was independently associated with all-cancer incidence and all-cancer mortality (20). However, this study was underpowered to examine the relationship between GV and hepatocellular carcinoma specifically. Therefore, in this study, we investigated the relationship between GV and hepatocellular carcinoma in patients with diabetes drawn from a nationwide population-based cohort.

Materials and Methods

Data source

The Republic of Korea (South) has a universal health coverage system with mandatory social health insurance. Therefore, virtually all Korean residents (~50 million individuals) are covered by the National Health Insurance System (NHIS; ref. 21). The NHIS catalogs comprehensive data for the health service utilization of the entire Korean population.

The NHIS also provides free biennial cardiovascular health screenings to all employed Koreans regardless of age and to all Koreans more than 40 years of age. The screening programs aim to detect and treat and subsequently manage cardiovascular health conditions, including hypertension, diabetes, and dyslipidemia. Therefore, the NHIS database contains a complete set of health records, which includes sociodemographic data (age, sex, place of residence, and income level), medical diagnosis [based on International Classification of Disease, 10th revision (ICD-10)], treatment data, and health examination results (lifestyle and laboratory test results) for the Korean population.

Study sample

A flow chart of study sample selection is shown in Supplementary Fig. S1. First, we included individuals who underwent health screening examinations in 2009 and 2010 (index year), and had three or more health examinations results within the 5 years prior to the index year ($n = 8{,}376{,}860$). Among the remaining subjects, 868,474 had diabetes at the index date. We excluded patients who were younger than 20 years ($n = 106$) and who had missing variables ($n = 165{,}191$). We excluded those who (i) had previous diagnoses of any type of cancer, including hepatocellular carcinoma, before the index date ($n = 18{,}887$) and (ii) had died or were diagnosed with hepatocellular carcinoma in the first 1 year of follow-up ($n = 10{,}112$) for a 1-year lag period from the index year. As a result, a total of 674,178 subjects were included in our analysis.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital [Seoul, Republic of Korea (South), E-1906-044-1038], and also conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. The requirement for informed consent from individual subjects was waived, as we used deidentified secondary data.

Definition of GV

In principle, national health checkups in Korea are conducted every 1 to 2 years. During a medical examination, fasting blood glucose level was measured only once per one subject. Most participants were tested in the morning after fasting overnight. GV was defined as variability in fasting glucose values measured between health examinations. GV was defined as variability in fasting glucose values measured at each health examination. Numerous indicators for measuring GV have been proposed, but there is no clear consensus on which method is the gold standard (22). Therefore, to minimize the limitations of each test, the four most commonly used indices of variability in clinical studies were selected: (i) SD, (ii) coefficient of variation (CV), (iii) variability independent of the mean (VIM), and (iv) average real variability (ARV; ref. 23). Four formulas were used in this study as shown below:

(a) $\mathrm{SD}(\mathrm{SD}) = \sqrt{\frac{\sum |x-\mu|^2}{N}}$, ($x$: value in the data set, μ: mean).

(b) $\mathrm{CV}(\mathrm{CV}) = \frac{SD}{mean}$.

(c) $\mathrm{VIM}(\mathrm{VIM}) = \frac{SD}{mean^{\beta}}$,($\beta$: regression coefficient based on the natural logarithm of SD over the natural logarithm of the mean; ref. 24).

(d) $\mathrm{ARV}(\mathrm{ARV}) = \frac{1}{N-1}\sum_{k=1}^{N-1} |Value_{K+1} - Value_K|$,($N$: number of measurements for glucose parameters; ref. 25).

Study outcome and follow-up

The primary endpoint of the study was newly diagnosed hepatocellular carcinoma. Hepatocellular carcinoma was defined as the recording of ICD-10 codes (C22.0) validated previously as reliable for research (26, 27). The study sample was followed from 1 year after the index date (1-year time lag) to the date of death or hepatocellular carcinoma, or until December 31, 2017, whichever came first.

Covariates

Data for alcohol, smoking, and exercise were acquired from the questionnaires administered on the index date. Smoking was divided into three categories: nonsmoking, past smoking, and current smoking. The amount of alcohol consumption was divided into three levels: nondrinking, average alcohol consumption (<30 g/day), and heavy drinking (≥30 g/day). Exercise regularity was defined as more than 30 minutes of moderate physical activity at least five times per week or more than 20 minutes of strenuous physical activity at least three times per week.

Diabetes mellitus was defined according to the following criteria: (i) fasting glucose level ≥ 126 mg/dL or (ii) prescription of antidiabetic medication history at least one claim per year under ICD-10 codes E11–14. Hypertension was defined according to (i) systolic blood pressure of more than 140 mmHg or diastolic blood pressure of more than 90 mmHg or (ii) prescription of antihypertensive agents history at least one claim per year under ICD-10 codes I10–13 or I15. Dyslipidemia was defined according to (i) total cholesterol level greater than 240 mg/dL or (ii) prescription of a lipid-lowering agent at least one claim per year under ICD-10 code E78. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate less than 60 mL/minute/1.73 m^2 by the modification of diet in renal disease equation. Chronic viral hepatitis (B15, B16, B17, and B18) and liver cirrhosis (K746 and K703) were defined according to ICD-10 codes. If a patient was diagnosed with both hepatitis and liver cirrhosis, they were classified as having liver cirrhosis.

Statistical analysis

Frequencies and percentages were used for descriptive statistics. Significant differences between groups were investigated using the χ^2 test for categorical variables and Student t test for continuous variables. Outcome incidence rates were presented per 1,000 person-years.

Cox proportional hazards regression analyses were used to evaluate the relationships between glucose level (seven levels) or quartiles of GV and the incidence of hepatocellular carcinoma. To minimize the influence of confounding factors, age and sex (model 1), smoking, drinking, exercise, income, body mass index (BMI), hypertension, dyslipidemia, liver cirrhosis, and chronic viral hepatitis (model 2), oral antidiabetic agents, insulin, duration of diabetes, and baseline glucose level (model 3) were serially adjusted in a Cox proportional hazard model.

Next, for the analysis of GV, we performed stratified analysis by the presence of fatty liver. Because the NHIS database did not contain imaging findings, the presence of fatty liver was evaluated by using fatty liver index (FLI; ref. 28). To test potential effect modification, forest plots for the risk of hepatocellular carcinoma according to risk factor subgroups (weight change, age, sex, duration of diabetes, oral diabetic medication, smoking status, amount of alcohol consumption, BMI, and presence of abdominal obesity) were constructed after dichotomizing GV groups into the highest quartile (Q4) group and the lower three quartiles (Q1–Q3).

To identify continuous trends, we also performed analyses on the basis of deciles of GV. Sensitivity analysis was performed with 2 years of lag period to account for potential issues of reverse causality. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc.) and statistical significance was defined as $P < 0.05$.

Data availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

Baseline characteristics and study sample

The characteristics of participants classified by quartiles of GV are described in **Table 1**. Subjects in higher quartiles were younger and the proportion of smokers was high. The number of patients taking antidiabetic medications for more than 5 years was low, and the percentage of patients using insulin was high. In subjects with higher GV, the prevalence of hypertension and dyslipidemia and the

Table 1. Baseline characteristics of participants according to quartiles of GV.

Characteristic	Q1 (lowest) *n* = 168,544	Q2 *n* = 168,545	Q3 *n* = 168,545	Q4 (highest) *n* = 168,544	*P*
Age (years)	59.2 ± 10.7	58.1 ± 11.1	57.2 ± 11.8	55.6 ± 13.2	<0.0001
Sex					<0.0001
Male	105,285 (62.5)	108,633 (64.5)	110,511 (65.6)	113,629 (67.4)	
Female	63,259 (37.5)	59,912 (35.6)	58,034 (34.4)	54,915 (32.6)	
Smoking					<0.0001
Nonsmoker	96,924 (57.5)	93,075 (55.2)	90,106 (53.5)	86,029 (51.0)	
Ex-smoker	36,657 (21.8)	36,365 (21.6)	34,385 (20.4)	31,614 (18.8)	
Current smoker	34,963 (20.7)	39,105 (23.2)	44,054 (26.1)	50,901 (30.2)	
Alcohol consumption					<0.0001
None	94,527 (56.1)	92,241 (54.7)	92,036 (54.6)	92,084 (54.6)	
<30 g/day	58,321 (34.6)	60,158 (35.7)	60,181 (35.7)	60,973 (36.2)	
≥30 g/day	15,696 (9.3)	16,146 (9.6)	16,328 (9.7)	15,487 (9.2)	
Regular exercise	43,490 (25.8)	41,246 (24.5)	38,774 (23.0)	35,260 (20.9)	<0.0001
Income (lowest 20%)	372,33 (22.1)	38,266 (22.7)	40,452 (24.0)	42,761 (25.4)	<0.0001
Weight (kg)	66.0 ± 10.9	66.7 ± 11.2	67.0 ± 11.5	66.8 ± 12.0	<0.0001
Height (cm)	162.6 ± 9.0	162.9 ± 9.0	163.1 ± 9.1	163.5 ± 9.3	<0.0001
Waist circumflex (cm)	85.3 ± 8.0	85.6 ± 8.0	85.7 ± 8.2	85.3 ± 8.6	<0.0001
BMI (kg/m^2)	24.9 ± 3.0	25.1 ± 3.1	25.1 ± 3.2	24.9 ± 3.3	<0.0001
Systolic blood pressure (mmHg)	128.8 ± 15.2	128.9 ± 15.1	128.7 ± 15.1	128.1 ± 15.1	<0.0001
Diastolic blood pressure (mmHg)	78.7 ± 9.9	79.1 ± 9.9	79.1 ± 9.9	78.8 ± 9.8	<0.0001
Status of diabetes					
Oral diabetic medication	124,916 (74.1)	115,618 (68.1)	107,671 (63.9)	94,114 (55.8)	<0.0001
Insulin	11,120 (6.6)	11,029 (6.54)	12,146 (7.2)	15,569 (9.2)	<0.0001
More than 5 years from diagnosis	69,665 (41.3)	62,538 (37.1)	57,085 (33.9)	50,868 (30.2)	<0.0001
Comorbidity					
Hypertension	100,287 (59.5)	98,338 (58.4)	95,383 (56.6)	88,967 (52.8)	<0.0001
Dyslipidemia	68,080 (40.4)	66,968 (39.7)	64,459 (38.2)	58,389 (34.6)	<0.0001
Chronic kidney disease	18,398 (10.9)	18,708 (11.1)	19,634 (11.7)	20,796 (12.4)	<0.0001
Heart disease	9,015 (6.1)	8,542 (5.9)	7,983 (5.6)	7,343 (5.4)	<0.0001
Stroke	3,722 (2.5)	3,494 (2.4)	3,219 (2.3)	3,018 (2.2)	<0.0001
Liver cirrhosis	245 (0.2)	297 (0.2)	311 (0.2)	337 (0.2)	0.0017
Chronic viral hepatitis	2,337 (1.4)	2,418 (1.4)	2,512 (1.5)	2,526 (1.5)	0.0213
Laboratory findings					
Serum glucose (mg/dL)	143.2 ± 40.2	141.5 ± 37.9	141.8 ± 41.1	145.1 ± 50.9	<0.0001
Total cholesterol (mg/dL)	194.5 ± 39.9	195.9 ± 40.4	196.3 ± 41.1	195.3 ± 41.3	<0.0001
HDL cholesterol (mg/dL)	51.9 ± 22.0	51.7 ± 21.3	51.5 ± 21.2	51.5 ± 20.9	<0.0001
LDL cholesterol (mg/dL)	110.8 ± 44.8	111.2 ± 44.5	110.8 ± 45.0	109.7 ± 46.4	<0.0001

Note: Data are presented as mean ± SD for continuous variables and *n* (%) for categorical variables.
Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; Q, quartile.

Table 2. Risk of hepatocellular carcinoma according to level of glucose.

	Population	Events (hepatocellular carcinoma)	Follow-up duration (person-year)	Incidence rate (per 1,000 p-y)	Model 1[a]	Model 2[b]	Model 3[c]
Glucose level (mg/dL)							
<80	12,235	126	80,185.7	1.57	1.13 (0.94–1.36)	1.08 (0.89–1.30)	0.99 (0.82–1.20)
80–99	57,360	551	382,122.1	1.44	1.10 (0.99–1.22)	1.08 (0.97–1.20)	1.06 (0.95–1.18)
100–119	103,590	898	695,611.3	1.29	1 (reference)	1 (reference)	1 (reference)
120–139	222,611	1,585	1,512,578.0	1.04	0.90 (0.83–0.98)	0.85 (0.78–0.92)	0.99 (0.86–1.03)
149–159	124,039	947	841,896.5	1.12	0.97 (0.88–1.06)	0.91 (0.83–1.00)	0.98 (0.89–1.07)
160–179	58,510	503	395,680.1	1.27	1.10 (0.99–1.23)	1.04 (0.93–1.16)	1.08 (0.96–1.20)
≥180	95,833	884	644,528.5	1.37	1.27 (1.15–1.39)	1.20 (1.09–1.32)	1.19 (1.08–1.31)

Abbreviation: p-y, person-year.
[a]Model 1: adjusted for age and sex.
[b]Model 2: adjusted for model 1 + smoking, drinking, exercise, income, BMI, hypertension, dyslipidemia, liver cirrhosis, and chronic viral hepatitis.
[c]Model 3: adjusted for model 2 + oral antidiabetic agents, insulin, duration of diabetes, and baseline glucose level.

percentage of people who exercised regularly were lower. Other factors, such as drinking rate, BMI, blood pressure, and cholesterol level, did not show clear tendencies to vary among groups.

Glucose level and hepatocellular carcinoma

During a mean follow-up of 6.75 years after 1 year of time lag, 5,494 (1.1%) individuals developed hepatocellular carcinoma. The correlation between glucose level and hepatocellular carcinoma showed a U-shape (**Table 2**; Supplementary Fig. S2). When the samples were classified into seven groups according to basal glucose level, the risk of hepatocellular carcinoma was the lowest in patients with blood glucose levels of 120 to 140 mg/dL, and increased in patients with either lower or higher levels of glucose. The highest risk of hepatocellular carcinoma was observed when the basal blood glucose level was 180 mg/dL or greater [adjusted HR, 1.20; 95% confidence interval (CI), 1.09–1.32].

GV and hepatocellular carcinoma

Even after adjusting for baseline glucose level, higher GV was associated with increased incidence of hepatocellular carcinoma (**Fig. 1**). The incidence rate and HR of hepatocellular carcinoma increased with increasing GV. The cumulative incidence of hepatocellular carcinoma increased continuously and linearly when divided by quartile group after adjusting for age, sex, smoking, amount of drinking, exercise, economic status, BMI, duration of diabetes, chronic viral hepatitis, and liver cirrhosis [HR (95% CI): Q2, 1.02 (0.94–1.10); Q3, 1.09 (1.01–1.18); and Q4, 1.27 (1.17–1.38); **Table 3**; Supplementary Fig. S3]. Moreover, the incidence of hepatocellular carcinoma was

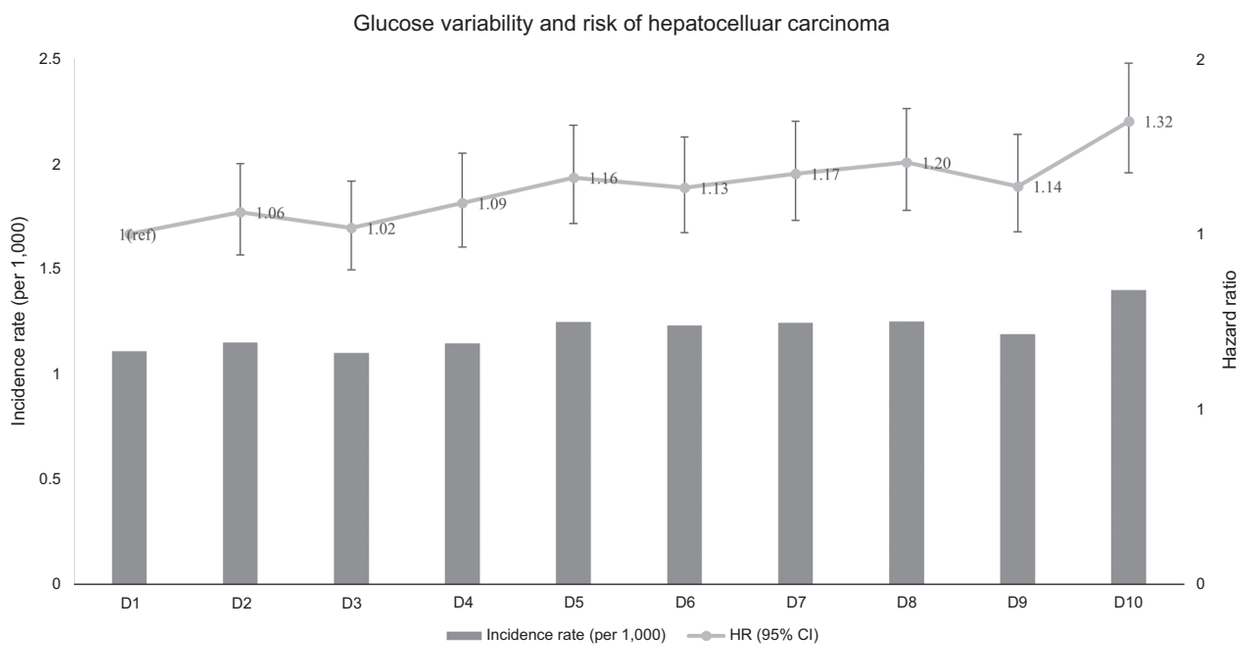

Figure 1.
GV and risk of hepatocellular carcinoma by decile groups. GV values were divided into 10 groups. The bar graph shows the incidence rate, and the solid line shows the HR.

Table 3. Risk of hepatocellular carcinoma according to GV.

	Population	Events (hepatocellular carcinoma)	Follow-up duration (person-years)	Incidence rate (per 1,000 p-y)	Model 1[a]	Model 2[b]	Model 3[c]
Indices: SD							
Q1	168,521	1,271	1,135,051.8	1.11	1 (reference)	1 (reference)	1 (reference)
Q2	168,759	1,235	1,144,794.1	1.07	1.03 (0.95–1.11)	1.00 (0.92–1.08)	1.01 (0.93–1.10)
Q3	168,386	1,322	1,141,724.3	1.15	1.15 (1.06–1.24)	1.10 (1.02–1.19)	1.09 (1.00–1.18)
Q4	168,512	1,666	1,131,032.1	1.47	1.46 (1.35–1.57)	1.41 (1.31–1.52)	1.27 (1.17–1.38)
Indices: CV							
Q1	168,547	1,273	1,134,492.8	1.12	1 (reference)	1 (reference)	1 (reference)
Q2	168,542	1,298	1,141,438.6	1.13	1.06 (0.98–1.15)	1.05 (0.97–1.13)	1.05 (0.97–1.13)
Q3	168,545	1,333	1,143,093.3	1.16	1.14 (1.06–1.23)	1.10 (1.02–1.19)	1.09 (1.01–1.18)
Q4	168,544	1,590	1,133,577.6	1.40	1.39 (1.29–1.50)	1.34 (1.24–1.45)	1.23 (1.14–1.33)
Indices: VIM							
Q1	168,544	1,268	1,133,907.7	1.11	1 (reference)	1 (reference)	1 (reference)
Q2	168,545	1,349	1,139,578.8	1.18	1.10 (1.01–1.18)	1.09 (1.01–1.18)	1.10 (1.02–1.19)
Q3	168,545	1,402	1,140,630.8	1.22	1.16 (1.08–1.26)	1.14 (1.06–1.23)	1.15 (1.07–1.24)
Q4	168,544	1,475	1,138,485.1	1.29	1.28 (1.18–1.38)	1.23 (1.14–1.33)	1.24 (1.14–1.33)
Indices: ARV							
Q1	168,914	1,215	1,142,805.6	1.06	1 (reference)	1 (reference)	1 (reference)
Q2	165,581	1,212	1,124,495.1	1.07	1.06 (0.98–1.15)	1.04 (0.96–1.12)	1.04 (0.96–1.13)
Q3	171,856	1,365	1,162,231.7	1.17	1.17 (1.08–1.27)	1.14 (1.05–1.23)	1.11 (1.02–1.20)
Q4	167,827	1,702	1,123,069.9	1.51	1.50 (1.40–1.62)	1.47 (1.36–1.58)	1.30 (1.20–1.41)

Abbreviations: p-y, person-year; Q, quartile.
[a]Model 1: adjusted for age and sex.
[b]Model 2: adjusted for model 1 + smoking, drinking, exercise, income, BMI, hypertension, dyslipidemia, liver cirrhosis, and chronic viral hepatitis.
[c]Model 3: adjusted for model 2 + oral antidiabetic agents, insulin, duration of diabetes, and baseline glucose level.

the highest in Q4, reaching 1.47/1,000 person-year. The finding of increased risk of hepatocellular carcinoma according to higher GV was the same for all four indices of GV: SD, CV, VIM, and ARV (all $P < 0.001$; **Table 3**).

Stratified analyses by baseline variables

Stratified analysis by the level of FLI showed that GV was related to hepatocellular carcinoma regardless of the degree of fatty liver evaluated by FLI (Supplementary Table S1).

Stratified analyses by baseline variables showed that relationship between higher GV and increased risk of hepatocellular carcinoma was generally consistent regardless of baseline characteristics, such as oral diabetic medication, smoking, BMI, and abdominal obesity. This relationship was modified by age such that association between GV and the risk of hepatocellular carcinoma was higher for younger subjects than older subjects ($P_{\text{interaction}} = 0.012$; **Fig. 2**; Supplementary Table S2).

Discussion

In this nationwide population-based long-term follow-up study, we detected an association between GV and hepatocellular carcinoma in patients with diabetes. We found that GV is an independent predictor of hepatocellular carcinoma, even after adjusting for possible confounding factors, including BMI. There was a linear association between the increase in GV and the risk of hepatocellular carcinoma. The results were consistent for different GV assessment methods and various sensitivity analyses. As far as we know, this is the first study to suggest that among several metabolic parameters, GV can be used to estimate the risk of hepatocellular carcinoma in patients with diabetes.

In our study, high fasting blood glucose level (>180 mg/dL) at baseline was associated with increased risk of hepatocellular carcinoma. This is consistent with the results of previous studies reporting that increased HbA1c is associated with risk of hepatocellular carcinoma, and hyperglycemia is a significant risk factor for early recurrence of hepatocellular carcinoma (29, 30). Although the findings remain controversial, hyperglycemia itself can cause hepatocellular carcinoma through the following mechanisms: dysregulation of the TSC1/TSC2/mTOR signaling pathway by IκB kinaseβ, and O-linked N-acetylglucosamination stimulation by advanced glycosylation end product–specific receptor (IKKβ; refs. 31–34).

In addition, in our study, we found that high GV was strongly associated with hepatocellular carcinoma, even more than glucose level itself. The exact mechanism underlying this phenomenon should be studied further, but several hypotheses are suggested. First, variability itself can cause oxidative stress and lead to hepatocellular carcinoma. Both diabetes mellitus and NAFLD are associated with increased oxidative stress and reactive oxygen species (ROS; ref. 35). Increased oxidative stress and ROS can lead to many types of cancer, including hepatocellular carcinoma (36, 37). This hypothesis is supported by the fact that hepatocellular carcinoma can occur in the absence of cirrhosis in patients with NAFLD. In animal experiments, glucose fluctuation leads to increased hepatocyte apoptosis through the involvement of mitochondrial permeability transition opening (38).

Second, high values of GV may mean that diabetes is not well-controlled. In our study, GV had greater effects on hepatocellular carcinoma in subjects of younger age, who were female, and who were diagnosed with early diabetes. If these characteristics represent early stages of diabetes, this implies that the role of GV is greater in low-risk or early-stage diabetic patients. In this context, we believe that GV is a new severity marker of diabetes that is not well-captured at the traditional glucose level. GV value increases in response to poor glycemic control (39). Diabetes can increase the risk of hepatocellular carcinoma due to the mechanisms of insulin resistance, increased

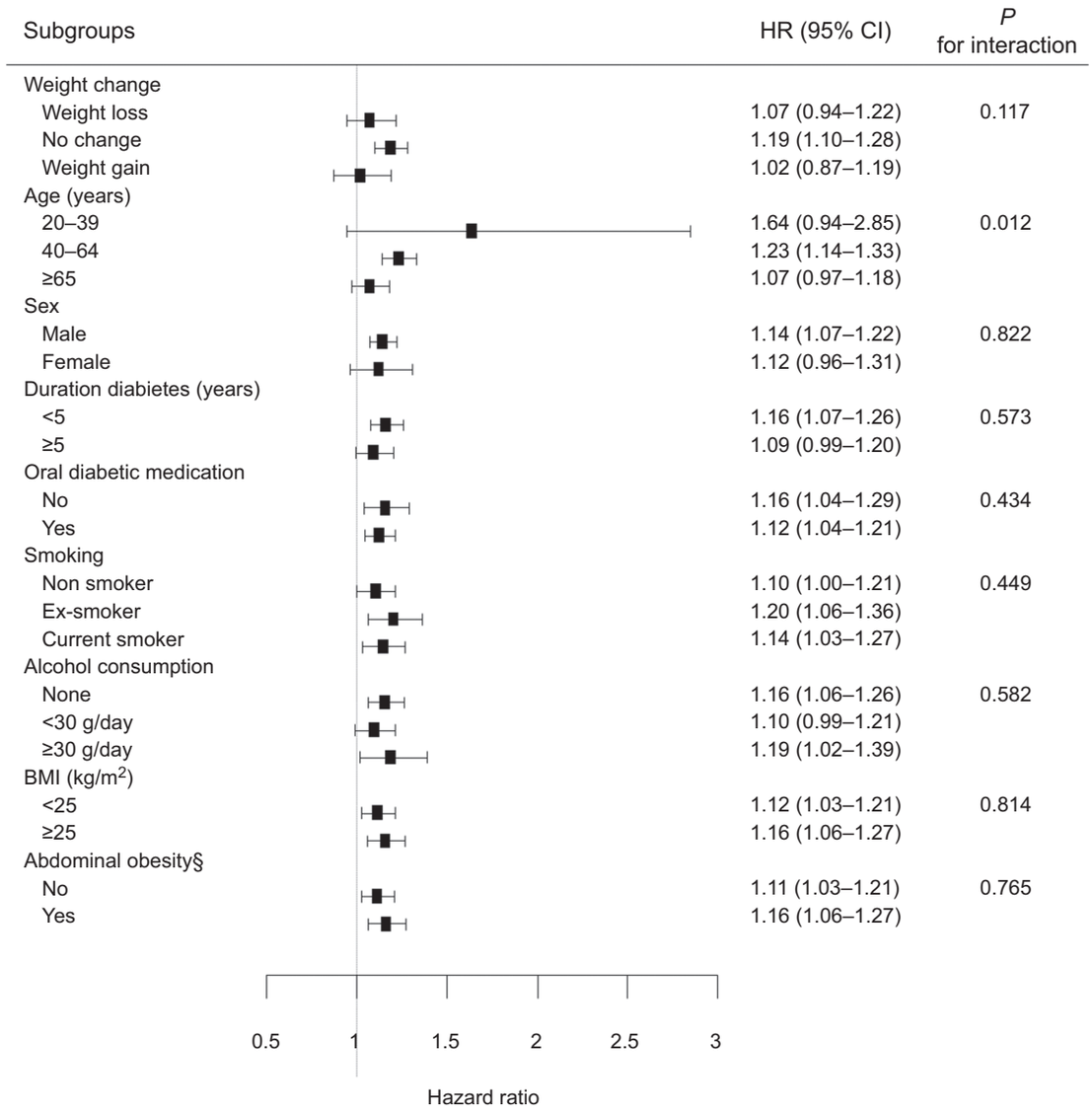

Figure 2.

Relationship between GV and hepatocellular carcinoma according to baseline characteristics. §, a waistline that measures at least 89 cm for women and 102 cm for men.

insulin growth factor-1, increased proinflammatory state, and intestinal dysbiosis (9). In patients with high GV values due to poor glycemic control, the above mechanisms are more active and more likely to cause hepatocellular carcinoma.

Third, the degree of variability might be related to hepatic fibrosis. Hepatic fibrosis may be a mediator between GV and hepatocellular carcinoma, but it was difficult to prove in our study. Therefore, additional basic or epidemiologic studies are needed.

The clinical implications of our study include that GV can be used as a surveillance marker to assess the risk of hepatocellular carcinoma in patients with diabetes. Therefore, we suggest that not only traditional markers, for example, HbA1c or glucose level, but also GV should be an important therapeutic target in diabetes. Because GV value tends to increase in patients with poor glycemic control, it is important to educate patients regarding the importance of medication adherence to prevent hepatocellular carcinoma. In addition, some oral antidiabetic agents have been reported to reduce GV, and the use of these agents may help prevent liver cancer in patients with diabetes (40).

There are several limitations in our study. First, the definition of GV used in our study was based on visit-to-visit GV only. Day-to-day (short term) GV was studied more as an indicator of glucose fluctuation. It has been reported to be associated with micro- and macrovascular complications (41). In our large-scale study at the national level, we used visit-to-visit data instead. However, visit-to-visit variability has been reported in numerous previous studies. It is associated with all-cause mortality, stroke, and dementia (42, 43). In addition, visit-to-visit variability data are easier to obtain for large-scale studies (18, 20, 25).

Second, we lacked data for HbA1c levels, so this variable is not reflected in the analysis. However, we tried to overcome these

shortcomings by adjusting for glucose level and duration of diabetes mellitus. Third, our consideration for the hepatic fibrosis is limited. We could not calculate FIB-4 or NAFLD fibrosis scores because platelet was not measured in the national health screening program. Instead, we tried to minimize this problem as much as possible by considering clinical diagnosis of liver cirrhosis as a variable.

Fourth, because this study was conducted among patients with diabetes, it remains unknown whether GV has the same meaning in the general population.

Finally, this was an observational study, and our findings should be interpreted accordingly. To minimize the possible effects of reverse causality, we excluded subjects with hepatocellular carcinoma that were diagnosed within 1 year after the index date.

In conclusion, GV was an independent predictor for developing hepatocellular carcinoma and exhibited a strong dose–response relationship in patients with diabetes. A greater understanding of the underlying pathophysiology might help in the future development of prevention and treatment strategies for patients with both diabetes and hepatocellular carcinoma.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

J.-J. Yoo: Conceptualization, writing–original draft. **E.J. Cho:** Writing–review and editing. **K. Han:** Formal analysis, visualization, methodology. **S.S. Heo:** Formal analysis. **B.-Y. Kim:** Validation, investigation, methodology. **D.W. Shin:** Conceptualization, investigation, writing–review and editing. **S.J. Yu:** Conceptualization, investigation, writing–original draft, writing–review and editing.

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