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Visit-to-visit changes in fasting blood sugar and the risk for cardiovascular disease and mortality in the Korean population: a nationwide population-based cohort study

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Abstract. – OBJECTIVE: The importance of continuous monitoring of fasting blood sugar (FBS) levels of diabetic patients has been established.

MATERIALS AND METHODS: An observational prospective study was conducted. Our analysis included 1,700,796 individuals from the nationwide South Korean National Health Insurance System cohort. FBS variability was measured by standard deviation (SD).

RESULTS: Kaplan-Meier curves demonstrated elevated disease probability in the higher FBS fluctuation group compared with the lower FBS fluctuation group. After adjusting for confounding variables, Cox proportional hazards analysis showed that the hazard ratios of 411 individuals in the highest quartile of SD variation of FBS were 1.77 (95% confidence interval 1.37-2.28, $p<0.001$) compared with the lowest quartile of SD variation of FBS. The impact of FBS fluctuation on the risk of cardiovascular diseases (CVDs), cerebrovascular diseases, CVD mortality and all-cause mortality in the highest quartiles of diabetic and non-diabetic individuals was statistically significant.

CONCLUSIONS: Visit-to-visit FBS variability has prognostic value for predicting micro- and macrovascular disease, cardiovascular mortality, and all-cause mortality.

Key Words:
Diabetes mellitus, Glucose variability, Visit-to-visit.

Introduction

Diabetic patients are at high risk of developing vascular complications, including cardiovascular diseases (CVDs), cerebrovascular diseases (CeVDs) and mortality[1]. The ultimate goal of managing a diabetic patient's blood glucose level is to lower micro and macro vascular complications[2]. To achieve this goal, numerous recommendations set certain ranges of blood glucose by managing spot fasting blood sugar (FBS), and glycated hemoglobin (HbA1c)[3]. The *Standards of Medical Care in Diabetes*, by the American Diabetes Association (ADA), recommends maintaining an HbA1c level below 7.0%; and the *Treatment Guideline for Diabetes*, by the Korean Diabetes Association (KDA), recommends maintaining an HbA1c level below 6.5%[2,4]. However, current diabetes management studies suggest that using not only spot blood sugar level testing but also a continuous glucose monitoring system (CGMS) can help predict the risk for CVD and CeVD with more accuracy[5-9]. CGMS can calculate daily glucose variability, which is short-term glycemic variability.

Glycemic variability can be used as a marker for uncontrolled glucose levels both short-term and long-term[10,11]. Some studies[10,12] have proposed

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that visit-to-visit glycemic variability, which is long-term glycemic variability, can also accurately detect the risk for newly diagnosed diabetes and CVD. With this proposed method, predicting CVD and CeVD risk in diabetic patients with less invasive and easy to measure through health screening test[10,13-15].

The importance of long-term visit-to-visit glycemic variability as a marker for the following complications remains controversial. In addition, there are studies reporting that fluctuating glycemic variability can be a risk factor for CVD and CeVD not only in diabetic but also in non-diabetic populations[16]. For the non-diabetic population, it may also pose a risk for developing diabetes[12].

Therefore, we aimed to investigate the prognostic value of long-term visit-to-visit glycemic variability for CVD, CeVD and all-cause mortality for 1.7 million individuals from the National Health Insurance Service (NHIS)–National Health Screening Cohort (HEALS).

Materials and Methods

Data Source and Study Population

We conducted a prospective cohort study using data collected from January 1, 2009 to December 31, 2011 using the NHIS-HEALS cohort database. The cohort profile of NHIS-HEALS has been described previously[17]. The NHIS is a social health insurance program operated by the South Korean government, covering 98% of all South Koreans. The South Korean National Health Examination is required and is performed annually or bi-annually; and the omission rate of this database throughout the follow-up period was low, as shown. The NHIS-HEALS database includes 10% of all participants who were over 40 years old and who had undergone the required national health examination provided by the South Korean government, according to NHIS protocol. The database is structured as a set of columns containing health data, including health examination values (answers to lifestyle questionnaires and results from laboratory measurements), baseline statistics (age, sex, socioeconomic variables taken from insurance fee information), and medical treatment data (past diagnosis, medication, admission to hospital, and mortality).

We evaluated the NHIS data of 8,992,940 Korean men and women who were older than 40 years and participated in health examinations from 2009 to 2011[18]. Individuals who underwent fewer than three health examinations throughout the period were excluded for evaluation of variability. Following individuals diagnosed with CVD were excluded. Individuals who did have missing health examination data were also excluded. After applying more exclusion criteria, 1,700,796 individuals were finally included in our study. Detailed inclusion and exclusion criteria were shown Figure 1. Blood samples were collected after complete overnight fasting, and quality control procedures were followed in accordance with the Korean Association of Laboratory Quality Control.

This study was approved by the Institutional Review Board, Yonsei University Wonju College of Medicine, Wonju Korea (Institutional Review Board Number: CR319320), in compliance with the 18th World Medical Assembly, Helsinki, Finland. NHIS's Institutional Review Board (NHIS-2019-1-448),

Definitions of Diseases

Diabetic patients were selected based on FBS levels of 126 mg/dL. Also, we included participants diagnosed with diabetes International Classification of Disease Tenth Revision (ICD-10) codes (E10-E14901) and prescribed with antidiabetic medication. Participants with CVD were defined as those diagnosed more than once with certain ICD-10 codes (I21-I23). Codes starting with I21 cover ST elevation and non-ST elevation myocardial infarction (MI), I22 cover subsequent ST elevation and non-ST elevation MI and I23 cover certain current complications following ST elevation and non-ST elevation MI. The presence of stroke was defined as those diagnosed with an I63 or I64 ICD-10 code at admission, with a history of brain computed tomography (CT) throughout admission. The definition of mortality number for all-cause mortality was taken from the NHIS-HEALS database and CVD mortality from the Statistics Korea Database.

Statistical Analysis

Baseline characteristics were expressed as means for continuous variables (with SD) or as numbers (with percentages) for categorical variables. Baseline for continuous variables, including laboratory measurements was made from mean values of multiple measurements. Differences in the distribution of baseline characteristics between the SD quartiles and FBS variability

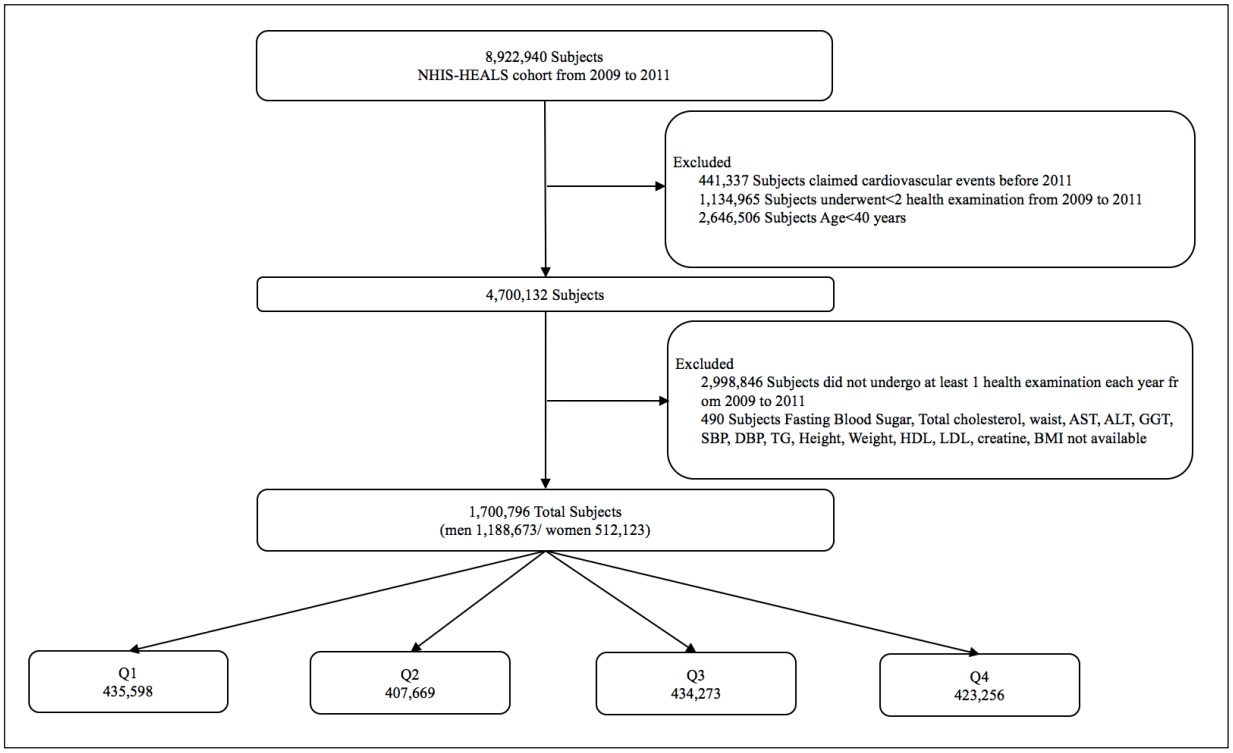

Figure 1. Flow chart showing the process for selection of members of the study cohort.

quartiles were examined using ANOVA or test each, appropriately. Participants had at least one annual examination during the observation period. Long-term visit-to-visit glycemic variability was estimated for FBS yearly and the standard deviation (SD) of all three measurements for each individual was calculated. Using the SD, each diabetic and non-diabetic patient was categorized by quartile from the 1st as least changed to the 4th as most changed. The first quartile had boundaries of standard deviation 4.51, second quartile 4.51 and 7.37, third quartile 7.37 and 11.79, and fourth quartile 11.79. Quartiles were divided such that each one had an even number of individuals.

The probability of CVD and CeVD for each quartile was calculated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence interval (CI) for CVD and CeVD were analyzed by quartiles using the Cox-hazard-regression model after adjusting for age, sex, waist circumference, alcohol consumption, smoking, regular exercise, dyslipidemia medication history, hypertension medication history, LDL and systolic blood pressure. All statistical results were analyzed using SAS version 9.4 and p-values <0.05 were considered statistically significant.

Results

Baseline Characteristics

Table I lists the baseline characteristics of the study participants grouped by fasting FBS variability defined with SDs. Subjects in groups of higher FBS variability were older, male, current smokers, higher prevalence of hypertension, higher body mass index, larger waist circumference, and higher proportion of use of drugs (antihypertensive, antidiabetic drugs, statins and aspirin). Higher FBS variability with women had higher LDL cholesterol levels.

Incidence of CVD, CeVD, All-Cause Mortality, and CV Mortality in Total Patients

During follow-up periods, 14,122 individuals developed CVD, 15,136 individuals developed CeVD and 23,069 individuals died. Compared to participants of the lowest groups the HRs (95% CIs) for CVD in the highest groups of variability of FBS was 1.32 (1.25-1.40), respectively. The adjusted HRs (95% CIs) for CeVD in the highest groups of variability of FBS was_1.43

Table I. Baseline characteristics of participants according to quartiles of standard deviations of glucose variability.

Characteristics	Standard deviations of glucose variability[a]				*p*-value
	Q1	Q2	Q3	Q4	
N (%)	435.598 (25.61)	407.669 (23.97)	434.273 (25.53)	423.256 (24.89)	
Male sex N (%)[e]	286.941 (65.87)	273.281 (67.04)	301.333 (69.39)	327.118 (77.29)	<.0001
Age (years)e	48.62 ± 6.55	48.81 ± 6.65	49.12 ± 6.79	50.17 ± 7.04	<.0001
Waist circumference (cm)					
Total[e]	80.51 ± 7.57	80.75 ± 7.61	81.21 ± 7.61	82.95 ± 7.68	<.0001
Male[e]	83.21 ± 6.44	83.34 ± 6.52	83.57 ± 6.61	84.58 ± 6.92	<.0001
Female[e]	75.29 ± 6.83	75.49 ± 6.91	75.86 ± 7.00	77.39 ± 7.50	<.0001
BMI (kg/m^2)[e]	23.75 ± 2.72	23.80 ± 2.75	23.89 ± 2.79	24.25 ± 3.30	<.0001
BMI ≥ 25 N (%)[e]	133.124 (30.56)	128.004 (31.40)	142.683 (32.86)	160.598 (37.94)	< 0.0001
SBP (mmHg)[e]	122.12 ± 11.33	122.61 ± 11.37	123.43 ± 11.42	125.79 ± 11.56	<.0001
DBP (mmHg)[e]	76.96 ± 7.76	77.25 ± 7.72	77.73 ± 7.69	78.95 ± 7.58	<.0001
Total cholesterol (mg/dL)	198.12 ± 30.19	198.33 ± 30.40	198.61 ± 30.64	198.57 ± 31.96	< 0.0001
Triglyceride (mg/dL)[e]	133.75 ± 81.93	137.07 ± 85.13	143.02 ± 90.40	166.26 ± 108.86	<.0001
LDL cholesterol (mg/dL)					
Total	117.46 ± 27.45	117.04 ± 27.68	116.28 ± 28.05	113.44 ± 29.35	<.0001
Male	117.26 ± 27.77	116.50 ± 27.97	115.38 ±28.33	111.96 ± 29.57	<.0001
Female[e]	117.85 ± 26.81	118.13 ± 27.06	118.33 ± 27.27	118.49 ± 28.00	<.0001
HDL cholesterol (mg/dL)					
Total	55.19 ± 18.60	55.23 ± 18.51	55.21 ± 18.45	54.12 ± 21.71	<.0001
Male	52.65 ± 18.02	52.88 ± 18.16	53.15 ± 18.11	52.71 ± 21.55	<.0001
Female	60.10 ± 18.73	60.03 ± 18.31	59.89 ± 18.37	58.92 ± 21.58	<.0001
ALT (IU/L)[e]	24.51 ± 15.15	25.00 ± 16.71	25.76 ± 16.51	31.85 ± 21.74	<.0001
AST (IU/L)[e]	25.02 ± 11.14	25.42 ± 12.82	26.03 ± 12.46	28.04 ± 17.20	<.0001
GGT (IU/L)[e]	36.35 ± 38.84	38.06 ± 41.52	40.94 ± 46.41	51.23 ± 60.64	<.0001
Fasting Blood Sugar (mg/dL)[e]	93.34 ± 9.99	94.05 ± 10.85	95.69 ± 12.65	113.07 ± 32.69	<.0001
Estimated GFR (mL/min/1.73 m^2)[e]	84.63 ± 19.59	84.76 ± 19.38	85.13 ± 18.83	85.78 ± 18.85	<.0001
Smoking status N (%)[b]					<.0001
Never	230.264 (53.28)	210.405 (52.01)	214.080 (49.55)	179.087 (42.54)	
Ex-smoker	93.664 (21.67)	86.769 (21.45)	92.473 (21.44)	92.211 (21.91)	
Current smoker[e]	108.270 (25.05)	107.372 (26.54)	124.659 (28.91)	149.648 (35.55)	
Moderate physical exercise N (%)[c]	115.186 (26.73)	107.238 (26.57)	113.758 (26.44)	112.012 (26.68)	0.0105
Heavy drinker N (%)[d,e]	33.248 (11.73)	33.785 (12.65)	40.448 (14.05)	50.083 (17.27)	<.0001
Insurance payment					<.0001
Upper 20% N (%)	161.314 (37.78)	141.312 (35.46)	136.471 (32.24)	116.570 (28.15)	
Lower 20% N (%)[e]	82.384 (19.30)	79.535 (19.96)	86.640 (20.47)	91.763 (22.16)	
Past history					
Diabetes mellitus N (%)	12.502 (4.22)	9.980 (3.63)	11.025 (3.84)	46.498 (16.27)	<.0001
Hypertension N (%)[e]	49.099 (16.54)	45.764 (16.65)	51.277 (17.83)	66.099 (23.11)	<.0001
Dyslipidemia N (%)	21.361 (7.20)	17.366 (6.32)	15.937 (5.54)	16.729 (5.85)	<.0001
Medication history					
Antihypertensive drug use N (%)[e]	107.202 (24.61)	105.342 (25.84)	121.564 (27.99)	152.727 (36.08)	<.0001
Antidiabetic drug use N (%)[e]	6.500 (1.49)	8.458 (2.07)	15.552 (3.58)	86.305 (20.39)	<.0001
Statin use N (%)[e]	54.899 (12.60)	53.840 (13.21)	62.766 (14.45)	90.737 (21.44)	<.0001
Aspirin use N (%)[e]	39.037 (8.96)	39.042 (9.58)	46.839 (10.79)	72.579 (17.15)	<.0001

All values are presented as number (%) or means ± SDs. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; N, number; SBP, systolic blood pressure. [a]Standard deviations of glucose variability: Q1 (SDs of glucose variability <4.51), Q2 (4.51≤ SDs of glucose variability <7.37), Q3 (7.37≤ SDs of glucose variability <11.79), Q4 (SDs of glucose variability ≥11.79). [b]Missing data were excluded from the health examination analysis. [c]Moderate physical exercise is defined as moderate or heavier regular physical exercise performed three or more days per week. [d]Heavy drinker was defined as consuming seven or more drinks on the same occasion more than three days per week. [e]Parameters that were higher among individuals with higher standard deviations of glucose variability.

(1.36-1.52), respectively. The adjusted HRs (95% CIs) for CVD mortality in the highest groups of variability of FBS was 1.77 (1.37-2.28), respectively. The adjusted HRs (95% CIs) for all-cause mortality in the highest groups of variability of FBS was 1.52 (1.45-1.59), respectively. While

very similar HR values were observed in the men, different patterns of HR values were observed in the women group with regard to CeVD and CVD mortality (Table II). There were clear associations of FBS variability with increased risk for CVD, CeVD, and all-cause mortality (**Supplementary Figures 1, 2, 3**).

Incidence of CVD, CeVD, All-Cause Mortality, and CV Mortality in Diabetic Patients

During follow-up periods, 2,677 individuals developed CVD, 3,028 individuals developed CeVD and 4,778 individuals died. Compared to participants of the lowest groups the HRs (95% CIs) for CVD in the highest groups of variability of FBS was 1.34 (1.08-1.68), respectively. The adjusted HRs (95% CIs) for CeVD in the highest groups of variability of FBS was 3.22 (0.79-13.05), respectively. The adjusted HRs (95% CIs) for CVD mortality in the highest groups of variability of FBS was 1.77 (1.37-2.28), respectively. The adjusted HRs (95% CIs) for all-cause mortality in the highest groups of variability of FBS was 1.29 (1.08-1.53), respectively. Similar patterns of HR values were observed in men with diabetes except with regard to CVD. In female with diabetes, similar patterns of HR values were observed except cardiovascular mortality. Because the number of CV mortality is zero in lowest diabetic women (Table III).

Incidence of CVD, CeVD, All-Cause Mortality, and CV Mortality in Patients without Diabetes

During follow-up periods, 11,445 individuals developed CVD, 12,108 individuals developed CeVD and 18,291 individuals died. Compared with participants of the lowest groups the HRs (95% CIs) for CVD in the highest groups of variability of FBS was 1.14 (1.07–1.22), respectively. The adjusted HRs (95% CIs) for CeVD in the highest groups of variability of FBS was 1.21 (1.14–1.29), respectively. The adjusted HRs (95% CIs) for CVD mortality in the highest groups of variability of FBS was 1.44 (1.09–1.92), respectively. The adjusted HRs (95% CIs) for all-cause mortality in the highest groups of variability of FBS was 1.33 (1.26–1.39), respectively. While very similar HR values were observed in the male group, different patterns of HR values were observed in the female group with regard to CVD and CeVD (Table IV).

Discussion

The effects of visit-to-visit FBS variability on CVD, CeVD, CVD mortality and all-cause mortality in diabetic and non-diabetic individuals shown that visit-to-visit FBS variability adds to the statistical relevance of the following macro- and microvascular diseases. This outcome was present in the overall NHIS-HEALS cohort database including diabetes mellitus (DM) patients and their non-DM counterparts. The effect of visit-to-visit glycemic variability was most pronounced for CVD mortality for all participants.

Several large randomized controlled studies and cohort studies[19-22] showed that glycemic variability was important parameters that was associated with cardiovascular complications and mortality in diabetic patients. However, there are only a few cohort studies that examined the prognostic significance of long-term glycemic variability that including non-diabetes. For general population, large cohort studies showed that long term glycemic variability was associated with development of type 2 diabetes, cardiovascular disease, and all-cause mortality[12,23,24].

However, most of cohort studies and meta-analysis did not consider gender differences[8,9,12-15,23-26]. One large cohort study[27] showed that gender difference (along with glucose variability) was one of the risk factors of cardiovascular disease in general population. Through our results, long term glycemic variability are more associated cardiovascular, cerebrovascular, cardiovascular mortality and all-cause mortality, especially men. Although the exact mechanism is not known, genetic difference and social behavioral disparities might be cause of difference[28].

Glycemic variability generating more reactive oxygen species (ROS) in complication-prone cells, because the overproduction of ROS by the mitochondrial electron-transport chain results in hyperglycemia-induced oxidative stress, which is the chief underlying mechanism of glucose-mediated vascular damage[29]. Furthermore, hyperglycemia induces an overproduction of superoxide by the mitochondrial electron-transport chain[30]. Superoxide overproduction is accompanied by increased nitric oxide (NO) generation due to endothelial NO synthase (eNOS) and inducible NO synthase (iNOS), a phenomenon that favors the formation of the strong oxidant peroxynitrite, which in turn damages DNA. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly [adenosine diphosphate (ADP)

Table II. Multivariate-adjusted HR (95% CI) of cardiovascular disease, cerebrovascular disease, cardiovascular mortality, and all cause mortality according to quartiles of standard deviations of glucose variability.

	Total subjects			Men			Women		
	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]
Cardiovascular disease									
Q1	2.853	2.768,200.75	1 (REF)	2.210	1.819,786.89	1 (REF)	643	948.413.86	1 (REF)
Q2	2.875	2.587,338.54	1.03 (0.96-1.10)	2.313	1.730,195.20	1.04 (0.97-1.12)	562	857.143.34	0.92 (0.77-1.10)
Q3	3.394	2.751,774.15	**1.07 (1.00-1.13)**	2.697	1.904,190.92	1.06 (1.00-1.14)	697	847.583.23	1.10 (0.92-1.30)
Q4	5.000	2.664,863.81	**1.32 (1.25-1.40)**	4.333	2.052,838.05	**1.34 (1.26-1.43)**	667	612.025.76	1.14 (0.95-1.37)
p for trend			<.0001			<.0001			<.0001
Cerebrovascular disease									
Q1	2.993	2.767,095.98	1 (REF)	2.184	1.819,248.03	1 (REF)	809	947.847.95	1 (REF)
Q2	3.052	2.586,168.63	1.05 (0.99-1.12)	2.311	1.729,711.30	1.07 (1.00-1.14)	741	856.457.32	1.00 (0.86-1.18)
Q3	3.548	2.750,633.78	**1.07 (1.01-1.13)**	2.770	1.903,622.89	**1.08 (1.02-1.16)**	778	847.010.90	0.98 (0.84-1.15)
Q4	5.543	2.662,755.05	**1.43 (1.36-1.52)**	4.730	2.051,127.10	**1.47 (1.39-1.56)**	813	611.627.95	1.16 (0.99-1.37)
p for trend			<.0001			<.0001			<.0001
Cardiovascular disease mortality									
Q1	141	2.776,640.87	1	136	1.826,360.48	1	5	950.280.39	1
Q2	168	2.595,839.46	1.05 (0.78-1.41)	162	1.737,040.35	1.02 (0.75-1.38)	6	858.799.10	3.14 (0.33-1.39)
Q3	242	2.761,938.17	**1.47 (1.13-1.93)**	216	1.912,378.29	**1.37 (1.04-1.80)**	26	849.559.88	**11.137 (1.44-86.35)**
Q4	411	2.679,994.93	**1.77 (1.37-2.28)**	386	2.065,908.63	**1.70 (1.32-2.20)**	25	614.086.30	7.01 (0.84-58.59)
p for trend			<.0001			<.0001			<.0001
All-cause mortality									
Q1	4.253	2.776,640.87	1	3.535	1.826,360.48	1	718	950.280.39	1
Q2	4.501	2.595,839.46	**1.08 (1.03-1.14)**	3.769	1.737,040.35	**1.08 (1.02-1.13)**	732	858.799.10	1.11 (0.94-1.32)
Q3	5.462	2.761,938.17	**1.13 (1.08-1.19)**	4.693	1.912,378.29	**1.13 (1.07-1.18)**	769	849.559.88	**1.22 (1.03-1.44)**
Q4	8.853	2.679,994.93	**1.52 (1.45-1.59)**	8.055	2.065,908.63	**1.51 (1.44-1.58)**	788	614.086.30	**1.54 (1.30-1.82)**
p for trend			<.0001			<.0001			<.0001

CI: Confidence interval, HR: hazard ratio, No.: number of events. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus smoking, alcohol drinking, and regular physical activity.Model 3 was adjusted for the variables in model 2 plus waist circumference and medication history for hypertension or dyslipidemia.Model 4 was adjusted for the variables in model 3 plus low density lipoprotein cholesterol and systolic blood pressure. [a]Adjusted by model 4 with 95% CI.

Table III. Multivariate-adjusted HR (95% CI) of cardiovascular disease, cerebrovascular disease, cardiovascular disease mortality, and all cause mortality according to quartiles of standard deviations of glucose variability in subjects with diabetes.

	Total subjects with dabetes			Men with diabetes			Women with diabetes		
	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]
Cardiovascular disease									
Q1	105	48.761.37	1 (REF)	91	38.694.18	1 (REF)	14	10.067.19	1 (REF)
Q2	151	65.663.44	0.96 (0.71-1.31)	135	52.508.84	1.00 (0.73-1.38)	16	13.154.60	0.48 (0.14-1.69)
Q3	275	122.996.96	0.98 (0.75-1.29)	226	99.227.36	0.99 (0.74-1.31)	49	23.769.59	0.91 (0.35-2.41)
Q4	2.146	716.173.95	**1.28 (1.01-1.63)**	1912	596.443.65	**1.28 (1.00-1.64)**	234	119.730.30	1.26 (0.55-2.88)
p for trend			<.0001			<.0001			<.0001
Cerebrovascular disease									
Q1	119	51.291.03	1 (REF)	94	40.294.93	1 (REF)	25	10.996.10	1 (REF)
Q2	164	68.043.50	0.91 (0.68-1.22)	138	54.019.32	0.94 (0.70-1.28)	26	14.024.18	0.62 (0.22-1.71)
Q3	289	125.783.18	0.92 (0.71-1.19)	246	100.935.18	0.96 (0.73-1.25)	43	24.848.00	0.52 (0.21-1.32)
Q4	2.456	717.493.62	**1.34 (1.08-1.68)**	2.141	597.403.30	**1.36 (1.08-1.72)**	315	120.090.31	1.15 (0.56-2.35)
p for trend			<.0001			<.0001			<.0001
Cardiovascular disease mortality									
Q1	5	49.090.63	1	5	38.956.29	1	0	10.134.33	N/A
Q2	11	66.134.28	1.46 (0.27-7.97)	10	52.930.18	1.09 (0.18-6.54)	1	13.204.10	-
Q3	19	123.886.19	1.71 (0.37-7.92)	16	99.961.36	1.32 (0.27-6.35)	3	23.924.83	-
Q4	196	722.813.88	3.22 (0.79-13.05)	188	602.359.03	3.13 (0.77-12.69)	8	120.454.85	-
p for trend			<.0001			<.0001			-
All cause mortality									
Q1	177	49.090.63	1	161	38.956.29	1	16	10.134.33	1
Q2	265	66.134.28	1.00 (0.80-1.25)	241	52.930.18	0.99 (0.79-1.25)	24	13.204.10	1.17 (0.42-3.21)
Q3	548	123.886.19	1.09 (0.90-1.33)	498	99.961.36	1.09 (0.89-1.34)	50	23.924.83	1.20 (0.47-3.04)
Q4	3.788	722.813.88	**1.29 (1.08-1.53)**	3.517	602.359.03	**1.28 (1.07-1.53)**	271	120.454.85	1.39 (0.61-3.17)
p for trend			<.0001			<.0001			<.0001

CI, confidence interval; HR, hazard ratio; No., number of events. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus smoking, alcohol drinking, and regular physical activity. Model 3 was adjusted for the variables in model 2 plus waist circumference and medication history for hypertension or dyslipidemia. Model 4 was adjusted for the variables in model 3 plus low density lipoprotein cholesterol and systolic blood pressure. [a]Adjusted by model 4 with 95% CI.

Table IV. Multivariate-adjusted HR (95% CI) of cardiovascular disease, cerebrovascular disease, cardiovascular disease mortality, and all cause mortality according to quartiles of standard deviations of glucose variability in subjects without diabetes.

	Total subjects with dabetes			Men with diabetes			Women with diabetes		
	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]	No.	Person years	Adjusted HR[a]
Cardiovascular disease									
Q1	2.748	2.719,439.38	1 (REF)	2.119	1.781,092.72	1 (REF)	629	938.346.67	1 (REF)
Q2	2.724	2.521,675.10	1.03 (0.96-1.10)	2.178	1.677,686.36	1.04 (0.97-1.12)	546	843.988.74	0.94 (0.78-1.12)
Q3	3.119	2.628,777.19	1.06 (0.99-1.13)	2.471	1.804,963.55	1.06 (0.99-1.13)	648	823.813.64	1.10 (0.92-1.31)
Q4	2.854	1.948,689.86	**1.14 (1.07-1.22**)	2.421	1.456,394.40	**1.16 (1.09-1.25)**	433	492.295.47	0.98 (0.80-1.20)
p for trend			<.0001			<.0001			<.0001
Cerebrovascular disease									
Q1	2.874	2.718,384.92	1 (REF)	2.090	1.780,610.25	1 (REF)	784	937.774.67	1 (REF)
Q2	2.888	2.520,614.58	1.06 (0.99-1.13)	2.173	1.677,261.29	1.07 (0.99-1.14)	715	843.353.29	1.01 (0.86-1.19)
Q3	3.259	2.627,646.30	1.06 (1.00-1.13)	2.524	1.804,412.58	**1.08 (1.01-1.15)**	735	823.233.72	1.00 (0.85-1.17)
Q4	3.087	1.947,633.32	**1.21 (1.14-1.29)**	2.589	1.455,502.15	**1.25 (1.17-1.34)**	498	492.131.17	0.98 (0.82-1.18)
p for trend			<.0001			<.0001			<.0001
Cardiovascular disease mortality									
Q1	136	2.727,550.24	1	131	1.787,404.19	1	5	940.146.05	1
Q2	157	2.529,705.17	1.04 (0.76-1.40)	152	1.684,110.17	1.02 (0.75-1.39)	5	845.595.01	2.07 (0.19-22.89)
Q3	223	2.638,051.98	**1.48 (1.13-1.95**)	200	1.812,416.93	**1.39 (1.05-1.84)**	23	825.635.05	**9.60 (1.22-75.84)**
Q4	215	1.957,181.04	**1.44 (1.09-1.92)**	198	1.463,549.60	**1.37 (1.03-1.83)**	17	493.631.44	8.01 (0.93-68.74)
p for trend			<.0001			<.0001			<.0001
All cause mortality									
Q1	4.076	2.727,550.24	1	3.374	1.787,404.19	1	702	940.146.05	1
Q2	4.236	2.529,705.17	**1.08 (1.02-1.14)**	3.528	1.684,110.17	**1.07 (1.02-1.13)**	708	845.595.01	1.11 (0.93-1.32)
Q3	4.914	2.638,051.98	**1.11 (1.06-1.17**)	4,195	1.812,416.93	**1.10 (1.05-1.16)**	719	825.635.05	**1.21 (1.02-1.44)**
Q4	5.065	1.957,181.04	**1.33 (1.26-1.39**)	4.548	1.463,549.60	**1.31 (1.25-1.39)**	517	493.631.44	**1.42 (1.18-1.71**)
p for trend			<.0001			<.0001			<.0001

CI, confidence interval; HR, hazard ratio; No., number of events. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus smoking, alcohol drinking, and regular physical activity. Model 3 was adjusted for the variables in model 2 plus waist circumference and medication history for hypertension or dyslipidemia. Model 4 was adjusted for the variables in model 3 plus low density lipoprotein cholesterol and systolic blood pressure. [a]Adjusted by model 4 with 95% CI.

ribose] polymerase that, in turn, depletes the intracellular concentration of its substrate nicotinamide adenine dinucleotide, slowing the rate of glycolysis, electron transport and adenosine triphosphate formation, and produces an ADP ribosylation of the glyceraldehyde-3-phosphate dehydrogenase. These processes result in acute endothelial dysfunction in blood vessels that, convincingly, contributes to the development of diabetes and CVD[12,31]. In addition, increased glucose variability more aggravates ROS production and eventually has more serious deleterious effects on endothelial function[32].

This study has several limitations. First, this study included only Korean men and women that our results confirmed in independent populations. Second, our study used the NHIS database that does not include HbA1c, oral glucose tolerance test, and other confounding variables. Third, this study was observational study that limits potential unrecognized confounding variables. Fourth, we did not compared coefficient of variation, variability independent of the mean, and other parameter with standard deviation that represents glucose variability. Fifth in this study, there were fewer female than male participants. Individuals who undergo yearly health examinations are non-office workers. The lack of female subjects was due to the difference in the number of each gender in non-office jobs.

Conclusions

This large number cohort study shows that long term visit-to-visit glucose variability are associated with cardiovascular disease, cerebrovascular disease, cardiovascular mortality, and all-cause mortality in general population. This association are more predominant in men without diabetes. We recommend monitoring long-term glucose variability in addition to routine glucose monitoring parameters.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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