Cumulative Exposure to High γ-Glutamyl Transferase Level and Risk of Diabetes: A Nationwide Population-Based Study

Ji-Yeon Park[1], Kyungdo Han[2], Hun-Sung Kim[1,3], Jae-Hyoung Cho[1,3], Kun-Ho Yoon[1,3], Mee Kyoung Kim[4], Seung-Hwan Lee[1,3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea; [2]Department of Statistics and Actuarial Science, Soongsil University; [3]Department of Medical Informatics, College of Medicine, The Catholic University of Korea; [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Elevated γ-glutamyl transferase (γ-GTP) level is associated with metabolic syndrome, impaired glucose tolerance, and insulin resistance, which are risk factors for type 2 diabetes. We aimed to investigate the association of cumulative exposure to high γ-GTP level with risk of diabetes.

Methods: Using nationally representative data from the Korean National Health Insurance system, 346,206 people who were free of diabetes and who underwent 5 consecutive health examinations from 2005 to 2009 were followed to the end of 2018. High γ-GTP level was defined as those in the highest quartile, and the number of exposures to high γ-GTP level ranged from 0 to 5. Hazard ratio (HR) and 95% confidence interval (CI) for diabetes were analyzed using the multivariable Cox proportional-hazards model.

Results: The mean follow-up duration was 9.2 ± 1.0 years, during which 15,183 (4.4%) patients developed diabetes. There was a linear increase in the incidence rate and the risk of diabetes with cumulative exposure to high γ-GTP level. After adjusting for possible confounders, the HR of diabetes in subjects with five consecutive high γ-GTP levels were 2.60 (95% CI, 2.47 to 2.73) in men and 3.05 (95% CI, 2.73 to 3.41) in women compared with those who never had a high γ-GTP level. Similar results were observed in various subgroup and sensitivity analyses.

Conclusion: There was a linear relationship between cumulative exposure to high γ-GTP level and risk of diabetes. Monitoring and lowering γ-GTP level should be considered for prevention of diabetes in the general population.

Keywords: Diabetes mellitus; Gamma-glutamyltransferase; Risk

INTRODUCTION

According to the Diabetes Atlas published by the International Diabetes Federation, approximately 463 million adults (20 to 79 years) had diabetes globally in 2019, and this number is expected to increase to 700 million by 2045 [1]. The prevalence of people with type 2 diabetes is increasing in most countries, causing major socioeconomic and health-related problems. In Korea, it is estimated that 4.94 million people older than 30 years have diabetes, which means that one in seven adults (13.8%) has diabetes [2].

Elevation in serum γ-glutamyl transferase (γ-GTP) is considered a surrogate marker of liver dysfunction or alcohol consumption. In addition, high γ-GTP level is regarded as an indicator of metabolic syndrome and is associated with fatty liver, obesity, insulin resistance, and type 2 diabetes [3,4]. A recent study also reported that high γ-GTP level is associated with hypertension, increased cardiovascular disease risk, and mortality [5,6]. Previous prospective studies have shown that elevated γ-GTP level is associated with metabolic syndrome (central obesity, increased fasting glucose, triglycerides, and blood pressure) and insulin resistance and has a role as a predictive marker of type 2 diabetes [7-9]. Epidemiological retrospective cohort studies also demonstrated that high γ-GTP activity is a strong predictor of diabetes [10]. However, another study showed a non-linear relationship between increase in γ-GTP level and incidence of type 2 diabetes [11], and some studies did not clarify the causal relationship between γ-GTP and type 2 diabetes [12,13], leaving controversy regarding this association.

In this study, we aimed to clarify the association between cumulative exposure to high γ-GTP level and risk of type 2 diabetes using data from a large-scale, nationwide, population-based database with consecutive health examinations for 5 years and long-term follow-up.

METHODS

Data source and study subjects

The Korean National Health Insurance Service (NHIS) is a single health insurance system managed by the government. Because the NHIS provides comprehensive medical coverage to most of the Korean population (97%, approximately 50 million people), this is a representative nationwide database. The NHIS database includes an eligibility database for all demographic data (age, sex, socioeconomic variables, type of eligibility), a medical treatment database (diagnoses encoded by the International Classification of Disease, Tenth Revision of Clinical Modification [ICD-10], treatment, and prescription at inpatient and outpatient services), a health examinations database (anthropometric measurements, regular blood tests, and self-reported questionnaires on lifestyle factors and medical history), a medical care institution database (types of medical care institutions, location, equipment, and number of physicians), and death information [14]. All NHIS enrollees are encouraged to undergo annual or biannual health examinations. Hospitals performing health examinations were certified by the NHIS, and quality control of the laboratory tests was conducted in accordance with the procedures of the Korean Association of Laboratory Quality Control.

Of 4,234,341 people aged ≥20 years who underwent health examination in 2009 (index year), 643,054 who underwent five consecutive annual health examinations from 2005 to 2009 were selected. We excluded people with a fasting glucose level ≥126 mg/dL (*n*=33,263), heavy alcohol drinker (*n*=55,959 with an average daily alcohol intake ≥30 g), at least one claim for liver disease (ICD-10 codes K70-K77) or biliary tract disease (ICD-10 codes K80–K87) (*n*=184,036), known diabetes (at least one claim for ICD-10 codes E10-14 and a prescription of anti-diabetic medication) (*n*=3,226), and missing data (*n*=20,364). Finally, 346,206 subjects were included in this analysis. This study was approved by the Institutional Review Board of The Catholic University of Korea (KC21ZASI0933). Anonymous and deidentified information was used for analysis, and informed consent was waived.

Measurements and definitions

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI ≥25 kg/m² following the guidelines of the Korean Society for the Study of Obesity [15]. Information on smoking and alcohol consumption was obtained by questionnaire. Regular exercise was defined as performing more than 20 minutes of strenuous activity ≥3 times/week or more than 30 minutes of moderate physical activity ≥5 times/week. Household income was dichotomized at the lower 25%. Blood samples for measurement of fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-GTP levels were collected after an overnight fasting. The cutoff values of γ-GTP quartiles were defined in a sex- and health examination year-specific manner (Supplemental Table S1). High γ-GTP level was arbitrarily de-

fined as those in the highest quartile (Q4), and the number of exposures to high γ-GTP level during 5 years ranged from 0–5. The presence of hypertension was diagnosed as at least one claim per year with ICD-10 code I10 or I11 and prescription of antihypertensive agents or systolic/diastolic BP ≥140/90 mm Hg. The presence of dyslipidemia was diagnosed as at least one claim per year with ICD-10 code E78 and a prescription of lipid-lowering agent or a total cholesterol level ≥240 mg/dL. The presence of chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 according to the abbreviated Modification of Diet in Renal Disease formula.

Study outcomes and follow-up

The outcome of this study was newly diagnosed diabetes, which was defined as at least one claim for prescription of anti-diabetic medication under ICD-10 codes E10-E14 or fasting glucose level ≥126 mg/dL. This operational definition of diabetes with use of the claim and health check-up database was recommended and validated by an expert committee from the Korean Diabetes Association [16]. The study population was followed to the date of incident diabetes or until 31st December 2018, whichever came first. The mean follow-up duration was 9.19± 1.04 years.

Statistical analysis

Baseline characteristics are presented as the mean±standard deviation, median (interquartile range), or number (%). The incidence rate of newly-diagnosed diabetes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). A multivariable-adjusted Cox proportional hazards analysis was used to estimate hazard ratio (HR) and 95% confidence interval (CI) values for diabetes according to baseline γ-GTP quartile or cumulative number of exposures to high γ-GTP level. We selected all available variables that could be collected from the NHIS database and are known to be associated with the risk of developing diabetes. Proportional hazards assumption was evaluated by the Schoenfeld residuals test with the logarithm of the cumulative hazards function based on Kaplan-Meier estimates. There was no significant departure from proportionality in hazards over time. Model 1 was unadjusted: model 2 was adjusted for age, sex, BMI, income status, alcohol consumption, smoking, regular exercise, and fasting blood glucose: and model 3 was additionally adjusted for hypertension, dyslipidemia, and CKD. A sensitivity analysis was performed after excluding cases with incident diabetes in the first 2 years

of follow-up to minimize the possibility of reverse causation. We performed another sensitivity analysis after excluding subjects with impaired fasting glucose (IFG; fasting blood glucose 100 to 125 mg/dL) at baseline. The potential effect modification by age, smoking, alcohol consumption, regular exercise, obesity, hypertension, dyslipidemia, IFG, and AST and ALT levels was tested through stratified analysis and interaction testing using a likelihood ratio test. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and a *P*<0.05 indicated significance.

RESULTS

Baseline characteristics of the study population

Characteristics of participants according to cumulative number of exposures to high γ-GTP level are described in Table 1 (men) and Table 2 (women). Among 255,870 men, 151,103 (59.1%) had never been exposed to high γ-GTP, whereas 30,454 (11.9%) had persistently high γ-GTP level over 5 years. Among 90,336 women, 47,621 (52.7%) had never been exposed to high γ-GTP, whereas 8,025 (8.9%) had persistently high γ-GTP level over 5 years. Subjects with higher number of exposures to high γ-GTP level were older, more obese or abdominally obese, and more likely to be current smoker or mild alcohol drinker. Higher blood pressure; higher levels of fasting blood glucose, total cholesterol, triglycerides, AST, and ALT; and presence of hypertension or dyslipidemia were also associated with a higher number of exposures to high γ-GTP level in both men and women. *P* values for the trend were <0.001 for all parameters.

Risk of incident diabetes according to baseline γ-GTP

During follow-up, there were 15,183 (4.4%) cases of incident diabetes (12,346 men and 2,837 women). We first examined the risk of incident diabetes according to quartile groups of baseline γ-GTP. An incrementally higher incidence rate and risk of diabetes were observed with higher baseline γ-GTP level in both men and women. The incident rate of diabetes in the highest baseline γ-GTP quartile (Q4) was approximately 6- to 7-fold higher than that in the lowest quartile (Q1) (1.77 vs. 10.27 per 1,000 person-years in men, 1.12 vs. 7.71 per 1,000 person-years in women). After adjusting for age, sex, BMI, alcohol drinking, smoking, regular exercise, income status, fasting blood glucose, hypertension, dyslipidemia, and CKD, the HR of diabetes in the Q4 group was 3.14 (95% CI, 2.93 to 3.36) in men and 2.85 (95% CI, 2.47 to 3.29) in women compared to the Q1 group (Table 3). Next, we performed subgroup analyses and compared

Table 1. Baseline Characteristics of Study Subjects According to Cumulative Number of Exposures to High γ-GTP over 5 Years in Men

Characteristic	0 (*n*=151,103)	1 (*n*=26,420)	2 (*n*=16,674)	3 (*n*=14,826)	4 (*n*=16,393)	5 (*n*=30,454)
Age, yr	42.1±9.1	43.0±9.0	42.8±8.8	42.9±8.6	43.2±8.5	43.6±8.1
Height, cm	171.0±6.0	171.0±6.0	170.6±5.9	1,706±5.9	170.6±5.9	170.2±5.9
Weight, kg	67.8±9.1	70.4±9.5	71.6±9.8	72.1±9.8	72.7±10.1	73.3±10.5
BMI, kg/m²	23.2±2.6	24.2±2.7	24.6±2.8	24.7±2.8	25.0±2.9	25.3±3.0
WC, cm	80.6±7.0	83.1±6.9	84.0±6.8	84.5±6.9	85.1±6.9	85.9±7.1
Systolic BP, mm Hg	121.4±12.4	123.7±12.7	124.7±12.8	125.4±13.1	126.0±13.1	127.4±13.6
Diastolic BP, mm Hg	76.5±8.8	78.1±9.0	79.0±9.1	79.4±9.3	79.9±9.2	80.9±9.6
FBG, mg/dL	91.9±11.1	93.3±11.5	93.9±11.7	94.3±11.7	94.8±12.0	95.7±12.1
TC, mg/dL	190.4±33.7	198.5±37.2	201.1±36.4	203.1±34.4	204.8±37.1	208.8±37.9
HDL-C, mg/dL	52.8±22.9	52.0±23.7	52.1±26.6	52.0±23.8	52.2±25.1	52.7±42.9
LDL-C, mg/dL	113.5±34.2	117.0±36.8	117.2±36.7	117.3±35.7	117.6±39.4	116.7±40.2
Triglyceride, mg/dL	107 (76–152)	131 (92–188)	142 (100–202)	149 (104–213)	156 (110–224)	175 (122–253)
AST, IU/L	20 (15–26)	24 (19–34)	27 (20–36)	28 (21–39)	30 (22–41)	34 (25–48)
ALT, IU/L	22 (19–26)	24 (20–29)	25 (21–30)	25 (21–31)	26 (22–32)	28 (24–35)
γ-GTP, IU/L	22 (17–28)	35 (28–43)	42 (34–51)	48 (39–59)	55 (45–72)	79 (61–111)
Smoking						
Non-smoker	49,287 (32.62)	7,174 (27.2)	4,045 (24.3)	3,545 (23.9)	3,703 (22.6)	6,227 (20.5)
Ex-smoker	40,658 (26.9)	7,330 (27.7)	4,591 (27.5)	4,020 (27.1)	4,145 (25.3)	7,311 (24.0)
Current smoker	61,158 (40.5)	11,916 (45.1)	8,038 (48.2)	7,261 (49.0)	8,545 (52.1)	16,916 (55.6)
Drinker						
Non	55,288 (36.6)	7,704 (29.2)	4,199 (25.2)	3,430 (23.1)	3,329 (20.3)	5,025 (16.5)
Mild	95,815 (63.4)	18,716 (70.8)	12,475 (74.8)	11,396 (76.9)	13,064 (79.7)	25,429 (83.5)
Physical activity	32,340 (21.4)	5,799 (22.0)	3,580 (21.5)	3,237 (21.8)	3,494 (21.3)	6,195 (20.3)
Low income	8,300 (5.5)	1,738 (6.6)	1,092 (6.6)	961 (6.5)	1,135 (6.9)	2,088 (6.9)
Hypertension	19,470 (12.9)	4,948 (18.7)	3,370 (20.2)	3,395 (22.9)	3,954 (24.1)	8,543 (28.1)
Dyslipidemia	12,254 (8.1)	3,521 (13.3)	2,483 (14.9)	2,418 (16.3)	2,940 (17.9)	6,375 (20.9)
Chronic kidney disease	12,098 (8.0)	2,001 (7.6)	1,245 (7.5)	1,081 (7.3)	1,141 (7.0)	2,062 (6.8)

Values are expressed as mean±standard deviation, median (interquartile range), or number (%). *P* values for the trend were <0.001 for all variables.
γ-GTP, gamma-glutamyl transferase; BMI, body mass index; WC, waist circumference; BP, blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

the risk of diabetes in baseline γ-GTP Q4 group with that of the lower three quartiles (Q1–Q3) groups (Supplemental Tables S2, S3). In all subgroups, the risk of diabetes was significantly higher in Q4 group versus Q1–Q3 groups both in men and women. The HR (95% CI) of diabetes were significantly higher in men with younger age, lower BMI, and without hypertension, dyslipidemia, or IFG, but no significant differences were noted between subgroups in women.

Risk of incident diabetes according to cumulative number of exposures to high γ-GTP

The number of exposures to high γ-GTP level over 5 years of

annual health examinations was counted (range of 0 to 5). An incrementally higher incidence rate and risk of diabetes were observed with more cumulative number of exposures to high γ-GTP level in both men and women (Table 4). The incident rate of diabetes in men and women with no exposure to high γ-GTP level was 2.80 and 1.43 per 1,000 person-years, respectively. The incident rate increased steadily as the cumulative number of exposures to high γ-GTP increased and reached 12.82 per 1,000 person-years in men and 10.92 per 1,000 person-years in women with persistent high γ-GTP level over 5 years. Similarly, the HR (95% CI) of diabetes continuously increased with increasing number of exposures to high γ-GTP in a

Table 2. Baseline Characteristics of Study Subjects According to Cumulative Number of Exposures to High γ-GTP over 5 Years in Women

Characteristic	0 (n=47,621)	1 (n=15,096)	2 (n=7,944)	3 (n=5,977)	4 (n=5,673)	5 (n=8,025)
Age, yr	38.9±9.9	41.2±10.3	42.0±10.4	43.0±10.5	43.8±10.5	45.7±10.1
Height, cm	158.9±5.5	158.3±5.7	158.0±5.7	157.7±5.7	157.5±5.8	156.8±5.9
Weight, kg	54.7±7.2	55.6±7.7	56.4±8.1	57.2±8.5	57.6±8.9	58.6±9.2
BMI, kg/m²	21.7±2.7	22.2±3.0	22.6±3.1	23.0±3.3	23.3±3.4	23.8±3.5
WC, cm	71.4±7.2	72.9±7.6	73.9±8.1	74.8±8.2	75.5±8.4	77.0±8.8
Systolic BP, mm Hg	113.8±12.4	115.7±13.1	117.2±13.7	118.3±13.8	118.9±14.1	120.7±14.6
Diastolic BP, mm Hg	71.6±8.6	72.7±9.0	73.5±9.3	74.4±9.4	74.8±9.6	76.0±9.8
FBG, mg/dL	88.4±10.1	89.3±10.7	89.7±10.7	90.3±11.1	90.9±11.4	92.1±11.6
TC, mg/dL	185.5±33.0	190.7±40.0	193.1±41.9	196.3±42.6	198.9±36.8	203.7±37.1
HDL-C, mg/dL	62.2±25.9	61.6±28.9	60.6±24.3	60.8±29.4	60.6±29.3	60.4±30
LDL-C, mg/dL	107.4±33.4	111.1±34.1	112.7±35.5	115.0±35.5	116.6±35.3	119.7±39.1
Triglyceride, mg/dL	72 (54–100)	80 (59–113)	85 (62–122)	91 (65–130)	96 (68–138)	105 (74–153)
AST, IU/L	13 (11–17)	15 (12–19)	16 (12–21)	17 (13–22)	18 (14–24)	21 (16–28)
ALT, IU/L	19 (16–22)	20 (17–23)	20 (17–24)	21 (18–25)	22 (18–26)	23 (19–28)
γ-GTP, IU/L	12 (10–15)	16 (13–19)	18 (15–22)	21 (18–25)	24 (20–30)	32 (25–43)
Smoking						
Non-smoker	46,168 (97.0)	14,637 (97.0)	7,665 (96.5)	5,736 (96.0)	5,430 (95.7)	7,690 (95.8)
Ex-smoker	876 (1.8)	218 (1.4)	118 (1.5)	116 (1.9)	111 (2.0)	120 (1.5)
Current smoker	577 (1.2)	241 (1.6)	161 (2.0)	125 (2.1)	132 (2.3)	215 (2.7)
Drinker						
Non	33,644 (70.7)	10,548 (69.9)	5,437 (68.4)	3,999 (66.9)	3,721 (65.6)	5,164 (64.4)
Mild	13,977 (29.4)	4,548 (30.1)	2,507 (31.6)	1,978 (33.1)	1,952 (34.4)	2,861 (35.7)
Physical activity	5,846 (12.3)	1,945 (12.9)	1,089 (13.7)	847 (14.2)	702 (12.4)	1,081 (13.5)
Low income	9,404 (19.8)	3,792 (25.1)	2,145 (27.0)	1,740 (29.1)	1,683 (29.7)	2,500 (31.2)
Hypertension	3,080 (6.5)	1,594 (10.6)	1,065 (13.41)	960 (16.1)	1,047 (18.5)	1,806 (22.5)
Dyslipidemia	3,058 (6.4)	1,464 (9.7)	936 (11.8)	821 (13.7)	934 (16.5)	1,651 (20.6)
Chronic kidney disease	3,656 (7.7)	970 (6.4)	509 (6.4)	407 (6.8)	389 (6.9)	574 (7.2)

Values are expressed as mean±standard deviation, median (interquartile range), or number (%). P values for the trend were <0.001 for all variables.
γ-GTP, gamma-glutamyl transferase; BMI, body mass index; WC, waist circumference; BP, blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

stepwise manner. In the fully adjusted model (model 3), the HR of diabetes in the persistent exposure group was 2.60 (95% CI, 2.47 to 2.73) in men and 3.05 (95% CI, 2.73 to 3.41) in women compared to that in the no exposure group. A linear increase in incidence rate and risk of diabetes according to cumulative number of exposures to high γ-GTP level was observed in both low (Q1–Q3) and high (Q4) baseline γ-GTP groups (Supplemental Table S4).

Sensitivity analysis

To minimize the possibility of reverse causality, we performed a

sensitivity analysis excluding subjects with incident diabetes in the first 2 years of follow-up (Supplemental Table S5). The results were very similar to those of the original analysis. In the fully adjusted model, the HR of diabetes in the persistent exposure group was 2.62 (95% CI, 2.49 to 2.75) in men and 3.15 (95% CI, 2.80 to 3.54) in women compared to the no exposure group. Because elevated blood glucose level itself is the most powerful risk factor for diabetes, we performed another sensitivity analysis after excluding subjects with IFG (Supplemental Table S6). Similarly, incrementally higher incidence rate and risk of diabetes were observed with larger cumulative number

Table 3. HR and 95% CI for Diabetes According to Quartile of Baseline γ-GTP Level

	Quartile	No.	No. of events	IR[a]	Model 1	Model 2	Model 3
Men	Q1	66,761	1,097	1.77	1 (Ref)	1 (Ref)	1 (Ref)
	Q2	60,181	1,862	3.35	1.90 (1.77–2.05)	1.54 (1.43–1.66)	1.52 (1.41–1.63)
	Q3	64,066	3,409	5.81	3.32 (3.10–3.55)	2.25 (2.10–2.41)	2.17 (2.03–2.33)
	Q4	64,862	5,978	10.27	5.91 (5.54–6.30)	3.341(3.12–3.57)	3.14 (2.93–3.36)
Women	Q1	22,016	230	1.12	1 (Ref)	1 (Ref)	1 (Ref)
	Q2	21,899	345	1.69	1.52 (1.28–1.79)	1.20 (1.01–1.42)	1.20 (1.02–1.42)
	Q3	23,762	672	3.05	2.75 (2.37–3.19)	1.81 (1.55–2.10)	1.77 (1.52–2.06)
	Q4	22,659	1,590	7.71	6.99 (6.09–8.02)	3.06 (2.66–3.53)	2.85 (2.47–3.29)

Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, income status, alcohol drinking, smoking, regular exercise, fasting blood glucose; Model 3: adjusted for Model 2+hypertension, dyslipidemia, and chronic kidney disease.
HR, hazard ratio; CI, confidence interval; γ-GTP, gamma-glutamyl transferase; IR, incidence rate.
[a]Per 1,000 person-years.

Table 4. HR and 95% CI for Diabetes According to Cumulative Number of Exposures to High γ-GTP over 5 Years

	No. of high γ-GTP	No.	No. of events	IR[a]	Model 1	Model 2	Model 3
Men	0	151,103	3,922	2.80	1 (Ref)	1 (Ref)	1 (Ref)
	1	26,420	1,291	5.34	1.92 (1.80–2.04)	1.48 (1.39–1.57)	1.44 (1.36–1.54)
	2	16,674	1,102	7.28	2.62 (2.45–2.80)	1.92 (1.79–2.05)	1.87 (1.74–2.00)
	3	14,826	1,123	8.37	3.02 (2.82–3.23)	2.13 (2.00–2.28)	2.05 (1.92–2.20)
	4	16,393	1,439	9.76	3.53 (3.33–3.75)	2.29 (2.15–2.44)	2.20 (2.06–2.34)
	5	30,454	3,469	12.82	4.66 (4.45–4.88)	2.75 (2.62–2.88)	2.60 (2.47- 2.73)
Women	0	47,621	637	1.43	1 (Ref)	1 (Ref)	1 (Ref)
	1	15,096	395	2.82	1.98 (1.74–2.24)	1.50 (1.32–1.70)	1.47 (1.29–1.66)
	2	7,944	312	4.26	2.99 (2.61–3.43)	2.09 (1.82–2.39)	2.01 (1.76–2.31)
	3	5,977	329	6.01	4.23 (3.70–4.83)	2.49 (2.18–2.85)	2.37 (2.07–2.72)
	4	5,673	378	7.30	5.15 (4.53–5.85)	2.59 (2.27–2.95)	2.46 (2.16–2.81)
	5	8,025	786	10.92	7.73 (6.96–8.58)	3.31 (2.97–3.69)	3.05 (2.73–3.41)

Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, income status, alcohol drinking, smoking, regular exercise, fasting blood glucose; Model 3: adjusted for Model 2+hypertension, dyslipidemia, and chronic kidney disease.
HR, hazard ratio; CI, confidence interval; γ-GTP, gamma-glutamyl transferase; IR, incidence rate.
[a]Per 1,000 person-years.

of exposures to high γ-GTP level in both men and women, with a more than 3-fold higher risk in the persistent exposure group compared to the no exposure group.

DISCUSSION

In this long-term, large-scale, nationwide, population-based cohort study, cumulative exposure to high γ-GTP level was associated with linear increase in incidence rate and risk of diabetes in both men and women. These associations remained evident even after adjusting for potential confounding factors by multivariate analysis and were confirmed in sensitivity analyses. Because elevated γ-GTP is a biomarker reflecting insulin resistance and metabolic syndrome, and therefore a potential risk factor for development of diabetes, efforts to manage underlying conditions that are associated with high γ-GTP level in the general population would be important for prevention of diabetes.

The mechanism of the relationship between high γ-GTP level and dysregulated glucose metabolism is not fully understood, although possible hypotheses have been suggested. First, γ-GTP

is an indicator of hepatocyte damage and hepatic dysfunction, and elevated γ-GTP level reflects hepatic steatosis. Nonalcoholic fatty liver disease (NAFLD) is a state in which fat is excessively accumulated in hepatocytes, causing hepatocyte damage and promoting the synthesis of γ-GTP. NAFLD is associated with increased hepatic insulin resistance and is linked to diabetes [17,18]. Also, elevated γ-GTP is associated with subclinical inflammation that causes liver damage. When fat accumulates in the liver, it can stimulate the production of cytokines such as tumor necrosis factor-α, interleukin 1β (IL-1β), and IL-6 and worsen liver dysfunction, and such inflammatory conditions provide an environment that are vulnerable to incident diabetes [19]. Second, γ-GTP is a cell surface glycoprotein that metabolizes extracellular reduced glutathione (GSH) and is reutilized for intracellular GSH synthesis, which serves as a protective molecule against intracellular oxidative stress [20]. γ-GTP plays an important role in antioxidant action by maintaining high intracellular glutathione concentration [21]. Therefore, a high γ-GTP level indicates an increase in intracellular oxidative stress, and pancreatic beta-cells are damaged in this condition, leading to a decrease in insulin secretion and impaired glucose absorption in muscle and adipose tissue. Thus, elevated γ-GTP could be a marker of oxidative stress in diabetic patients. Oxidative stress also affects signaling pathways involving p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), glycogen synthase kinase-3 (GSK-3), and inhibitor of nuclear factor kappa B kinase subunit beta (IKK-β), which induce insulin resistance, and inhibition of translocation of glucose transporter type 4 (GLUT4) to cell membrane can lead to decreased glucose transport activity [21].

Several studies have reported a relationship between γ-GTP and diabetes. German Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) Augsburg survey study observed the association between γ-GTP and type 2 diabetes during 14.7 years of follow-up. There were 172 cases and 109 cases of diabetes among 1,851 men and 1,836 women in the middle aged (25 to 64 years old) group, respectively. Similar to our study, both men and women had an increased risk of diabetes as serum γ-GTP level increased. The association between obesity and diabetes was stronger in women with γ-GTP greater than the median compared to the women with γ-GTP below the median [22]. The Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort study found that γ-GTP increase over 3 years was associated with incident diabetes in middle-aged people. Even in the normal range of γ-GTP, unchanged or increased γ-GTP level over time correlated with

an increase in insulin resistance and was associated with a higher risk of diabetes in both men and women (adjusted odds ratio, 2.49; 95% CI, 1.28 to 4.86 in men; adjusted odds ratio, 2.53; 95% CI, 1.01 to 6.40 in women) [7]. According to a study of 25 to 55-year-old male workers of steel companies in Korea, there was a dose-response relationship between high γ-GTP level and incidence of diabetes within the physiological range of γ-GTP level [8]. In addition, a result of the Korean Genome and Epidemiology Study including 7,739 nondiabetic adults aged 40 to 69 years living in the community confirmed that higher serum γ-GTP level was positively associated with incident diabetes [23]. In an observational study of 6 years in China, the cumulative incidence of IFG increased in the groups with higher γ-GTP level is a dose-dependent manner [24]. In Japan, several studies have shown that γ-GTP is positively correlated with the incidence of diabetes in both men and women [25,26]. These data support that higher γ-GTP level can be used as a predictive marker for future diabetes in both Caucasians and East Asian populations.

Our study has strength in that it is a large-scale, long-term follow-up study using the NHIS database that generally represents the entire Korean population. We included subjects who received 5 yearly health examinations to evaluate the effects of long-term cumulative exposure to high γ-GTP level on incidence rate and risk of diabetes. However, there are some limitations that should be acknowledged. First, because this was not a prospective study, causality cannot be confirmed. However, to overcome this problem, we performed a sensitivity analysis excluding diabetes cases developed in the first 2 years of follow-up, which showed similar results. Also, the group without IFG was analyzed, showing the same trend. Second, we tried to adjust as many confounding factors as possible, but possible influence of other uncontrolled factors such as drugs that affect γ-GTP could not be excluded. The status of NAFLD, which is closely associated with hepatic insulin resistance and linked to diabetes, could not be identified. Third, because of the lack of data on postprandial glucose level and hemoglobin A1c, the diagnosis of diabetes might have been underestimated. We combined disease code, prescription, and fasting glucose level to increase the accuracy of diagnosis. Lastly, the data might not be generalized to other ethnic populations because this study only used Korean people.

In conclusion, using the nationwide population-based cohort database, we observed a linear relationship between baseline γ-GTP level or cumulative exposure to high γ-GTP level and risk of diabetes. Thus, serum γ-GTP level and greater cumula-

tive exposure to high γ-GTP could be regarded as an independent predictive marker for incident diabetes although further studies are needed to clearly elucidate the pathophysiological mechanisms related to diabetes. Regular monitoring and managing underlying conditions that are associated with high serum γ-GTP level should be considered for prevention of diabetes in the general population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.Y.P., K.H., S.H.L. Acquisition, analysis, or interpretation of data: K.H., H.S.K., J.H.C., K.H.Y., M.K.K., S.H.L. Drafting the work or revising: J.Y.P., S.H.L. Final approval of the manuscript: J.Y.P., K.H., H.S.K., J.H.C., K.H.Y., M.K.K., S.H.L.

ORCID

Ji-Yeon Park *https://orcid.org/0000-0002-6824-8753*
Mee Kyoung Kim *https://orcid.org/0000-0003-3205-9114*
Seung-Hwan Lee *https://orcid.org/0000-0002-3964-3877*

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