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RESEARCH ARTICLE

Gamma-glutamyltransferase, cardiovascular disease and mortality in individuals with diabetes mellitus

Diewertje Sluik[1]*
Joline W.J. Beulens[2]
Cornelia Weikert[1,3]
Susan van Dieren[2]
Annemieke M.W. Spijkerman[4]
Daphne L. van der A[5]
Andreas Fritsche[6]
Hans-Georg Joost[7]
Heiner Boeing[1]
Ute Nöthlings[1,8]

[1]*Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany*
[2]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*
[3]*Institute for Social Medicine, Epidemiology, and Health Economics, Charité University Medicine Berlin, Berlin, Germany*
[4]*Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*
[5]*Center for Nutrition and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*
[6]*Department of Internal Medicine, Division of Endocrinology, Diabetology, Nephrology, Vascular disease, and Clinical Chemistry, University of Tübingen, Tübingen, Germany*
[7]*Department of Pharmacology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany*
[8]*Epidemiology Section, Institute for Experimental Medicine, Christian-Albrechts-University of Kiel, Kiel, Germany*

*Correspondence to: Diewertje Sluik, German Institute of Human Nutrition Potsdam-Rehbrücke, Arthur-Scheunert-Allee 114–116, 14558 Nuthetal, Germany
E-mail: Diewertje.Sluik@dife.de

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Abstract

Background Increased plasma activity of gamma-glutamyltransferase (GGT) is associated with cardiovascular diseases (CVD) and mortality in the general population. We investigated the association between GGT, CVD and mortality in individuals with diabetes mellitus.

Methods Data used were from 1280 participants, aged 35–70 years, with a confirmed diagnosis of diabetes mellitus in the European Prospective Investigation into Cancer and Nutrition in Potsdam (Germany), Bilthoven and Utrecht (the Netherlands). Multivariate hazard ratios (HR) and 95% confidence intervals (CI) for CVD (non-fatal and fatal events) and overall mortality were estimated using sex-specific quartiles of GGT.

Results After 8.2 years follow-up, 108 incident CVD cases and 84 deaths were observed. Participants with high GGT activity had an increased mortality risk: HR in the highest quartile was 3.96 (95% CI 1.74, 9.00). This association was in particular present in former and current smokers, younger persons and those with a higher waist–height ratio and alcohol consumption. No associations were observed for non-fatal CVD and non-fatal and fatal CVD events combined.

Conclusions Higher GGT plasma activity is associated with increased all-cause mortality in individuals with diabetes.

Keywords gamma-glutamyltransferase; diabetes mellitus; mortality; cardiovascular diseases; myocardial infarction; stroke

Abbreviations: GGT, gamma-glutamyltransferase; EPIC, European Investigation into Cancer and Nutrition; HbA_{1c}, glycated haemoglobin; ICD, International Classification of Diseases, Injuries and Causes of Death.

Introduction

Gamma-glutamyltransferase (GGT) is a liver enzyme which is traditionally used in clinical practice as a marker for liver function and alcohol abuse [1]. More recently, it has been found that increased plasma activity of GGT is also associated with cardiovascular disease (CVD), mortality and incident diabetes mellitus in the general population [2]. Since individuals with diabetes mellitus are at increased risk for complications such as CVD and premature mortality [3,4] and GGT has been found to be elevated in individuals with diabetes [5], we investigated the association between GGT and non-fatal and fatal CVD (respectively and combined) and all-cause mortality in individuals with diabetes.

Materials and methods

Study design

Analyses were performed within the European Prospective Investigation into Cancer and Nutrition (EPIC), a multi-centric cohort study [6]. Data was available

from the study centres of EPIC-Potsdam (Germany) and EPIC-NL (Bilthoven, Utrecht; The Netherlands). In the EPIC-Potsdam cohort, 27 548 participants, aged 35–65 years, were recruited between 1994 and 1998, based on general population registries [7]. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by ethical review boards of the single centres and the International Agency for Research on Cancer in Lyon, France. All subjects provided written informed consent.The EPIC-NL cohort consists of the Prospect cohort and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort. Prospect is a prospective population-based cohort of 17 357 women, aged 49–70 years, who underwent breast cancer screening between 1993 and 1997. The MORGEN cohort consists of 22 654 men and women, aged 20–59 years, recruited from three Dutch towns. From 1993 to 1997 each year, a random sample of approximately 5000 participants was examined [8]. Within these cohorts, self-reported diagnoses of diabetes mellitus at baseline were confirmed by medical practitioner records, self-reported use of diabetes-related medication or by repeated self-report of diagnosis during follow-up, as has been reported previously [9,10].

Study population

Identified were 1332 and 574 participants with a confirmed diabetes diagnosis at baseline, respectively, at EPIC-Potsdam and EPIC-NL. After exclusions, a total of 1280 ($n = 929$ in Potsdam and $n = 351$ in NL) were available for this analysis. Exclusion criteria were as follows: type 1 diabetes ($n = 38$), prevalent CVD ($n = 228$), missing information on blood pressure, dietary intake or anthropometry ($n = 136$), missing age at diabetes diagnosis ($n = 24$), follow-up information on vital status below 1 month ($n = 74$) and no blood sample or biomarker information available ($n = 310$).

Exposure and covariate assessment

Participants provided a blood sample which was stored at $-80°C$, and a percentage of EPIC-NL blood samples was stored at $-196°C$. In EPIC-Potsdam, GGT citrate plasma activity was measured with the automatic ADVIA 1650 analyzer (Siemens Medical Solutions, Erlangen, Germany). In EPIC-NL, GGT activity was measured using enzymatic methods on an auto-analyzer (LX20, Beckman Coulter, Mijdrecht, the Netherlands); in EDTA or citrate plasma. Levels were fairly similar for both study centres: median and interquartile range (IQR) was 31.0 [20.0–53.0] U/L in men and 21.0 [14.0–36.0] U/L in women in EPIC-Potsdam. In EPIC-NL, the median [IQR] was 36.2 [26.6–52.0] U/L in men and 27.8 [21.8–36.9] U/L in women. A GGT activity of <28 U/L in men and <18 U/L in women are considered normal [11].

Duration since diabetes diagnosis was calculated by subtracting the self-reported year of diagnosis or, when available, the exact date of diagnosis supplied by the medical practitioner from the age at baseline examination. Information on insulin use and use of oral blood glucose lowering drugs according to the Anatomical Therapeutic Chemical classification of the World Health Organization was either self-reported medication for treatment or obtained during medical verification.

Weight, height and waist circumference were measured during the visit to the study centre at baseline, as well as diastolic and systolic blood pressures. Lifestyle-related and health-related variables were collected using questionnaires which included questions on smoking, education, physical activity and medical history including prevalent heart disease and stroke. Baseline dietary intake and alcohol consumption was derived from a food frequency questionnaire, which assessed intake during the previous 12 months. Hypertension at baseline was based on a self-reported diagnosis or use of medication or high blood pressure values. Hyperlipidaemia at baseline was based on self-reported diagnosis or medication use.

Outcome ascertainment

Non-fatal CVD was defined as incident myocardial infarction (MI), ischaemic heart disease or stroke [International Classification of Diseases, Injuries and Causes of Death (ICD)-9 codes 410–414, 430–438; ICD-10 codes: 120–125, 160–167, 169]. Cases were obtained through linkage with the Dutch National Medical Registry which holds a standardized computerized database of hospital discharge diagnoses (EPIC-NL) or recorded in routine follow-up mailings which were mailed to all participants every 2 years and verified by participants' medical practitioners (EPIC-Potsdam). In EPIC-NL, vital statistics were obtained through linkage with the municipal population registries. Subsequently, causes of death were obtained through linkage with 'Statistics Netherlands'. In EPIC-Potsdam, deceased subjects were identified via follow-up mailings and subsequent inquiries to municipality registries, regional health departments, physicians or hospitals.

Statistical analysis

All statistical analyses were performed using SAS 9.2 for Windows (SAS Institute, Inc., Cary, North Carolina, United States). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using multivariate Cox proportional hazard regression. Age at enrolment in 1-year categories was entered as stratum variables. Moreover, analyses were stratified by study centre to take differences between centres into account. Age was used as the primary time variable, with entry time defined as the subject's age in years at recruitment. Exit time was defined as the subject's age in years at CVD, death or censoring (lost to follow-up or end of follow-up period). Sex-specific quartiles were built based on the overall

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distribution of GGT activity. For the analyses of non-fatal CVD, deceased individuals were censored. Subjects with incident non-fatal CVD were censored in the overall mortality analyses. Multivariate HR were adjusted for sex; diabetes duration (years); insulin use (yes/no/don't know or missing); use of oral blood glucose lowering medication (yes/no/don't know or missing); HbA_{1c} (%) (model 1); waist–height ratio; body mass index (kg/m^2); hyperlipidaemia or hypertension (yes/no/missing); smoking status (never/former/current/missing); alcohol consumption (g/day); fruit, vegetable and legume intake (g/day); physical activity (four categories); education attainment (five categories) (model 2); systolic blood pressure; total cholesterol; HDL-cholesterol; triglycerides; C-reactive protein; and uric acid (model 3). Since the association between GGT, CVD and mortality may differ for age groups, adiposity level, smoking status and alcohol consumption, subgroup analyses were performed, and we tested for statistical interaction by adding a product term [1].

Results

After a median follow-up of 8.2 years, 108 incident cases of non-fatal CVD (38 stroke, 65 MI and 5 both) and 84 cases of all-cause mortality were observed. Of the 84 mortality cases, 21 (25%) were due to CVD, 34 (40%) due to cancer and 26 (31%) due to other known causes; for three cases (4%), the cause of death was not yet verified or was unknown. Ten participants experienced a non-fatal and subsequently a fatal CVD event during follow-up.

Participants in the highest quartile of GGT were more likely to have a higher waist–height ratio or alcohol consumption, be physically inactive or have shorter diabetes duration and were less likely to use insulin or to have never smoked. Furthermore, participants with a higher GGT activity had more unfavourable levels of blood lipids and other biomarkers (Table 1).

No association was observed between higher GGT activity and non-fatal CVD events: HR in the highest quartile was 0.83 (95% CI 0.39–1.79) (Table 2). Moreover, no relationship was seen between plasma levels of GGT and non-fatal and fatal CVD events combined; HR in the full model was 1.21 (95% CI 0.61–2.42). However, participants in the fourth quartile of GGT had a HR of 3.96 (95% CI 1.74–9.00) for all-cause mortality in the fully adjusted model. Cause-specific analyses showed that this was due to non-CVD/non-cancer mortality: HR for a 1-unit (log-transformed) increase was 3.24 (95% CI 1.53–6.86). Most frequent causes of death included in this category were mortality due to diabetes mellitus ($n = 9$) and digestive diseases ($n = 4$).

The positive association between GGT and overall mortality was particularly present in former and current smokers, younger persons and those with higher waist–height ratio and higher alcohol consumption (Table 3). Statistically significant interaction was not observed for these factors.

Discussion

In this population of individuals with diabetes, high GGT plasma activity was associated with all-cause mortality. This association was particularly present in persons who were younger, obese, former or current smoker and reported alcohol consumption above the median.

Prospective studies in the general population have shown a relationship between GGT and mortality as well as CVD [2]. Since GGT is the main determinant of extracellular hydrolysis of glutathione, the main cellular antioxidant, it is suggested to be a marker for oxidative stress. This might be the biological mechanism driving the association between high GGT activity and non-vascular and vascular outcomes [12].

We observed a higher mortality risk with increasing GGT activity, especially among former or current smokers, younger persons and persons with a higher level of abdominal adiposity and higher alcohol consumption. GGT activity was more strongly associated with mortality in younger age. This has been reported previously and is probably caused by the phase 2 enzyme system, including glutathione, which seems to function less with older age [13]. Furthermore, smoking status, adiposity and alcohol consumption have been shown to be important factors to consider when studying GGT activity [1,2]. Waist–height ratio as an indicator of abdominal adiposity was found to be strongly associated with mortality risk in diabetic persons [14]. Although we adjusted for these factors and no statistical interaction was found, residual confounding might have been present.

Because GGT activity is related to the incidence of diabetes and values are elevated in diabetes patients, the question rises whether associations between GGT and CVD may be different among diabetic persons. In contrast to studies in non-diabetic individuals [2,15], we did not observe an association between GGT and CVD. In a cohort of 1952 type 2 diabetes patients, Monami *et al*. observed that an increase of GGT was associated with a higher risk of all-cause and cancer mortality, but not with CVD mortality after a median follow-up of 6.4 years and adjustment for Hb_{A1c}, metabolic syndrome, Charlson Comorbidity Score, insulin therapy and metformin doses [16]. Furthermore, in an analysis of EUROSTROKE, a collaboration of three European cohort studies, an association was found between GGT and stroke among non-diabetic persons but not in diabetic persons [17]. However, serum GGT predicted risk of coronary heart disease events among 1120 Finnish men and women with a history of diabetes at baseline, and strength of association was suggested to be somewhat stronger than in the general population [18]. Diabetes mellitus, in particular type 2 [1,5], and the higher prevalence of non-alcoholic fatty liver disease in diabetes [19] have been associated with increased GGT activity, which might explain the difference in associations between GGT and CVD in people with and without diabetes. Moreover, because a majority of the studies which showed an association had a follow-up time

Table 1. Baseline characteristics[a] of individuals with diabetes (n = 1280) from EPIC-Potsdam and EPIC-the Netherlands according to sex-specific quartiles of gamma-glutamyltransferase

	Sex-specific quartiles of gamma-glutamyltransferase (GGT)				
	1	2	3	4	p trend
n	334	315	311	320	
GGT, U/L (men)	16 [12–19]	26 [24–30]	42 [37–48]	83 [65–121]	<0.0001
GGT, U/L (women)	13 [10–15]	21 [19–23]	30 [27–33]	53 [42–77]	<0.0001
Age at recruitment, years	57.4 ± 7.2	58.5 ± 6.4	58.1 ± 6.5	57.2 ± 6.5	0.61
Waist–height ratio	0.55 ± 0.08	0.58 ± 0.07	0.59 ± 0.07	0.60 ± 0.07	<0.0001
Body mass index, kg/m^2	27.7 ± 4.9	29.1 ± 4.5	29.9 ± 4.7	30.5 ± 5.0	<0.0001
HbA_{1c}, %	7.2 [6.3–8.6]	7.6 [6.6–9.0]	7.6 [6.7–9.3]	7.9 [6.8–9.8]	<0.0001
Diabetes duration, months	84 [36–156]	60 [24–120]	48 [24–108]	48 [17–120]	<0.0001
Age at diagnosis, years	48.0 ± 11.2	51.4 ± 8.9	51.9 ± 8.6	50.9 ± 8.4	<0.0001
Insulin use, n (%)	79 (25%)	59 (22%)	64 (24%)	59 (20%)	0.16
Oral blood glucose lowering drug use, n (%)	115 (36%)	132 (48%)	150 (55%)	162 (55%)	<0.0001
Fruit, vegetable and legume intake, g/day	299 ± 112	316 ± 127	322 ± 137	303 ± 129	0.61
Alcohol consumption, g/day	3.8 [0.8–10.2]	3.1 [0.5–11.6]	3.7 [0.5–13.9]	5.2 [0.8–24.8]	<0.0001
Smoking status, n (%)					
Never	148 (44%)	127 (40%)	126 (41%)	123 (38%)	0.15
Former	127 (38%)	128 (41%)	114 (37%)	130 (41%)	0.74
Current	59 (18%)	59 (19%)	70 (23%)	67 (21%)	0.17
Physical activity, n (%)					
Inactive	95 (29%)	85 (28%)	90 (30%)	98 (32%)	0.46
Moderately inactive	121 (36%)	109 (36%)	103 (34%)	116 (37%)	0.90
Moderately active	70 (21%)	64 (20%)	53 (17%)	61 (20%)	0.36
Active	47 (14%)	48 (16%)	57 (19%)	36 (12%)	0.55
Education level, n (%)					
None	3 (1%)	5 (2%)	2 (1%)	4 (1%)	0.95
Primary school	108 (32%)	96 (31%)	119 (38%)	118 (37%)	0.07
Technical/professional school	112 (34%)	119 (38%)	112 (36%)	117 (37%)	0.53
Secondary school	13 (4%)	22 (7%)	22 (7%)	8 (3%)	0.48
Longer (including university degree)	98 (29%)	71 (23%)	55 (18%)	71 (22%)	0.01
Blood pressure, mmHg					
Diastolic	83.2 ± 9.6	84.8 ± 10.7	85.5 ± 10.7	87.8 ± 11.2	<0.0001
Systolic	136.3 ± 17.4	141.6 ± 19.7	143.5 ± 20.2	144.7 ± 19.2	<0.0001
Hyperlipidaemia, n (%)	142 (43%)	125 (40%)	116 (37%)	162 (51%)	0.08
Hypertension, n (%)	228 (68%)	241 (77%)	260 (84%)	271 (85%)	<0.0001
Total cholesterol, mg/dL	174.0 ± 34.4	186.5 ± 39.5	189.5 ± 41.8	197.9 ± 40.6	<0.0001
HDL-cholesterol, mg/dL	43.0 [36.0–50.0]	39.0 [33.0–46.0]	37.5 [32.5–44.1]	38.0 [33.0–45.0]	<0.0001
Triglycerides, mg/dL	47.1 [32.1–69.8]	67.6 [46.0–96.4]	72.0 [53.0–100.3]	84.1 [56.7–129.9]	<0.0001
C-reactive protein, mg/dL	0.11 [0.04–0.29]	0.17 [0.07–0.41]	0.23 [0.09–0.52]	0.27 [0.10–0.57]	<0.0001
Uric acid, mg/dL	4.0 [3.3–4.8]	4.3 [3.7–5.2]	4.4 [3.9–5.2]	4.7 [3.9–5.6]	<0.0001

[a]Data are shown as mean ± SD, median [IQR] or n (%)

Table 2. Hazard ratios (95% CI) of associations between gamma-glutamyltransferase and non-fatal CVD events, fatal and non-fatal CVD events combined and overall mortality

	Sex-specific quartiles of gamma-glutamyltransferase (GGT)				
	1	2	3	4	p trend
Non-fatal CVD					
Cases/Person-Years (PY)	21/2671	30/2620	36/2571	21/2583	
Model 1[a]	1	1.00 (0.53–1.91)	1.35 (0.72–2.52)	0.84 (0.42–1.67)	0.53
Model 2[b]	1	0.89 (0.46–1.74)	1.07 (0.56–2.04)	0.75 (0.36–1.57)	0.49
Model 3[c]	1	0.89 (0.45–1.75)	1.12 (0.58–2.18)	0.83 (0.39–1.79)	0.74
Fatal and non-fatal CVD					
Cases/Person-Years (PY)	22/2671	30/2620	38/2571	29/2583	
Model 1[a]	1	1.01 (0.54–1.88)	1.44 (0.79–2.63)	1.20 (0.64–2.24)	0.49
Model 2[b]	1	0.89 (0.47–1.71)	1.14 (0.61–2.13)	1.12 (0.57–2.17)	0.49
Model 3[c]	1	0.88 (0.46–1.70)	1.18 (0.62–2.24)	1.21 (0.61–2.42)	0.34
Overall mortality					
Cases/Person-Years (PY)	12/2749	22/2745	21/2733	29/2681	
Model 1[a]	1	1.86 (0.87–3.97)	2.93 (1.34–6.42)	4.13 (1.99–8.55)	<0.0001
Model 2[b]	1	1.92 (0.86–4.27)	2.76 (1.21–6.31)	4.26 (1.90–9.56)	0.0002
Model 3[c]	1	1.85 (0.83–4.12)	2.63 (1.15–6.04)	3.96 (1.74–9.00)	0.001

[a]Model 1 age-stratified and centre-stratified and adjusted for sex, diabetes duration, insulin use, use of oral blood glucose lowering medication and HbA_{1c}.
[b]Model 2: Model 1 additionally adjusted for waist–height ratio, body mass index, self-reported hyperlipidaemia, hypertension, smoking status, alcohol consumption, fruit, vegetable and legume intake, physical activity and educational level.
[c]Model 3: Model 2 additionally adjusted for systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, C-reactive protein and uric acid.

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Table 3. Hazard ratios (95% CI) of associations between gamma-glutamyltransferase and overall mortality, stratified for smoking status, body mass index, waist–height ratio, age at recruitment, and alcohol consumption

	n	HR (95% CI) for 1 U/L increase [a,b]
Smoking status		
Never smokers	524	0.98 (0.34, 2.83)
Former and current smokers	754	2.26 (1.38, 3.69)
Body mass index		
<28.8 kg/m²	640	1.93 (1.12, 3.34)
≥28.8 kg/m²	640	1.90 (1.08, 3.34)
Waist–height ratio		
<0.58	640	1.55 (0.87, 2.74)
≥0.58	640	2.03 (1.13, 3.65)
Age at recruitment		
<60 years	697	3.81 (1.83, 7.96)
≥60 years	583	1.49 (0.95, 2.34)
Alcohol consumption		
<4.0 g/day	640	1.49 (0.81, 2.71)
≥4.0 g/day	640	2.63 (1.50, 4.62)

[a]Age-stratified and centre-stratified and adjusted for sex, diabetes duration, insulin use, use of oral blood glucose lowering medication, HbA_{1c}, self-reported hyperlipidaemia, hypertension, fruit, vegetable and legume intake, physical activity, educational level, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, C-reactive protein and uric acid. It was adjusted for smoking status, waist–height ratio, body mass index or alcohol consumption when not stratified for.
[b]Levels of GGT were log-transformed.

of at least 10 years, the relationship between GGT and CVD might only become apparent in studies with longer follow-up. Since CVD incidence in our study was relatively low [20] as well as the mean age at recruitment, more CVD events may occur with a longer follow-up time and an ageing population, and power will increase accordingly. Finally, more research is needed to reveal if and why associations between GGT and CVD are different in people with and without diabetes.

In conclusion, we observed that high GGT plasma activity was associated with all-cause mortality in a population of individuals with diabetes. Since GGT is easy to assess, it might be a useful biomarker in diabetes management by detecting individuals at high mortality risk.

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