ORIGINAL ARTICLE

Serum γ-glutamyltransferase and the risk of heart failure in men and women in Finland

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ABSTRACT

Objectives To evaluate the association of serum γ-glutamyltransferase (GGT) levels with heart failure (HF) risk in the Finnish population.

Design Prospective population-based cohort study.

Setting The present study, which is a part of FINRISK study, was carried out in Finland.

Subject study cohorts included 18 353 Finnish men and 19 726 women who were 25–74 years of age and free of HF at baseline.

Main outcome measures HF (636 men and 445 women) during a mean follow-up of 14.5 years.

Results Baseline measurement of different levels of serum GGT was used to predict incident HF. The multivariable-adjusted (age, sex, study area, study year, smoking, education, alcohol consumption, physical activity, valvular heart disease, body mass index (BMI), systolic blood pressure, total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up) HRs of HF at five GGT groups (using the 25th, 50th, 75th and 90th percentiles) were 1.00, 1.16 (95% CI: 0.97 to 1.38), 1.20 (1.00 to 1.45), 1.29 (1.04 to 1.60) and 1.82 (1.45 to 2.29) (P_{trend}<0.001). Stratification by smoking status, alcohol consumption and BMI gave similar results, while stronger association was observed among subjects aged <60 years (P_{trend}=0.001) compared with subjects 60+ years of age (P_{trend}=0.173).

Conclusions Moderate to high levels of serum GGT (from the 50th to the 90th percentiles) were significantly associated with incident HF in men and women in Finland, and the predictive power was stronger in subjects aged <60 years.

INTRODUCTION

Heart failure (HF) is a worldwide epidemic which is associated with high morbidity and mortality. In addition to its high prevalence, HF has created heavy economic burdens on society. In the US alone, HF costs were over US$33 billion in 2007 according to the estimation of the American Heart Association.[1] In response to this severe situation, increasing attention has been drawn to identifying the risk factors of HF. Serum γ-glutamyltransferase (GGT), a widely used index of liver dysfunction, was found to be positively associated with incident cardiovascular disease (CVD), including coronary heart disease (CHD),[2 3] stroke[3] and HF,[4] and also mortality from CVD,[2 5–7] including CHD,[2 5 6] stroke,[5 6] as well as congestive HF.[5–7] It has been proposed that the pro-oxidant effects of GGT, which result from the production of reactive oxygen species superoxide anion and hydrogen peroxide during the process of glutathione hydrolysis by GGT, might be the biological mechanism linking GGT to various cardiovascular events.[8] This is supported by the findings that GGT activity has been detected in atheromatous plaques of carotid and coronary arteries where a catalytically active enzyme has been identified.[9] So far, very limited information is available on the role of GGT in predicting incident HF. Thus, the aim of this study is to examine the association between GGT and the risk of incident HF.

METHODS

Participants

Five independent cross-sectional population-based health examination surveys were carried out in six geographic areas of Finland in 1982, 1987, 1992, 1997 and 2002.[10] The original random sample was stratified by area, gender and 10-year age group according to WHO Monitoring Trends and Determinants of Cardiovascular Disease protocol.[11] The participation rate varied by year from 65% to 88%.[10] The participants included in the five surveys were 25–64 years old, and the 1997 and 2002 surveys also included individuals 65–74 years old. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the five surveys was 38 737. The final sample comprised 18 353 men and 19 726 women after excluding the participants with a history of HF (n=457) at baseline, and those with incomplete data on any variables required for this analysis (n=201). The participants gave an informed consent (verbal consents in 1982–1992, and signed consents in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were conducted in accordance with the Declaration of Helsinki.

Measurements

A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits and alcohol consumption. Education level, measured as the total number of school years, was divided into birth and cohort-specific tertiles. Information on occupational, commuting and leisure-time physical activity was merged and regrouped into three categories: low, moderate and high.[12 13] Participants were

classified as never, ex-smokers and current smokers. Alcohol consumption was categorised into four groups: none, 1–34, 35–209, ≥210 g per week in men; none, 1–34, 35–139, ≥140 g per week in women. Data on diabetes and myocardial infarction at baseline and during follow-up were obtained from the questionnaire and completed by the National Hospital Discharge Register and National Social Insurance Institution's Drug Register (diabetes only).[14] Data on the history of valvular heart disease at baseline were collected by hospital discharge register. Data on liver cirrhosis at baseline and during follow-up were collected by the National Hospital Discharge Register.

At the survey site, specially trained research nurses measured participants' height and weight by using a standardised protocol.[11] Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in metres. Blood pressure was measured from the right arm after 5min of sitting using a mercury sphygmomanometer in each survey. After blood pressure measurement, a venous blood specimen was taken. The serum total cholesterol level was determined by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany). GGT was determined from fresh venous blood serum samples using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) based on the recommendation of the European Committee for Clinical Laboratory Standards. All samples were analysed in the same central laboratory at the National Public Health Institute.

Prospective follow-up

Follow-up information was from the Finnish Hospital Discharge Register and the National Social Insurance Institution's Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Causes of Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen of Finland.[15] The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic CHD) (ICD-9), and I 50, I11.0 (hypertensive heart disease with HF), I13.0 and I13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify HF cases in any one of the above mentioned national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatment. Follow-up of each cohort member continued until the date of the diagnosis of HF from the Hospital Discharge Register, Causes of Death Register or from the National Social Insurance Institution's Drug Reimbursement Register, or death resulting from causes other than HF, or 31 December 2007. The overall positive predictive value of HF diagnosis in this FINRISK study was 85.9% (negative predictive value 97.9%).[15]

Statistical analyses

Serum GGT levels were classified into five groups using the 25th, 50th, 75th and 90th percentiles as cut-points (quartiles with the top quartile split). The cut-points were 17.1, 25.7, 40.1 and 68.0 U/l among men, and 11.0, 15.1, 22.1 and 35.0 U/l among women for the categories of GGT used, respectively. Differences in risk factors based on different levels of serum GGT were tested using General Linear Models after adjustment for age and study year. Cox proportional hazards regression models were used to analyse the association of serum GGT level with the risk of incident HF. All proportionality assumptions were appropriate. The analyses were first carried out adjusting for age, study area and study year at baseline, then for smoking, education, alcohol consumption and physical activity at baseline, and further for BMI, history of valvular heart disease, systolic blood pressure and total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up. Diabetes and myocardial infarction at baseline and during follow-up were used as time-dependent covariates in Cox models. To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first 2 years of follow-up (n=289), and subjects who were diagnosed with liver cirrhosis at baseline and during follow-up (n=223). Statistical analyses were performed with PASW for Windows, V.19.0 (IBM SPSS Inc, Chicago, Illinois, USA).

RESULTS

During a mean follow-up period of 14.5 years, 636 men and 445 women developed HF. General characteristics of the study population by different levels of GGT at baseline are presented in table 1. High levels of GGT were strongly associated with alcohol consumption. The age-adjusted, study area-adjusted and study year-adjusted partial correlations were 0.22 in men ($p<0.001$), and 0.11 in women ($p<0.001$) for GGT and alcohol consumption.

The age-adjusted, study area-adjusted and study year-adjusted HRs of HF at five GGT groups (using the 25th, 50th, 75th and 90th percentiles) were 1.00, 1.46, 1.60, 2.09 and 3.13 ($P_{trend}<0.001$) among men, and 1.00, 1.12, 1.64, 1.92 and 2.79 ($P_{trend}<0.001$) among women (table 2). Considering the strong associations between serum GGT and many CVDs, we presented a model further adjusting for smoking, education, alcohol consumption and physical activity at baseline, and not adjusting any clinical variable in order to avoid over-adjustment. Like the previous model, serum GGT predicted incident HF even in the normal range. Further adjustment for other clinical risk factors (history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up) attenuated this relationship; however, the highest category of GGT was still associated with a higher risk of HF in both men (HR 1.79; 95% CI 1.31 to 2.43) and women (HR 1.76; 95% CI 1.25 to 2.48). When men and women were combined, the sex-adjusted and multivariable-adjusted HRs of HF across categories of GGT were 1.00, 1.16 (95% CI 0.97 to 1.38), 1.20 (95% CI 1.00 to 1.45), 1.29 (95% CI 1.04 to 1.60), and 1.82 (95% CI 1.45 to 2.29) ($P_{trend}<0.001$), which suggested that the risk of HF significantly increased from the 50th to the 90th percentiles. Exclusion of the participants who died during the first 2 years of follow-up (n=289), and subjects who were diagnosed with liver cirrhosis at baseline and during follow-up (n=223), did not appreciably change the results above (data not shown).

When stratified by age at 60 years, the association between serum GGT and HF risk was only observed among subjects <60 years; the multivariable-adjusted HRs of HF across categories of GGT were 1.00, 1.36 (95% CI 1.09 to 1.71), 1.30 (95% CI 1.02 to 1.66), 1.41 (95% CI 1.07 to 1.86) and 1.90 (95% CI 1.42 to 2.55) ($P_{trend}=0.001$) (table 3). Stratification by smoking status, alcohol consumption and BMI gave similar results to the pooled multivariable-adjusted HRs in table 2. The interaction between age and GGT was significant ($p=0.014$), while no significant interactions between GGT and other stratification variables were found. Of note, after stratification by alcohol consumption, the positive association between the highest category of serum GGT and HF risk was observed in both non-drinkers and drinkers.

Table 1 General characteristics of study subjects at baseline*

	Baseline GGT level					
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	p for trend
Men (n=18 353)	<17.1 U/l	17.1 to <25.7 U/l	25.7 to <40.1 U/l	40.1 to <68.0 U/l	≥68.0 U/l	
Subjects (n)	4659	4517	4593	2739	1845	
Age at baseline (years)	44.3	46.3	48.1	47.8	48.8	<0.001
Body mass index (kg/m^2)	25.0	26.2	27.4	28.4	29.0	<0.001
Diastolic blood pressure (mm Hg)	81	83	86	88	90	<0.001
Systolic blood pressure (mm Hg)	138	139	142	143	147	<0.001
Serum cholesterol (mmol/l)	5.53	5.72	5.93	6.14	6.26	<0.001
Education (years)	10.6	10.5	10.5	10.4	10.5	0.538
Alcohol drinker (%)	55.5	62.5	67.9	73.6	76.9	<0.001
Current smoker (%)	28.4	35.0	38.0	42.0	45.7	<0.001
Low physical activity (%)	6.6	6.9	9.2	11.5	13.5	<0.001
History of myocardial infarction (%)	3.9	3.9	3.4	4.4	5.2	0.011
History of valvular heart disease (%)	0.2	0.2	0.2	0.2	0.3	0.755
History of diabetes (%)	2.4	2.3	3.0	2.9	4.6	<0.001
Women (n=19 726)	<11.0 U/l	11.0 to <15.1 U/l	15.1 to <22.1 U/l	22.1 to <35.0 U/l	≥35.0 U/l	
Subjects (n)	4598	5572	4756	2793	2007	
Age at baseline (years)	41.7	44.3	47.2	49.9	51.7	<0.001
Body mass index (kg/m^2)	24.7	25.4	26.4	27.6	28.6	<0.001
Diastolic blood pressure (mm Hg)	78	79	81	82	83	<0.001
Systolic blood pressure (mm Hg)	132	134	136	138	140	<0.001
Serum cholesterol (mmol/l)	5.60	5.68	5.72	5.81	5.91	<0.001
Education (years)	11.2	11.2	11.1	11.0	10.7	<0.001
Alcohol drinker (%)	39.5	44.6	47.9	50.2	52.5	<0.001
Current smoker (%)	13.5	18.9	23.3	25.6	29.3	<0.001
Low physical activity (%)	7.1	7.9	9.7	11.0	14.7	<0.001
History of myocardial infarction (%)	0.8	0.9	0.9	1.6	1.6	0.001
History of valvular heart disease (%)	0.2	0.1	0.2	0.0	0.3	0.005
History of diabetes (%)	1.4	1.7	1.8	2.8	5.0	<0.001

*Baseline characteristics represent mean or percentage; adjusted for age, study area and study year.

Table 2 HRs of heart failure according to different levels of serum GGT

	Baseline serum GGT level					
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	p for trend
Men						
Incidence case (n)	149	153	151	100	83	
Person-years	83542	63716	58828	34195	20886	
Age, area and study years adjusted HR (95% CI)	1.00	1.46 (1.16 to 1.84)	1.60 (1.27 to 2.02)	2.09 (1.61 to 2.71)	3.13 (2.37 to 4.14)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	1.41 (1.12 to 1.77)	1.51 (1.19 to 1.91)	1.92 (1.47 to 2.51)	2.70 (2.02 to 3.62)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	1.25 (1.00 to 1.58)	1.18 (0.92 to 1.50)	1.32 (1.00 to 1.74)	1.79 (1.31 to 2.43)	0.006
Women						
Incidence case (n)	98	115	102	63	67	
Person-years	91860	86478	58944	32512	22844	
Age, area and study years adjusted HR (95% CI)	1.00	1.12 (0.85 to 1.46)	1.64 (1.24 to 2.18)	1.92 (1.39 to 2.66)	2.79 (2.02 to 3.84)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	1.13 (0.86 to 1.48)	1.59 (1.20 to 2.11)	1.83 (1.32 to 2.54)	2.60 (1.88 to 3.59)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	0.98 (0.75 to 1.29)	1.19 (0.89 to 1.59)	1.21 (0.86 to 1.70)	1.76 (1.25 to 2.48)	0.006
Men and women combined‡						
Incidence case (n)	247	268	253	163	150	
Person-years	175403	150193	117772	66707	43729	
Age, area and study years adjusted HR (95% CI)	1.00	1.33 (1.12 to 1.59)	1.64 (1.37 to 1.97)	2.05 (1.67 to 2.50)	3.08 (2.49 to 3.80)	<0.001
Multivariable adjustment HR (95% CI)*	1.00	1.30 (1.09 to 1.55)	1.57 (1.31 to 1.88)	1.91 (1.55 to 2.34)	2.74 (2.21 to 3.40)	<0.001
Multivariable adjustment HR (95% CI)†	1.00	1.16 (0.97 to 1.38)	1.20 (1.00 to 1.45)	1.29 (1.04 to 1.60)	1.82 (1.45 to 2.29)	<0.001

*Adjusting for age, study area, study year, smoking, education, alcohol consumption, physical activity.
†Further adjusting for history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline and myocardial infarction, diabetes at baseline and during follow-up.
‡Adjusted also for sex.
GGT, γ-glutamyltransferase.

Table 3 HRs of heart failure according to different levels of serum GGT stratified by age, smoking status, alcohol consumption and BMI*

		Baseline GGT level					
	Cases (n)	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	p for trend
Age at baseline (years)							
25–60	655	1.00	1.36 (1.09–1.71)	1.30 (1.02–1.66)	1.41 (1.07–1.86)	1.90 (1.42–2.55)	0.001
60–74	426	1.00	0.93 (0.70–1.24)	1.10 (0.82–1.48)	1.03 (0.73–1.47)	1.43 (0.99–2.08)	0.173
Smoking status							
Never or ever	737	1.00	1.02 (0.83–1.26)	1.14 (0.92–1.42)	1.21 (0.93–1.57)	1.67 (1.26–2.20)	0.004
Current	344	1.00	1.48 (1.06–2.08)	1.37 (0.97–1.95)	1.51 (1.02–2.25)	2.29 (1.51–3.46)	0.003
Alcohol consumption							
Never drinker	614	1.00	1.13 (0.89–1.39)	1.13 (0.88–1.43)	1.50 (1.13–2.00)	1.99 (1.47–2.70)	<0.001
Alcohol drinker	467	1.00	1.20 (0.89–1.60)	1.32 (0.99–1.76)	1.15 (0.82–1.60)	1.80 (1.28–2.52)	0.010
Body mass index (kg/m^2)							
<25	239	1.00	1.21 (0.85–1.72)	1.60 (1.10–2.33)	1.99 (1.24–3.20)	3.28 (2.02–5.33)	<0.001
25–29.9	448	1.00	1.13 (0.88–1.47)	1.06 (0.80–1.41)	1.15 (0.83–1.60)	1.58 (1.10–2.26)	0.161
≥30	394	1.00	1.13 (0.80–1.61)	1.15 (0.81–1.63)	1.24 (0.85–1.82)	1.66 (1.12–2.45)	0.094

*Adjusting for age, study area, study year, smoking, education, alcohol consumption, physical activity, history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline and myocardial infarction, diabetes at baseline and during follow-up.
GGT, γ-glutamyltransferase.

DISCUSSION

The present study suggested a positive association between serum GGT and the risk of HF. This association was more pronounced among subjects aged <60 years, which is in line with the finding of our previous study[2] which evaluated the association between serum GGT and incident CHD with the FINRISK dataset. A similar trend was also observed in two other studies[6 7] on the association of GGT with CVD mortality. Lee *et al*[7] proposed that the observed age difference might be explained by the difference in the ability of maintaining homeostasis[16] and clearing xenobiotics[17] in people of different ages. Xenobiotics, which could be understood as substances foreign to an entire biological system, were directly associated with CVD.[18 19] Serum GGT has been considered as an exposure marker of xenobiotics.[20] However, serum GGT may not reflect the extent of exposure to xenobiotics in older people as in younger people because older people have a reduced hepatic ability to clear xenobiotics, and serum GGT may increase proportional to the amount of glutathione conjugates, but not the amount of xenobiotics.[7] Therefore, the prognostic role of serum GGT in older subjects was not as strong as in younger subjects.

Besides the association of serum GGT with incident CVD or CVD mortality that have already been observed,[3–8 29 30] the other clue that led us to investigate the association between serum GGT and incident HF was that serum GGT has been found to be a risk marker for hypertension,[21] CHD,[2] insulin resistance,[22] type 2 diabetes,[21] dyslipidemia[23] and inflammation,[24] all of which are known risk factors of HF. In our previous study,[2] it was shown that a high level of serum GGT was associated with an increased risk of CHD. The current findings on the relationship between serum GGT and the risk of HF are similar to the previous findings about the association between serum GGT and the risk of CHD. In the present study, the positive association between serum GGT and the risk of HF remained after adjusting for major HF risk factors.

In the present study, alcohol consumption was considered as a confounding factor in the multivariable model and the positive association between serum GGT, and the risk of HF was found in both alcohol and non-alcohol drinkers, which suggests that there are other mechanisms linking serum GGT to the risk of HF besides liver pathology. However, given the temporal lag between the assessment of serum GGT at baseline and the measurement of the outcome, it is not possible to determine the pathways by which GGT resulted in higher risk of HF. Although the precise underlying mechanisms remain unclear, oxidative stress,[25 26] exposure to environmental pollutants[18] and non-alcoholic fatty liver disease (NAFLD),[27] all of which are considered to be involved in the pathogenesis of CVD, were proposed to be partly responsible for the observed association. Serum GGT may predict CVD as a marker of oxidative stress related to glutathione (GSH),[28] exposure to environmental pollutants which need to be conjugated to GSH[5] and NAFLD.[29] Also, previous results of our group have shown that the correlation between GGT and N-terminal prohormone of brain natriuretic peptide was weak (r=−0.09) in the FINRISK 1997 cohort, which suggests that the elevation of GGT is not secondary to early subclinical HF.[30]

There are several strengths and limitations in our study. First, a major strength of the study is the large number of both men and women from a homogeneous population who participated in the study. Second, the mean follow-up period was sufficiently long to ascertain a large number of HF endpoint events. Finally, we also carried out additional analyses excluding the subjects who died during the first 2 years of follow-up, and subjects who were diagnosed with liver cirrhosis at baseline and during follow-up to avoid a potential bias due to a severe disease at baseline, and confounding from liver disease at baseline and during follow-up. A limitation of our study is that GGT was recorded only once at baseline. Therefore, we are not able to test the reproducibility and validity of GGT reflecting liver dysfunction. In addition, we cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured factors such as other causes for HF.

In conclusion, our study indicated a direct association between serum GGT and the risk of HF in men and women in Finland, especially in those aged <60 years, and this association was independent of self-reported alcohol intake. Although GGT is often measured as a marker of liver health, this study provides evidence that it may also be useful in the identification of patients at elevated risk of CVD and HF. Future studies are required to determine the clinical utility of serum GGT in monitoring subjects at risk of developing HF.

Contributors GH had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YW, GH. Analysis and interpretation of data: YW, GH, JT, PJ, VS, RA, MM, PTK, BL. Drafting of the manuscript: YW, GH. Critical revision of the manuscript for important intellectual content: YW, GH, JT, PJ, VS, RA, MM, PTK, BL. Study supervision: GH.

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