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Objective—To examine the association of serum γ-glutamyltransferase (GGT) with incident heart failure.

Methods and Results—We related serum GGT to the incidence of heart failure in 3544 (mean age, 44.5 years; 1833 women and 1711 men) Framingham Study participants who were free of heart failure and myocardial infarction. On follow-up (mean, 23.6 years), 188 participants (77 women) developed new-onset heart failure. In multivariable Cox proportional hazards regression models adjusting for standard risk factors and alcohol consumption as time-varying covariates (updated every 4 years), each SD increase in log-GGT was associated with a 1.39-fold risk of heart failure (95% CI, 1.20 to 1.62). The linearity of the association was confirmed by multivariable-adjusted splines, and the relations remained robust on additional adjustment for hepatic aminotransferases and C-reactive protein. Participants with a serum GGT level at the median or greater had a 1.71-fold risk of heart failure (95% CI, 1.21 to 2.41) compared with individuals with GGT concentrations less than the median. GGT marginally increased the model C-statistic from 0.85 to 0.86 but improved the risk reclassification modestly (net reclassification index, 5.7%; $P=0.01$).

Conclusion—In this prospective study of a large community-based sample, higher serum GGT concentrations within the "normal" range were associated with greater risk of heart failure and incrementally improved prediction of heart failure risk. (***Arterioscler Thromb Vasc Biol*. 2010;30:1855-1860.**)

Key Words: epidemiology ■ heart failure ■ risk factors ■ oxidative stress ■ γ-glutamyl transferase

In clinical practice, serum γ-glutamyltransferase (GGT) is measured as a marker of excessive alcohol consumption or hepatic disease.[1,2] Researchers,[3,4] during the past 3 decades, have reported that GGT is not only secreted by the liver but also by several other tissues, including the kidneys and vascular pericytes in the brain. Indeed, GGT has a primary role in glutathione metabolism and acts as an antioxidant in the metabolism of amino acids to maintain intracellular glutathione levels.[5] Experimentally, GGT may also have pro-oxidant activity by promoting the generation of free radical species in the presence of free metal ions, such as iron.[6] Overall, evidence from epidemiological studies shows that higher serum GGT concentrations within the so-called normal range are associated with greater risk of hypertension,[7] incident diabetes mellitus,[8–10] metabolic syndrome,[10,11] cardiovascular disease,[11–14] cardiovascular disease–associated mortality,[15,16] and all-cause mortality.[17] These associations of GGT with adverse sequelae were independent of alcohol consumption.

More recently, investigators have focused on serum GGT concentrations in those with heart failure. Limited data indicate that GGT concentrations are higher in patients with prevalent heart failure[18,19] and are a marker of increased mortality risk.[15] However, the association of serum GGT concentrations with the incidence of heart failure has not been elucidated. Therefore, in the present study, we evaluated the association of serum GGT concentrations with the incidence of heart failure prospectively in a large community-based sample of individuals who were free of heart failure and myocardial infarction (MI).

Methods

Study Participants

The Framingham Heart Study began in 1948 with the enrollment of 5209 participants into the original cohort. In 1972, the children (and the respective spouses) of the original cohort participants were enrolled into the Framingham Offspring Study (N=5124).[20] All participants from the Framingham Offspring Study (n=3792) who attended the second examination cycle (1978 to 1982) with available data on serum GGT concentrations were eligible for the present investigation (n=3696). In addition, we excluded participants with prevalent heart failure or a previous MI, yielding a final sample of

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3544 individuals (1833 women) for the present study. All participants provided written informed consent, and the study protocol was approved by the institutional review board of Boston University Medical Center.

Measurement of Risk Factors

At each Framingham Heart Study visit, attendees undergo a physical examination and complete a medical history form (by a heart study physician), take anthropometric tests, and undergo a laboratory assessment of vascular risk factors. For the present investigations, hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.[21] Participants who smoked cigarettes regularly during the year preceding the heart study visit were considered "current" smokers. Alcohol intake was assessed by averaging the self-reported weekly consumption of alcoholic drinks. Valve disease was defined as the presence of any diastolic murmur or of a systolic murmur of grade 3/6 or greater on physical examination. Diabetes was defined as a fasting blood glucose level of 126 mg/dL or greater or the use of any hypoglycemic agent.

Measurement of GGT and Other Biomarkers

After an overnight fast, participants underwent phlebotomy, the blood was immediately centrifuged, and plasma and serum were separated and stored under −20°C until assayed. GGT activity was measured in plasma by spectrophotometry (Quest Diagnostics, MedPath, Teterboro, NJ), as previously described.[11] The interassay coefficient of variation for GGT measured using spectrophotometry is less than 6%.[22]

Serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels were measured using standardized assays. High-sensitivity C-reactive protein (hsCRP) was measured using a nephelometer (model BN100; Dade Behring, Deerfield, Ill).

Assessment of Heart Failure on Follow-Up

The follow-up for the current investigation was from the second examination (1979–1982) through December 2007. All Framingham Heart Study participants are under continuous surveillance for the development of new cardiovascular disease events, including heart failure. A team of 3 physician investigators reviews all medical records (findings from heart study examinations, physician office visits, and hospitalization records) for adjudicating possible heart failure events. A diagnosis of heart failure in the Framingham Heart Study is based on the presence of 2 major, or 1 major and 2 minor, criteria. Briefly, the major criteria include the presence of paroxysmal nocturnal dyspnea, jugular venous distension, orthopnea, hepatojugular reflux, pulmonary rales, acute pulmonary edema, third heart sound, cardiomegaly on a chest radiograph, central venous pressure of greater than 16 cm H_2O, and weight loss of greater than 4.5 kg during the first 5 days of treatment for suspected heart failure. Minor criteria include bilateral ankle edema, exertional dyspnea, nocturnal cough, hepatomegaly, pleural effusion, and heart rate of greater than 120 bpm. A detailed description of the adjudication of heart failure events has been previously published.[23]

Statistical Analyses

The baseline characteristics of the study sample were assessed according to sex. First, we calculated the age-adjusted cumulative incidence of heart failure for values of GGT less than versus at or greater than the median level using Poisson regression. Cumulative incidence curves were constructed for these 2 groups, and the incidence of heart failure was compared using the log-rank test. Then, after confirming that the assumption of proportionality of hazards was met, we used multivariable Cox proportional hazards regression models to relate serum GGT concentrations to the incidence of heart failure. GGT concentrations were sex pooled and naturally logarithmically transformed to normalize the skewed distribution. Serum GGT was also modeled as a binary variable comparing categories at median or greater levels with less than median concentrations (that served as the referent category).

Table 1. Baseline Characteristics of Study Participants*

Characteristic	Men (n=1717)	Women (n=1833)
Age, y	44.7 (10.3)	44.3 (9.9)
Height, cm	175.0 (6.9)	161.0 (6.4)
Weight, kg	81.9 (12.2)	63.9 (13.1)
Body mass index†	26.9 (3.7)	24.9 (4.8)
Blood pressure, mm Hg		
Systolic	126 (16)	119 (17)
Diastolic	81 (9)	75 (9)
Hypertension, %	28.0	17.2
Treatment for hypertension, %	10.3	8.5
Diabetes mellitus, %	6.0	2.7
Smoking, %	35.4	36.8
Alcohol, drinks/wk	5.1 (6.2)	2.2 (3.1)
Valve disease, %‡	0.3	0.7
Total to HDL cholesterol ratio	5.1 (1.6)	4.0 (1.3)
Aspartate aminotransferase, IU/L	24 (12)	19 (11)
Alanine aminotransferase, IU/L	31 (19)	21 (15)
hsCRP, mg/dL	2.7 (5.3)	2.3 (4.4)
GGT, median (Q1–Q3), U/L§	16 (11–25)	9 (7–14)
Log GGT	2.8 (0.6)	2.3 (0.6)

GGT indicates γ-glutamyltransferase; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Q, quartile.

*Data are given as mean (SD) unless otherwise indicated.

†Calculated as weight in kilograms divided by height in meters squared.

‡Defined as the presence of any diastolic murmur or a systolic murmur of 3/6 or greater on physical examination findings.

§Q1 is 0.43 U/L; and Q3, 2.46 U/L.

All models were adjusted for the following covariates in a hierarchical fashion: (1) age and sex; (2) age, sex, body mass index, diabetes, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total to HDL cholesterol ratio, valve disease, and history of MI; (3) all covariates in model 2 were updated every 4 years as time-dependent covariates; and (4) all covariates in model 3, with additional adjustment for aspartate aminotransferase, alanine aminotransferase, and hsCRP (all measured at the baseline examination).

Secondary Analyses

To assess for any potential nonlinearity of relations between serum GGT and incidence of heart failure, we examined multivariable generalized additive models using penalized splines,[24,25] adjusting for all the covariates in multivariable model 2. We also evaluated for effect modification by age, body mass index, hypertension, and alcohol intake by incorporating interaction terms in the multivariable models examining the association of serum GGT (log-transformed) with heart failure risk. We examined the incidence of heart failure using Cox models by comparing heart failure incidence in the 2 groups, defined by the sex-specific median cutoff for GGT level (versus using the sex-pooled median threshold of our primary analyses).

We also assessed the incremental contribution of GGT levels to the prediction of congestive heart failure risk by estimating the increment in the model C-statistic (comparing multivariable models with and without GGT) by calculating the proportion of people at risk reclassified appropriately (risk reclassification) and calibration indexes.[26] Because risk reclassification requires categorization of

Table 2. Age-Adjusted Cumulative Incidence Rates of Heart Failure According to Serum GGT Level

Serum GGT Level*	No. of Events	No. of Individuals at Risk	Age- and Sex-Adjusted Incidence Rates of Heart Failure per 1000 Person-Years (95% Poisson CI)
Less than the median	53	1845	1.93 (1.45–2.53)
At or greater than the median	135	1699	3.35 (2.81–3.96)

GGT indicates γ-glutamyltransferase.
*The median cut point for serum GGT concentration was 12 U/L.

longitudinal risk (in this instance, 20-year risk of heart failure), we empirically (in the absence of an accepted grouping of risk) defined "low," "intermediate," and "high" risk categories as follows (for both outcomes): 0% to less than 2%, 2% to 8%, and greater than 8%.

All analyses were performed using commercially available software (SAS 9.1; SAS Institute Inc, Cary, NC), and S-plus, Version 8.0, was used for plotting regression splines. $P<0.05$ (2 sided) was considered statistically significant.

Results

The baseline characteristics of study participants are given in Table 1 according to sex. Median GGT concentrations in our young middle-aged sample ranged from 9 U/L (women) to 16 U/L (men). As previously reported,[11] the clinical correlates of circulating GGT included age, male sex, smoking, alcohol consumption, body mass index, low-density lipoprotein cholesterol concentration, triglyceride levels, diastolic blood pressure, and use of antihypertensive medications.

On follow-up (mean, 23.6 years; range, 0 to 28.2 years), 188 participants (77 women) developed heart failure. Age- and sex-adjusted incidence rates of heart failure were approximately 75% higher for participants with a serum GGT concentration at the median or greater (versus those with a concentration less than the median) (Table 2).

Continuous Increase in Serum GGT Concentration and Heart Failure Risk

In age- and sex-adjusted Cox models, each SD increase in log GGT was associated with a 49% higher risk of heart failure (Table 3). In multivariable models, each SD increase in log GGT was associated with a 26% to 36% higher risk of heart failure in models with baseline and time-varying covariates, respectively. These results remained unchanged after adjustment for hsCRP and other liver enzymes (aminotransferases). Additional adjustment for alkaline phosphatase also did not change our primary results (hazard ratio per SD increase in log GGT, 1.31; 95% CI, 1.09 to 1.57). Penalized splines demonstrated a graded linear increase in the risk of heart failure with increasing serum GGT concentrations (Figure 1). In addition, when individuals with a serum GGT concentration higher than the normal levels (>40 U/L in women and >50 U/L in men) were excluded (n=3162), the association of higher log GGT with incident heart failure remained robust (hazard ratio, 1.36; 95% CI, 1.08 to 1.67; $P=0.007$).

Serum GGT Concentration at or Greater Versus Less Than the Median and Heart Failure Risk

Cumulative incidence curves demonstrated a greater risk of new-onset heart failure among individuals with a serum GGT concentration at or greater than the median compared with those with levels less than the median ($P<0.001$, log-rank test) (Figure 2). In Cox regression models adjusting for age and sex, participants with a median or greater serum GGT concentration had a more than 2-fold risk of heart failure compared with individuals with concentrations less than the median (Table 3). After adjustment for baseline covariates, the risk of heart failure was attenuated, with a 55% higher risk in those with GGT concentrations at or greater than the median. These results remained robust when covariates were updated every 4 years and after adjusting for liver enzymes and hsCRP (Table 3).

Secondary Analyses

We did not observe any effect modification by age, sex, hypertension, body mass index, or alcohol intake in the relations of log GGT to incident heart failure ($P>0.05$ for all probability values for interaction terms). When individuals were dichotomized using the sex-specific median concentrations of serum GGT, the association of GGT with heart

Table 3. Cox Proportional Hazard Regression Models Examining the Relations of Serum GGT Concentration to the Incidence of Heart Failure

	Age- and Sex-Adjusted Data		Multivariable Model 1*		Multivariable Model 2†		Multivariable Model 3‡	
Variable	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value
Log GGT per SD increment	1.49 (1.30–1.69)	<0.001	1.26 (1.09–1.46)	0.002	1.39 (1.20–1.62)	<0.001	1.36 (1.15–1.62)	<0.001
Categorical model								
Less than the median	Referent	<0.001	Referent	0.02	Referent	0.003	Referent	0.02
At or greater than the median	2.19 (1.57–3.01)		1.55 (1.09–2.20)		1.71 (1.21–2.41)		1.57 (1.08–2.30)	

GGT indicates γ-glutamyltransferase.
*Multivariable model 1 was adjusted for age, sex, body mass index, diabetes mellitus, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total to high-density lipoprotein cholesterol ratio, valve disease, and history of myocardial infarction.
†Multivariable model 2 was adjusted for all covariates in model 1 in time-varying fashion (updating every 4 years), except for age and sex.
‡Multivariable model 3 was adjusted for all covariates in model 2 plus aspartate aminotransferase, alanine aminotransferase, and high-sensitivity C-reactive protein.

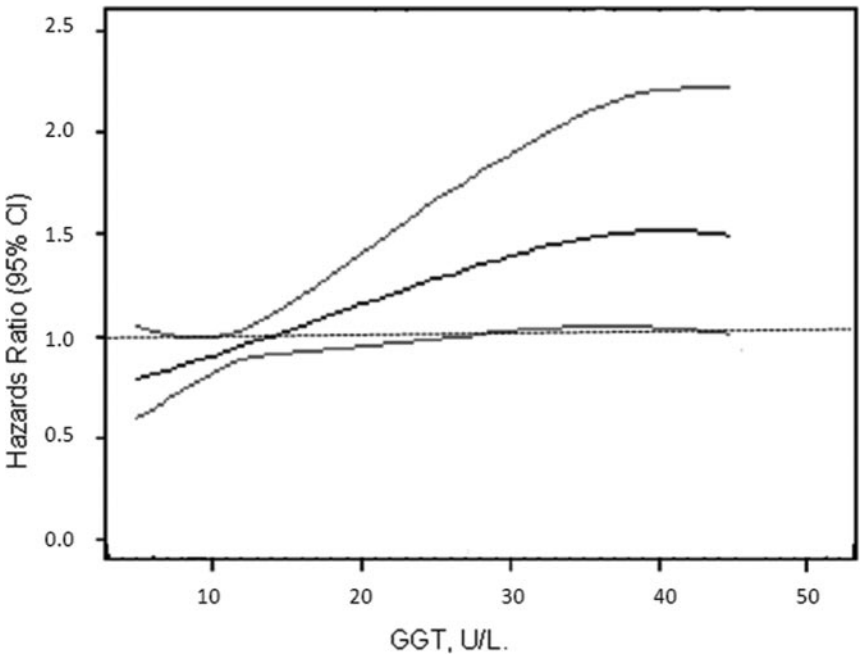

Figure 1. Regression spline curve based on multivariable models (adjusted for all baseline covariates) examining relations of serum GGT to the incidence of heart failure on follow-up. The estimated multivariable hazard ratios for heart failure in relation to serum GGT as a function of penalized regression splines are shown.

failure risk remained robust (hazard ratio, 1.68; 95% CI, 1.20 to 2.34) compared with those with levels less than the median (results for models adjusted for time-varying covariates, as in model 3 [described in the "Statistical Analyses" subsection of the "Methods" section]).

The addition of GGT to a multivariable model incorporating baseline covariates increased the C-statistic from 0.85 to 0.86 and improved the risk reclassification (net reclassification index, 5.7%; $P=0.01$) (Figure 3).

Discussion

Principal Findings

Our results were 3-fold. First, within the so-called normal range of serum GGT, higher concentrations were associated with greater risk of heart failure in a graded fashion. Values greater than the median level of serum GGT were associated with a 55% to 71% greater risk of heart failure compared with individuals with less than median levels. Second, relations of higher serum GGT to heart failure risk were maintained in models adjusting for MI and other covariates on follow up and on adjustment for aspartate aminotransferase or alanine aminotransferase and hsCRP. Third, GGT modestly improved prediction of heart failure risk, as judged by an improvement in the C-statistic and risk reclassification.

In prior studies, higher serum GGT concentration has been associated cross-sectionally with impaired coronary reserve flow in hypertensive patients[27] and in patients with cardiomyopathy[28] and longitudinally with greater mortality in patients who experienced heart failure.[15] To our knowledge, the present study is the first to examine the relations of serum GGT and risk of developing heart failure in a community-based sample.

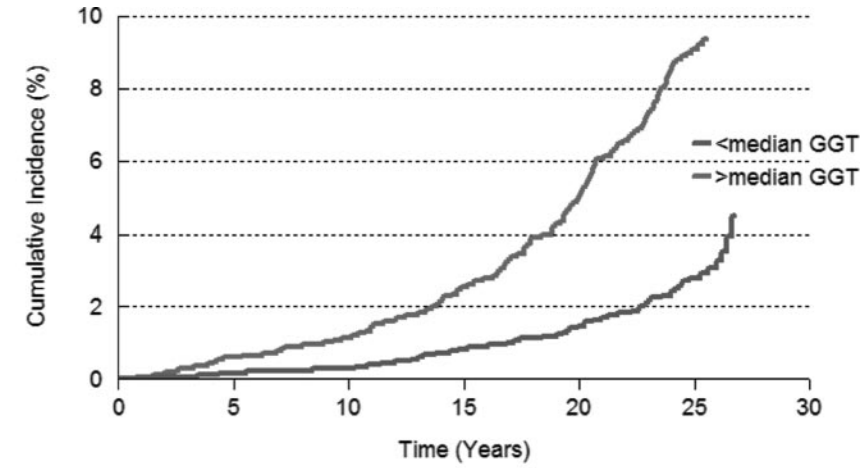

Figure 2. Age- and sex-adjusted cumulative incidence of heart failure by serum GGT median levels (at or greater than and less than the median).

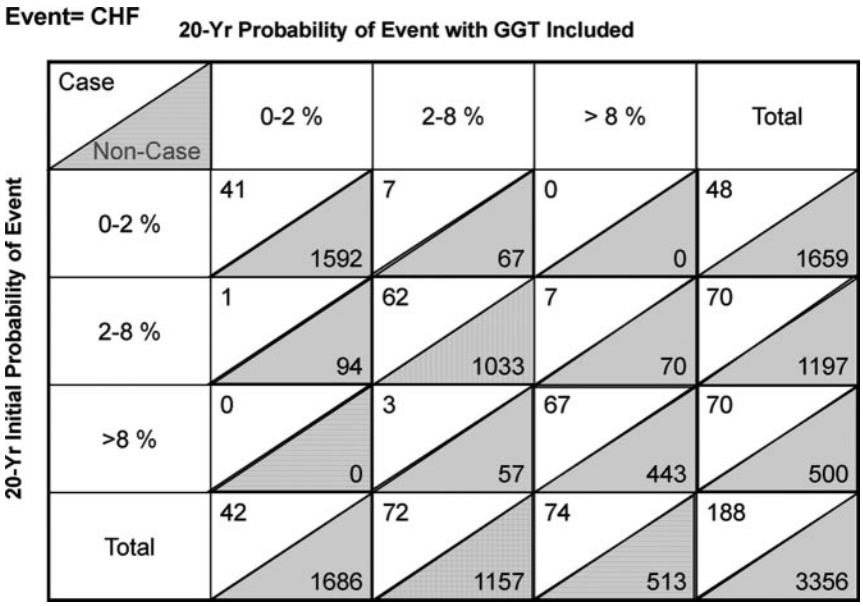

Figure 3. Risk reclassification table with and without serum GGT incorporation into the model on follow-up using the following "low-," "intermediate-," and "high" risk GGT categories of 0% to less than 2%, 2% to 8%, and greater than 8%, respectively.

Mechanisms

Several mechanisms are postulated in relation to serum GGT with greater cardiovascular disease risk, which may also be implicated in the development of heart failure. Higher serum GGT activity has been reported in atherosclerotic plaques and foam cells.[29] Because higher serum GGT levels have been associated with greater incidence of metabolic syndrome and incident diabetes,[10] GGT may also reflect the development of fatty liver and greater insulin resistance. However, our results were independent of the development of MI or diabetes on follow up and remained robust in analysis adjusting for other liver enzymes and hsCRP.[30,31]

Serum GGT has also been associated with production of reactive oxygen species and subsequent oxidation of lipids,[32] nucleic acids, and transcription factor proteins. These findings have suggested that GGT levels may be a marker of greater oxidative stress,[33] which has also been postulated as a mechanism for the development of heart failure.[34] In addition, serum GGT levels are inversely associated with several antioxidants, such as beta carotene, lycopene, and vitamin C,[35] and positively related to other biomarkers of oxidative stress, such as F-2 isoprostanes.[8] Thus, it is plausible that serum GGT concentrations reflect systemic oxidative stress and, therefore, can predict the development of heart failure. Another possible explanation of these relations could be the association of serum GGT with inflammation and atherogenesis.[14,29,30] Last, hepatic congestion as the result of heart failure could increase serum GGT levels, although this would likely happen in patients with chronic heart failure.[19,36,37] It is unclear whether the first episode of heart failure (as opposed to chronic heart failure) would have significant hepatic sinusoidal injury and would elevate serum GGT levels.[37,38]

Overall, the exact mechanism of GGT to predict the incidence of heart failure remains unclear. However, GGT does provide incremental risk prediction and the current information may warrant testing this biomarker in relation to other biomarkers (eg, B-type natriuretic peptide and growth-differentiating factor-15) for the prediction of heart failure using a multimarker approach.[39,40]

Strengths and Limitations

The present study has several strengths, including the community-based sample of men and women, a prospective design with a long follow-up, comprehensive adjustment for covariates at baseline, accounting for MI on follow-up as a time-varying covariate, and consistency of results in multiple analyses. However, there are several study limitations. We did not measure other biomarkers that reflect oxidative stress (eg, isoprostanes), which may have enabled us to elucidate the mechanisms underlying the observed association. Given the long follow-up, we were unable to characterize separately the association of GGT with incidence of heart failure with reduced versus preserved ejection fraction. Also, participants in our study were white Americans of European descent, which limits the generalizability of our results to other ethnic groups.

In conclusion, in a community-based sample, higher concentrations of serum GGT within the normal range were associated with greater risk of developing heart failure in individuals without a history of MI. Additional studies are needed to confirm our findings and to elucidate the underlying pathogenetic mechanisms.

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We had full access to the data, take responsibility for its integrity, and have read and agree to the manuscript as written.

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Disclosures

None.

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