γ-Glutamyl Transferase and Metabolic Risk Factors for Cardiovascular Disease

Hidenari SAKUTA, Takashi SUZUKI*, Hiroko YASUDA and Teizo ITO

Abstract

Objective **To elucidate the mechanism of the reported association between serum γ-glutamyl transferase (GGT) activity and cardiovascular mortality.**

Methods **Cross-sectional analysis of the relationship between serum GGT activity and the risk factors for cardiovascular disease was performed.**

Patients and materials **Middle-aged Japanese male personnel of the Self-Defense Forces who underwent retirement check-up.**

Results **Serum GGT activity was associated with total cholesterol, triglyceride, fasting plasma glucose, total homocysteine and systolic blood pressure. The association remained in the analysis adjusted for possible confounders including cigarette smoking, ethanol consumption and body mass index.**

Conclusion **The observed association between serum GGT and cardiovascular risk factors may partly explain the reported relationship between serum GGT activity and cardiovascular disease. Serum GGT activity may be regarded as a marker of cardiovascular risk factors or oxidative stress rather than a mere indicator of excessive ethanol consumption or obesity.**

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Key words: γ-glutamyl transferase, cardiovascular risk factor, glucose, cholesterol, homocysteine, blood pressure

Introduction

γ-Glutamyl transferase (GGT) is used as a sensitive indicator of hepatobiliary disorders including alcohol-related liver disease and fatty liver. Serum GGT activity is also associated with other pathological conditions, such as diabetes (1–5), obesity (5–8) and congestive heart failure (4, 9). Longitudinal clinical studies show that GGT activity predicts diabetes (10), development of diabetic complication (11), and mortality from ischemic heart disease and all causes (4, 5, 12, 13).

But the mechanism by which GGT is associated with cardiovascular disease is not elucidated. Several risk factors for cardiovascular disease, including body mass index (BMI), systolic blood pressure (SBP), physical inactivity, serum triglyceride (TG) and total cholesterol (TC), and fasting plasma glucose (FPG) (5, 6) have been shown to correlate with GGT. The correlation may partly explain the association between GGT and cardiovascular disease.

The association between GGT and total homocysteine (tHcy) has not been reported to date. In the present study we cross-sectionally analyzed the relationship between GGT and risk factors for cardiovascular disease including tHcy (14, 15) in middle-aged men.

Methods

Middle-aged male personnel of the Self-Defense Forces (SDFs) who underwent retirement check-up were studied (age 51–59, n=974). Serum TC, triglyceride, GGT and tHcy, and SBP were measured and BMI was calculated. Blood sample was collected early in the morning. Plasma tHcy was measured using a fluorescence polarization immunoassay kit (Abbott IMx™ Homocysteine, Dainabot, Tokyo, Japan) (16). Information about cigarette smoking, drinking habit and physical activity was obtained using a self-administered questionnaire. The average number of cigarettes smoked per day was asked. Daily consumption of ethanol was calculated from the information about type and volume of alcoholic beverage consumed. Physical activity was presented as the average frequency of physical activity (causing sweat) per week. The frequency was significantly correlated with the duration of both moderate and high intensity exercise in the population studied. Informed consent was obtained in order

From the Department of Internal Medicine and *the Department of Research and Laboratory, Self-Defense Forces Central Hospital, Tokyo
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Reprint requests should be addressed to Dr. Hidenari Sakuta, the Department of Education, GSDF Medical School, 1-2-24 Ikejiri, Setagaya-ku, Tokyo 154-8566

to participate in the study. The study protocol was approved by the Ethical Committee of the SDFs Central Hospital.

Means and standard deviation according to potential covariates were calculated. For continuous variables, categories were defined as quartiles according to the distribution across the entire study population. Subjects were categorized by quartiles of levels of cardiovascular risk factors. Actually, subjects were divided according to each variable, into four groups such that the number in each group was similar; there were no overlapping of categories. For quartiles of continuous variables, a trend test consisted of assessing the significance of the regression coefficient corresponding to the ordinal variables in the model. All analyses for GGT were done on logarithm of GGT, and the results were transformed back to the original scale. Thus, geometric means were used for GGT. The 95% confidence interval of the geometric mean was found by taking the antilogarithm of the 95% confidence interval of logarithm of GGT. The age was not taken into account in the analysis since the age ranged from 51 to 59 years in the study population. To elucidate the possible confounding effects of lifestyle factors, univariate regression analysis was undertaken with GGT as the dependent variable, and cigarette smoking, physical activity, ethanol consumption and BMI as independent variables. Descriptive data were expressed as mean±SD. Statistical analysis was performed with the statistical program Stat View ver. 5.0.

Results

Characteristics of the population studied are shown in Table 1. Serum GGT values did not show normal distribution (Fig. 1). Serum GGT activity was associated positively with cigarette smoking, ethanol consumption and BMI but not with physical activity in a simple regression analysis (Table 2). Serum GGT activity [geometric mean (95% confidence interval)] of current smokers was significantly higher than that of non-current smokers [44 (21–91) IU/*l* vs 40 (20–78) IU/*l*, p=0.019].

The association between serum GGT activity and quartiles of cardiovascular risk factors is presented in Table 3. A significant positive association between serum GGT activity and TC, TG, FPG, tHcy and SBP was observed. The association was also observed in the analysis adjusted for lifestyle-associated confounders including cigarette smoking, ethanol consumption, physical activity and BMI (Table 3).

Discussion

In the present study tHcy correlated with GGT activity. It has been shown that plasma tHcy is correlated with serum GGT activity in recipients of liver transplantation in univariate analysis but not in multivariate analysis (17). Cigarette smokers show elevated tHcy levels and GGT activity. But, the correlation between tHcy and GGT activity does not seem to be simply explained by cigarette smoking, since the correlation remained significant after adjustment for the

Table 1. Characteristic of the Middle-aged Men Studied

Number of cigarettes smoked	10.5±12.5/day
Frequency of exercise sufficient to induce a sweat	2.3±2.2/week
Ethanol consumption	35±31 ml/day
Body mass index	23.6±2.4 kg/m^2
Serum γ-glutamyl transferase*	42 [21–84] IU/*l*
Serum total cholesterol	213±33 mg/dl
Serum creatinine	0.86±0.13 mg/dl
Plasma fasting glucose	101±13 mg/dl
Plasma homocysteine	9.6±2.8 μmol/*l*
Systolic blood pressure	122±13 mmHg

Values are mean±SD (n=974). *Geometric mean [95% confidence interval].

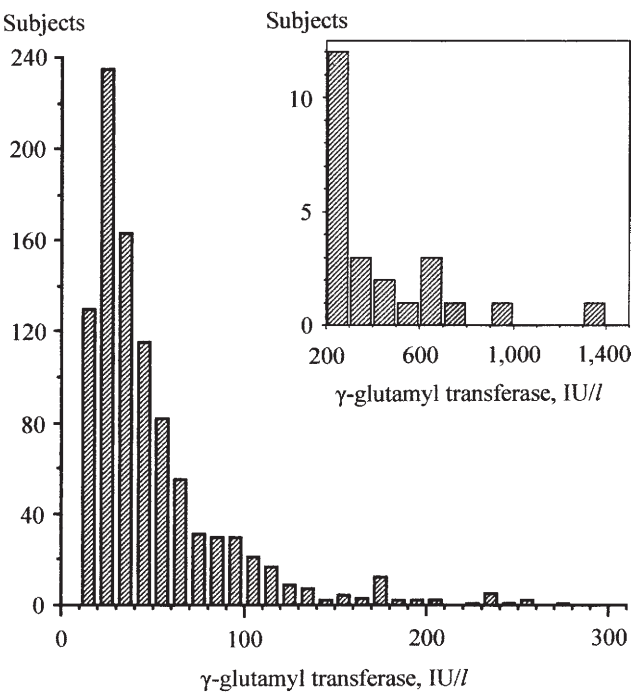

Figure 1. Distribution of serum γ-glutamyl transferase activity. Inset: Detailed distribution of the 24 subjects with a level of over 200 IU/*l*.

Table 2. Simple regression analysis of the correlation between serum γ-glutamyl transferase (logarithm) and lifestyle factors

	β	P value
Number of cigarettes smoked, /day	0.104	0.001
Frequency of exercise, /week	–0.043	0.176
Ethanol consumption, ml/day	0.327	<0.001
Body mass index, kg/m^2	0.196	<0.001

n=974. The logarithm of γ-glutamyl transferase is the dependent variable. β, standard regression coefficient.

Table 3. Serum γ-glutamyl transferase activity (geometric mean [95% confidence interval]) by quartiles of cardiovascular risk factors

	Quartile				P for trend
	1	2	3	4	
TC, mg/dl	–189	190–212	231–235	236–	<0.001
Case, n	243	246	238	247	0.001*
GGT, IU/*l*	35 [18–36]	39 [20–78]	45 [22–94]	48 [24–96]	
TG, mg/dl	–94	95–126	127–169	170–	<0.001
Case, n	246	242	241	245	<0.001*
GGT, IU/*l*	32 [16–63]	37 [20–68]	45 [24–86]	56 [27–115]	
FPG, mg/dl	–93	94–98	99–104	105–	<0.001
Case, n	232	255	232	255	<0.001*
GGT, IU/*l*	33 [18–61]	39 [21–73]	40 [21–74]	54 [24–121]	
tHcy, μmol/*l*	–7.89	7.90–9.10	9.11–10.69	10.70–	0.015
Case, n	240	253	234	247	0.009*
GGT, IU/*l*	39 [21–73]	39 [21–75]	43 [21–88]	45 [21–97]	
SBP, mmHg	–112	113–121	122–130	131–	<0.001
Case, n	235	266	241	232	<0.001*
GGT, IU/*l*	31 [17–56]	41 [21–84]	45 [22–93]	52 [26–104]	

*P values: adjusted for daily ethanol consumption, daily number of cigarettes smoked and body mass index. TC: total cholesterol, TG: triglyceride, FPG: fasting plasma glucose, tHcy: total homocysteine, SBP: systolic blood pressure.

number of cigarettes smoked and other lifestyle factors (Table 3). Furthermore, it remains to be significant in a stratified analysis confined to non-smokers (data not shown). Alcohol abuse is associated with higher levels of tHcy (18), but the relationship between tHcy levels and GGT activity may not be explained by alcoholism since alcoholics were not included in the present study. As far as we know, this is the first report which showed the positive association between tHcy levels and GGT activity in a relatively healthy population. This finding may partly explain the mechanism by which GGT activity predicts cardiovascular disease.

Free radical production leads to depletion of glutathione, induces the expression of GGT in liver (19) and subsequently elevates serum activity of GGT (20). It has been shown that GGT counteracts oxidative stress by breaking down extracellular glutathione and making component amino acids of glutathione available to the cells (20) and GGT inhibits tHcy-induced LDL oxidation *in vitro* (21). Homocysteine is a prooxidant. Thus, the prooxidant property of tHcy might explain the association between tHcy and GGT. Increased γ-GT might reflect a counter-reaction of human bodies against increased oxidative stress. The association between tHcy and direct markers of oxidative stress, however, must be investigated before proposing the hypothesis. In the present study TC, TG, FPG and SBP were also correlated with GGT. Interestingly these factors are implicated for the free radical production (21–26).

Alternatively, elevation of GGT might precede tHcy elevation. It has been shown that GGT shows a prooxidant property at the extracellular level, while GGT exerts a protective effect at intracellular levels (20). Although the mechanism has not been elucidated, GGT elevation precedes the occurrence of diabetes (10) and cardiovascular disease (4, 5). In this homology, GGT might precede tHcy elevation, but to clarify this, a prospective cohort study is necessary.

In conclusion, a significant association was observed between serum GGT activity and the cardiovascular risk factors studied including TC, TG, FPG, tHcy and SBP, independent of lifestyle factors.

References

1) Oli JM, Onwuamaeze IC, Okonkwo PO. Raised gamma glutamyl transferase in Nigerian diabetics: possible clinical implications. J Trop Med Hyg **86**: 179–183, 1983.
2) Salmela PI, Sotaniemi EA, Niemi M, Maentausta O. Liver function tests in diabetic patients. Diabetes Care **7**: 248–254, 1984.
3) Umeki S, Hisamoto N, Hara Y. Study on background factors associated with impaired glucose tolerance and/or diabetes mellitus. Acta Endocrinol (Copenh) **120**: 729–734, 1989.
4) Karlson BW, Wiklund O, Hallgren P, Sjolin M, Lindqvist J, Herlitz J. Ten-year mortality amongst patients with a very small or unconfirmed acute myocardial infarction in relation to clinical history, metabolic screening and signs of myocardial ischemia. J Intern Med **247**: 449–456, 2000.
5) Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyl-transferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol **142**: 699–708, 1995.
6) Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. J Intern Med **248**: 230–238, 2000.
7) Nilssen O, Forde OH, Brenn T. The Tromso Study. Distribution and population determinants of gamma-glutamyltransferase. Am J

Epidemiol **132**: 318–326, 1990.
8) Poikolainen K, Vartiainen E. Determinants of γ-glutamyltransferase: Positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol **146**: 1019–1024, 1997.
9) Betro MG, Oon RC, Edwards JB. Gamma-glutamyl transpeptidase and other liver function tests in myocardial infarction and heart failure. Am J Clin Pathol **60**: 679–683, 1973.
10) Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum γ-glutamyltransferase and risk of NIDDM. Diabetes Care **21**: 732–737, 1998.
11) Arkkila PE, Koskinen PJ, Kantola IM, Ronnemaa T, Seppanen E, Viikari JS. Diabetic complications are associated with liver enzyme activities in people with type 1 diabetes. Diabetes Res Clin Pract **52**: 113–118, 2001.
12) Brenner H, Rothenbacher D, Arndt V, Schuberth S, Fraisse E, Fliedner TM. Distribution, determinants, and prognostic value of γ-glutamyltransferase for all-cause mortality in a cohort of construction workers from southern Germany. Prev Med **26**: 305–310, 1997.
13) Emdin M, Passino C, Michelassi C, et al. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. Eur Heart J **22**: 1802–1807, 2001.
14) Welch GN, Loscalzo J. Homocysteine and atherosclerosis. N Engl J Med **338**: 1042–1050, 1998.
15) Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. Lancet **354**: 407–413, 1999.
16) Shipchandler MT, Moore EG. Rapid, fully automated measurement of plasma homocyst(e)ine with the Abbott IMx analyzer. Clin Chem **41**: 991–994, 1995.
17) Herrero JI, Quiroga J, Sangro B, et al. Hyperhomocysteinemia in liver transplant recipients: prevalence and multivariate analysis of predisposing factors. Liver Transpl **6**: 614–618, 2000.
18) Hultberg B, Berglund M, Andersson A, Frank A. Elevated plasma homocysteine in alcoholics. Alcohol Clin Exp Res **17**: 687–689, 1993.
19) Moriya S, Nagata S, Yokoyama H, et al. Expression of gamma-glutamyl transpeptidase mRNA after depletion of glutathione in rat liver. Alcohol Alcohol 29, Suppl **1**: 107–111, 1994.
20) Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci **38**: 263–355, 2001.
21) Bessede G, Miguet C, Gambert P, Neel D, Lizard G. Efficiency of homocysteine plus copper in inducing apoptosis is inversely proportional to γ-glutamyl transpeptidase activity. FASEB J **15**: 1927–1940, 2001.
22) Bhardwaj SK, Sharma P, Kaur G. Alterations in free radical scavenger system profile of type 1 diabetic rat brain. Mol Chem Neuropathol **35**: 187–202, 1998.
23) Lacy F, O'Connor DT, Schmid-Schonbein GW. Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. J Hypertens **16**: 291–303, 1998.
24) Ross R. Atherosclerosis—An inflammatory disease. N Engl J Med **340**: 115–126, 1999.
25) Haffner SM. Clinical relevance of the oxidative stress concept. Metabolism **49**: 2 Suppl 1: 30–34, 2000.
26) Zalba G, Beaumont J, San Jose G, Fortuno A, Fortuno MA, Diez J. Vascular oxidant stress: molecular mechanisms and pathophysiological implications. J Physiol Biochem **56**: 57–64, 2000.