Gamma-Glutamyl Transferase as a Risk Biomarker of Cardiovascular Disease

— Does It Have Another Face? —

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Serum γ -glutamyl transferase (GGT) is a major biomarker of hepatobiliary diseases and excessive alcohol intake,¹ but some previous studies have reported that serum GGT levels are associated with cardiovascular diseases (CVD). Initial studies focused on the role of serum GGT level in patients with coronary artery disease (CAD).^{2–4} A prospective study from Italy revealed a positive association of serum GGT level with the incidence of cardiac death and myocardial infarction (MI) in 469 ischemic patients with angiographically documented atherosclerotic CAD.⁴ Interestingly, the prognostic impact was particularly evident in a subset of patients who had multi-vessel disease and a history of MI. Moreover, the events were concentrated within the first 2 years of follow-up, and coronary revascularization abolished the prognostic value of GGT. Based on their findings, some authors suggested the prognostic significance of GGT correlates not only with the extent of CAD but also with plaque instability.⁵ Later, the same group confirmed GGT activity was detected in atheromatous plaques of the coronary and carotid arteries, which were colocalized with oxidized density lipoproteins and CD68⁺ foam cells.^{5–7} The hypothetical mechanism that links serum GGT level and CAD is the pro-oxidant effects of GGT.^{1,6} GGT induction can occur as a protective adaptation that allows cells access to more cysteine and thereby increases intracellular glutathione (GSH), which is protective against oxidative stress. On the other hand, there is evidence that GGT and GSH, particularly in the presence of iron, can lead to the formation of free radicals, lipid peroxidation, and mutagenesis, and therefore GGT activity is potentially harmful.¹ Namely, the catalytic activity of GGT, which is present on the surface of cell membranes and in serum, is responsible for the extracellular catabolism of the antioxidant GSH (**Figure**). Hydrolysis of GSH performed by GGT generates cysteinyl glycine, which has a role as a trigger of iron-dependent production of reactive oxygen species.^{1,6} As mentioned before, the pathological findings in coronary and carotid plaques support a mechanism of the evolution of atherosclerotic plaque and its destabilization through low-density lipoprotein oxidation within the plaque. Thus, serum GGT has been developed as a risk marker of clinical outcome in patients with CAD. During the past decade, evidence for

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GGT as a risk maker of CVD has accumulated through several population-based studies (**Table**). In a large-scale prospective cohort study from Austria,⁸ a significant dose-response relationship between serum GGT level and CVD mortality was confirmed, even after adjustment for established risk factors such as triglycerides, body mass index, cholesterol, systolic blood pressure, glucose, and smoking. Similarly, the Framingham Offspring Study predicted the association of GGT with adverse cardiovascular outcomes and death after adjustment for traditional cardiac risk factors and C-reactive protein.⁹

When focusing on heart failure (HF) as an epidemic of CVD, associations of serum GGT level with incidence have been reported.^{8,10,11} In particular, the Framingham Offspring Study revealed that higher GGT levels, even within the normal range, were associated with greater risk of developing HF in individuals without a history of MI.¹¹

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Table. Summary of Representative Studies of the Association of GGT With CVD

Study	Study population (% women)	Age (years)	Length of follow up (years)	Primary endpoint	HR
Ruttman et al (2005) ⁸ from VHM&PP Study	n=163,944 (54) Austria	19–95	Men 10.1±5.0 Women 10.8±4.9	CVD mortality	Men 1.66 (1.40–1.98)* Women 1.64 (1.36–1.97)
Lee et al (2007) ⁹ from Framingham Offspring Study	n=3,451 (52) USA	44±10	Mean 19.1	1. Onset of MetS 2. Incidence of CVD 3. All-cause mortality	1. 1.26 (1.18–1.35) [†] 2. 1.13 (1.03–1.26) 3. 1.26 (1.13–1.40)
Wang et al (2013) ¹⁰ from Health Examination Surveys	n=38,079 (52) Finland	25–74	Mean 14.5	Onset of heart failure	Men 1.79 (1.31–2.43) [‡] Women 1.76 (1.25–2.48)
Hozawa et al (2007) ¹⁵ from NIPPON DATA90	n=6,846 (60) Japan	≤30	Mean 9.6	CVD mortality [in never-drinkers]	Men 0.93 (0.62–1.41) [§] [0.58 (0.29–1.13)] Women 1.73 (1.13–2.63) [1.62 (1.11–2.37)]

*Per log increase, adjusted for age, BMI, systolic BP, cholesterol, triglycerides, glucose, smoking, work status, and year of examination. [†]Per log increase, adjusted for age, sex, BMI, diabetes, systolic BP, total/high-density lipoprotein cholesterol (HDL-C) ratio, current smoking, alcohol consumption, and CRP. [‡]Men: GGT <17.1 U/L vs. >68.0 U/L; women: GGT <11.0 U/L vs. >35 U/L; adjusted for age, sex, study area, study year, smoking, education, alcohol consumption, physical activity, history of valvular heart disease, BMI, systolic BP, total cholesterol at baseline and myocardial infarction, diabetes at baseline and during follow-up. [§]Per log increase, adjusted for age, alcohol consumption, cigarette smoking, HDL-C, total cholesterol, triglycerides, GOT, GPT, BMI, habitual exercise, systolic BP, use of antihypertensive medication and diabetes. BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; GGT, γ -glutamyl transferase; MetS, metabolic syndrome; NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged; VHM&PP, Vorarlberg Health Monitoring and Promotion Program.

The mechanism of predicting HF development remains unclear. In this issue of the Journal, Ryu et al¹² report that serum GGT levels were associated with left ventricular (LV) diastolic dysfunction and LV hypertrophy in a large cohort from South Korea. As the first point of the study, LV diastolic dysfunction and LV hypertrophy are proposed as the mechanism for developing HF in relation to elevation of serum GGT with the incidence of HF. Secondly, serum GGT might be a novel biomarker to stratify the risk of HF development in the subclinical population, because the findings are derived from a large sample and independent of potential cofounders. As well as plaque destabilization by oxidative stress, these authors suggest that such LV remodeling and impaired diastolic function also might be associated with oxidative stress.¹²

Despite the accumulated evidence, there are several concerns about using GGT as a risk maker of CVD. First, the serum GGT level may be a marker of alcohol consumption.¹³ A meta-analysis study reported GGT was positively associated with incident CAD and stroke in both women and men in European populations and among self-reported nondrinkers;¹⁴ however, a study based on the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA) revealed a positive association between GGT and CVD mortality among women only.¹⁵ Thus, even in nondrinkers, further evidence is needed and, furthermore, it may be hard to establish that evidence in drinkers. In addition, of major concern is the relationship of GGT with metabolic factors.^{8,16,17} Although the serum GGT level was an independent risk factor after adjustment for metabolic factors in previous studies,^{8–10} metabolic syndrome itself can affect the incidence and prognosis of HF.¹⁷ As many biomarkers linked to the metabolic syndrome have been reported, the incremental value of GGT to predict CVD should be revealed in addition to its independence of metabolic factors.

However, GGT is a very common, low-cost, and highly reproducible biomarker. There is great potential that such a major biomarker may have another “face” as a risk biomarker of CVD. To overcome several concerns related to

alcohol intake and metabolic factors, the hypothetical mechanism on the way from bench to bed should be clarified. Therefore, further studies are needed to open the black box in a rich field of future research.

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