Review

# Gamma-glutamyltransferase to Determine Cardiovascular Risk: Shifting the Paradigm Forward

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**Gamma-glutamyltransferase (GGT), regarded as a marker of excessive alcohol consumption or liver disturbances, is an enzyme catalyzing the first step in the extracellular degradation of the antioxidant glutathione (GSH) and may take part in atherogenesis. The marked relationship between GGT and the atherosclerotic process has shifted attention to the issue of whether its serum levels can aid in the detection of individuals at high risk for incident cardiovascular events. It is likely that the process entails the oxidation of low-density lipoprotein through GSH/GGT-dependent iron reduction within the plaque. In this context, oxidative stress is a probable mediator. Recent insights into the pathophysiological background of GGT in the precipitation and progression of atherosclerosis appear to be supported by relevant epidemiological observations as a cardiovascular risk predictor. Further understanding is, nevertheless, warranted to ameliorate the prognostic stratification of patients through GGT.**

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**Key words;** Cardiovascular risk, Gamma-glutamyltranferase, Oxidative stress, Prognosis

## Introduction

Many markers have been established as risk factors for atherosclerosis, which is the major cause of cardiovascular disease (CVD); however, this does not necessarily mean that they are suitable parameters for cardiovascular risk stratification. Association between the accumulation of risk factors and the estimated risk of CVD has often been a subject of interest as prophylactic strategies directed against these risk factors may contribute to reduce the burden of atherosclerosis, leading to a healthy life for people at increased risk[1-5]. In fact, the ability to reflect upstream inflammatory activity, steady levels without any significant circadian variation in persons of differing sexes, ages and ethnicities, and high stability with a long half-life of the actual substance are additional important criteria for an ideal biomarker in CVD. Gamma-glutamyltransferase (GGT), an enzyme catalyzing the first step in the extracellular degradation of the antioxidant glutathione (GSH), seems to have all the features of a true prognostic marker. It has been solely touted as a valid test for excessive alcohol consumption or liver disturbances in clinical practice. Mounting evidence shows that GGT may indeed take part in atherogenesis[6, 7], and emerge as an appealing biochemical risk indicator of cardiovascular morbidity and mortality. The marked relationship between GGT and atherosclerotic process has shifted attention to the principal issue of whether its serum levels can aid in the detection of individuals at high risk for incident cardiovascular events.

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## Landmark Clinical Trials

Several population-based investigations have noted relatively independent cross-sectional and prospective associations between serum GGT levels and certain cardiovascular risk factors[8-16]. Most of these studies refer to 'normal' serum GGT levels, which would otherwise raise no specific health concern. In a large longitudinal study (7613 middle-aged British men with 11-year follow-up), GGT levels in the normal range were strongly associated with all-cause mortality, and the association was mainly due to a significant in-

crease in deaths from ischemic heart disease (IHD) in the top quintile of GGT distribution[8]. Serum GGT was positively correlated with preexisting IHD, diabetes mellitus (DM), body mass index (BMI), antihypertensive medication, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, heart rate, smoking and blood glucose, while an inverse correlation was observed with physical activity and lung function. After adjustment for these variables, elevated GGT (highest quintile, ≥ 24 U/L, versus the remaining subjects) was still associated with a significant increase in mortality from all causes and from IHD. The increased risk of IHD mortality was more marked in patients with evidence of IHD at screening, particularly those with prior myocardial infarction (MI). The increased mortality in men without IHD was obviously dependent on other causes, whereas the findings in ischemic patients clearly pointed to a connection of GGT with underlying IHD.

The link between GGT and cardiovascular risk was likewise ascertained in a prospective cohort, which included a 6-year follow-up of 469 patients with angiographically documented coronary atherosclerosis[9]. After correction for other cardiovascular risk factors (age, smoking, serum cholesterol, left ventricular ejection fraction, BMI and DM) or confounding factors (serum alanine aminotransferase and self-reported alcohol consumption), the prognostic relevance of serum GGT levels for cardiac death and non-fatal MI was confirmed. In particular, the predictive power of serum GGT was higher in a subset of patients more prone to plaque complications characterized by the association of diffuse atherosclerosis ('multi-vessel disease') and previous MI (approximately 36% of the whole population). The risk progressively increased at two different GGT cut-off values (25 or 40 U/L, both considered within the normal range), and the event excess was concentrated in the first 3-year period. The prognostic value of serum GGT was thus related to the extent of coronary artery disease (CAD) and, interestingly, the prognostic significance of serum GGT disappeared among patients undergoing revascularization by angioplasty, regarded as a procedure capable of stabilizing plaque. Therefore, the unfavorable prognosis signaled by elevated serum GGT might specifically apply to patients with vulnerable plaques, and/or GGT likely interacts with the processes involved in plaque instability.

An Austrian study using a database collected over 17 years (1985-2001) from 163,944 volunteers of the Vorarlberg Health Monitoring and Promotion Program verified the prognostic value of serum GGT in discerning fatal events in chronic CAD, congestive heart failure and ischemic or hemorrhagic stroke[10]. The receiver operating characteristic analyses determined GGT cut-off values of 15.5 U/L for men and 10.5 U/L for women with corresponding sensitivities of 66% and 74%. A stronger (1.5-2 fold higher) prognostic significance was observed in younger (< 60 years of age) participants.

A recent investigation evaluated 3451 individuals in the Framingham Offspring Heart Study by looking at the cross-sectional correlation of GGT with multiple variables and longitudinal GGT correlation with new-onset metabolic syndrome, incident CVD, and death[11]. The study population was examined every 4 years over a 20-year span between 1971 and 1991. Cross-sectional analysis disclosed a significant positive GGT correlation with BMI, blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and blood glucose. Longitudinal 20-year study results revealed that 968 participants developed metabolic syndrome, 535 developed incident CVD, and 362 died. The risk of metabolic syndrome increased with higher GGT. After adjusting for established CVD risk factors, cumulative incidence of CVD and death displayed an increasing gradient of risk across GGT quartiles. Hozawa *et al.* documented that GGT displays a strong positive association with CVD mortality among Japanese women[12]. Even more recently, Emdin *et al.* reported the additive prognostic value of GGT in CAD along with C-reactive protein (CRP), an acute-phase reactant of hepatic origin and a sensitive marker for systemic inflammation, and fasting glucose[13].

Kawamoto *et al.* performed a cross-sectional study to examine whether serum GGT was associated with the prevalence of metabolic syndrome among community-dwelling individuals in Japan[14]. The authors recruited 793 men (mean age, 60 ± 14 years), and 1,073 women (mean age, 62 ± 12 years), free from any history relating to CVD during their annual health examination, from a single community. After adjustment for age, smoking status, drinking status, LDL cholesterol, uric acid, estimated glomerular filtration rate and alanine aminotransferase, the odds ratios for metabolic syndrome increased across serum GGT tertiles. Serum GGT was also significantly associated with the presence of individual components of metabolic syndrome in both genders. They concluded that higher serum GGT was significantly associated with metabolic syndrome and its components in the general population.

The relation of GGT and alcohol drinking with incident DM was recently scrutinized in the HIPOP-

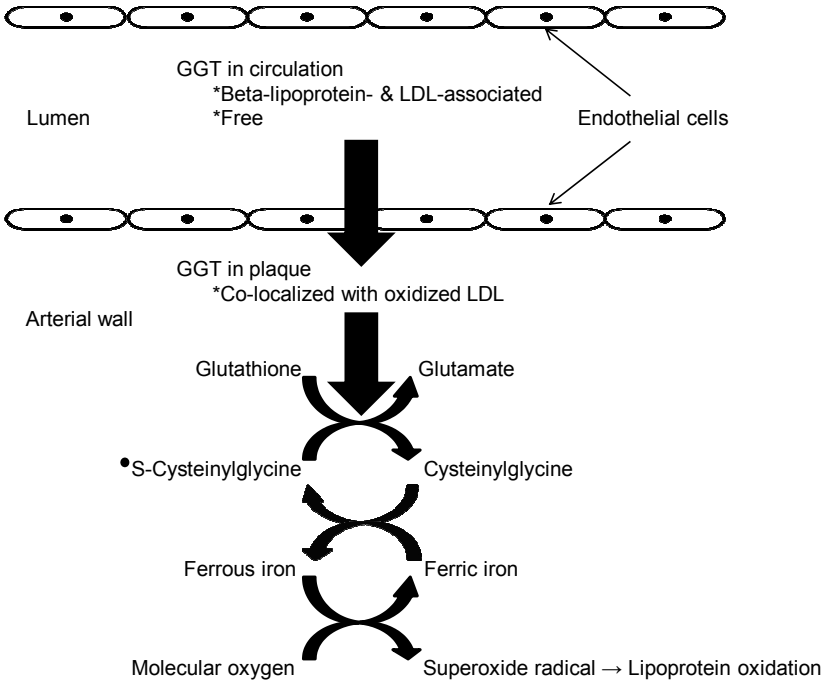


**Fig. 1.** Role of GGT in the formation of atheromatous plaque.
GGT, gamma-glutamyltransferase; LDL, low-density lipoprotein.

OHP Study[15]. A total of 3095 healthy male Japanese workers who did not have DM at baseline were followed for 4 years. Participants with higher GGT (≥ 27 U/L) showed an increased risk of incident DM irrespective of their drinking status or obesity.

Lastly, Ishizaka *et al.* explored the association between GGT and a marker of insulin resistance, homeostasis model assessment for insulin resistance (HOMA-IR), according to the drinking and smoking status[16]. After excluding former smokers and/or former drinkers, the data of 10,482 men who underwent general health screening were analyzed. The authors concluded that, although alcohol consumption showed a graded association with GGT and a U-shaped association with HOMA-IR, serum GGT can be used as a predictor of insulin resistance in current drinkers.

## Pathogenetic Role

The precise mechanism behind these associations remains largely unknown. It is likely that the pathogenesis entails the oxidation of LDL through GSH/GGT-dependent iron reduction within the plaque[17]. Hence, there are two possible explanations for the association between serum GGT and cardiovascular risk: either GGT derives in part from atheromatous plaques, which would be more common and diffuse in patients with adverse cardiovascular risk profiles, or GGT is associated with the risk factors even before the plaques are fully developed. In this context, oxidative stress might be a unifying mediator, because it is closely related to numerous pathological conditions, including atherosclerosis[6, 18]. It is also a fundamental component of various pathways implicated in inflammation[19]. A substantial association between GGT and CRP has been described implying that the elevation of serum GGT (conceivably acting as a marker of oxidative stress) is correlated with the subclinical microinflammatory response involved in the pathogenesis of atherosclerosis[20]; therefore, baseline GGT testing can plausibly have an adjunctive merit in estimating cardiovascular risk.

In essence, circulating GGT forms complexes with lipoproteins, thus suggesting that intense GGT levels within atheromatous lesions, co-localized with oxidized LDL, may derive from the deposition of LDL-associated GGT within the arterial wall and beta-lipoprotein-associated GGT increases with total serum GGT, supporting the hypothesis that increasing serum GGT levels may augment the entry of GGT-bound lipoproteins into the plaque (**Fig. 1**)[6, 7, 21]. A key question is whether GGT is just an innocent bystander or is causally involved in atherogenesis. In-

creased GGT levels are not simple side effects of the liver damage associated with metabolic syndrome. It has been observed that elevated serum GGT is an independent marker of the activation of systemic inflammation and increased oxidative stress, independent of its relationship with metabolic syndrome[22]. Based on current available data, it has recently been purported that an increase in serum levels of GGT, although within its reference range, is a promising predictor of cardiovascular risk[21, 23-26].

## Interventions and Implications

It is also pertinent to assess whether the incremental prognostic value of a novel risk marker can be modified by therapeutic interventions, thus decreasing the occurrence of cardiovascular events. Although no definite treatment has been developed to reduce GGT, and there is no direct evidence that the risk for incident cardiovascular events is lessened by decreasing GGT, data exist showing that fibrate therapy has favorable efficacy on diminishing serum GGT levels in hypertriglyceridemic patients as well as improving the lipid profile[27]. This is consistent with a seminal role for fatty liver in generating increased serum GGT and being associated with an increase in cardiovascular risk, and it provides a practical means of risk reduction[28].

On the other hand, a short-term trial of fibrate treatment among subjects with alcoholic fatty liver failed to lower serum GGT significantly, although serum TG levels fell substantially[29]. We do not know, at this stage, whether GGT would remain a significant cardiovascular risk index if serum levels of TG and very low-density lipoprotein were reduced by treatment, but published epidemiological studies suggest that it would. These outcomes thus may help toward a better comprehension of the reciprocal interrelationship between lipid variables and serum GGT levels. Moreover, compelling evidence indicates that human platelets may be a source of GGT[30, 31]. Accordingly, increased platelet turnover at the sites of atheromatous plaques may contribute to an increase in serum GGT levels. Similarly, other interventions, such as lifestyle changes, stopping alcohol drinking, and weight loss are also expected to have beneficial effects on serum GGT levels. Global cardiovascular risk reduction by agents possessing anti-inflammatory properties might be tentatively due to their lowering influences on both CRP and GGT.

In brief, it has been clarified that increased GGT levels are connected with the clinical course of coronary artery stenoses assessed by angiography. GGT may presumably reflect oxidative stress related to the extent and severity of atherosclerosis. Accumulating data indicate that GGT deposits in the arterial wall are a culprit during atherogenesis, colocalizing with oxidized LDL. In addition, GGT can actually catalyze the oxidation of LDL, a process implicated in the initiation and evolution of atherosclerotic lesions. Large-scale randomized trials are necessary to evaluate the effect of drugs currently used for the treatment of atherosclerosis on serum GGT levels.

## Concluding Considerations

Overall, subtle gradations in serum GGT may help predict the long-term cardiovascular prognosis, and GGT determination complementary to conventional risk models has potential implications for identifying those at increased cardiovascular risk who may benefit from preventive measures and need increased therapeutic effects[24]. Recent insights into the pathophysiological background of GGT in the precipitation and progression of atherosclerosis appear to be supported by epidemiological observations of its relevance as a cardiovascular risk predictor. It has been reported that serum GGT may contribute to the accumulation of GGT inside plaque[32]. Further understanding is nevertheless warranted regarding the interaction of GGT inside plaque with inflammation biomarkers, plasma lipoproteins, and other independent determinants to pinpoint the most risky combination and ameliorate the prognostic stratification of patients[21].

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