Role of gamma-glutamyltransferase in cardiovascular diseases

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Cardiovascular diseases are threatening human health with rising morbidity and mortality rates. Gamma-glutamyltransferase (GGT) has been found to be involved in the pathogenesis of cardiovascular diseases, especially coronary artery disease, and the prognosis of cardiovascular disease may be predicted by increasing GGT levels. GGT levels are related to cardiovascular emergencies of chronic heart failure, and an elevated GGT level has been shown to be an independent predictive maker for cardiac death and cardiac transplantation. Investigation of the role of GGT in the mechanism of cardiac diseases will be helpful in developing preventive strategies and treatment methods.

Key Words: *Coronary artery disease; Gamma-glutamyltransferase; Heart failure; Hypertension*

Cardiovascular diseases have been attracting increasing attention because of increasing morbidity and mortality rates, and threat to human health. Gamma-glutamyltransferase (GGT), an important enzyme in glutathione (GSH) metabolism, was previously found to be an indicator of liver or biliary tract diseases and alcohol consumption; however, more recently, GGT has shown to be involved in the development of cardiovascular disease. The progress and prognosis of cardiovascular disease may be predicted by increasing GGT levels, a tool preferable to other biochemical indicators such as analysis of blood lipid levels. Serum GGT levels have been shown to be an independent predictor of diabetes, hypertension, the metabolic syndrome and coronary artery disease (CAD) (1). The present review discusses GGT in cardiovascular and related diseases.

BIOCHARACTERISTICS OF GGT

Human GGT is a multigene family of proteins composed of seven GGT genes and pseudogenes. To date, the exact protein structure, gene-expression patterns and regulatory mechanisms of GGT have not been elucidated. Several GGT complementary DNA segments have been obtained from hepatoma cells, placenta, lung, pancreas and other tissues. These GGT complementary DNA transcripts share the same coding sequence, but their 5′-untranslated regions are different. Therefore, the transcriptional process of GGT was presumed to be controlled by multiple promoters in a linear arrangement similar to the TRE, AP-2 combining site and SP-1 cis elements that exist in the proximal region of the GGT gene.

GGT is a glycosylated protein that is partially embedded in the outer surface of the plasma membrane at the N-terminal transmembrane domain. Franzini et al (2) performed quantitative analysis of serum GGT fractions. In that study, four GGT fractions: big-GGT, medium-GGT, small-GGT and free-GGT fractions of different molecular weight (molecular masses >2000 kDa, 940 kDa, 140 kDa and 70 kDa, respectively) were detected by a procedure based on gel filtration chromatography, followed by postcolumn injection of a fluorescent GGT substrate. Comparatively, GGT activity was decided primarily by the free-GGT and small-GGT fractions. GGT catalyzes the transfer of the gamma-glutamyl moiety from GSH or GSH conjugated to acceptors such as amino acids, dipeptides and molecules with similar traits. GGT can provide cysteine, the rate-limiting amino acid, for GSH de novo synthesis by breaking down extracellular GSH into its constitutive amino acids. It is a vital step in maintaining in vivo homeostasis of GSH and cysteine.

GGT is an enzyme normally present in the serum and on the outer surface of numerous cell types (3). Serum GGT is especially active in the proximal renal tubule, pancreas and intestine, but primarily in the liver. In most cases, serum GGT levels are examined for the diagnosis of liver, gallbladder and biliary tract diseases (4), especially in alcoholic liver disease (5). GGT is particularly sensitive to alcohol consumption and may be elevated even when other liver function tests remain normal. Its circulating half-life is seven to 10 days, which is increased in alcohol-associated liver injury because of impaired clearance (6). In addition, changes in serum GGT levels can be affected by waist circumference and body mass index (7), hypertension (8), diabetes (9), hyperuricemia (10) and genetic factors (11).

GGT AND HYPERTENSION

Hypertension is the most common modifiable risk factor for cardiovascular disease, especially in middle-age individuals and the elderly. Recently, GGT has been found to be involved in the pathogenesis of hypertension. In a three-year follow-up study by Cheung et al (8), 235 hypertensive and 708 normotensive Hong Kong Chinese subjects were investigated for plasma alanine aminotransferase, alkaline phosphatase and GGT levels. Statistical analysis showed that plasma GGT, but not alkaline phosphatase, alanine aminotransferase or aspartate aminotransferase levels, was an independent predictor of new-onset hypertension. In another research project involving 10,988 participants (12), GGT showed strong positive correlations with systolic blood pressure and diastolic blood pressure, while demonstrating a positive linear correlation with body mass index, waist circumference, fasting plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid and high-sensitivity C-reactive protein (CRP) levels. Elevated serum GGT levels within the normal range are considered to be associated with a higher risk of incident hypertension, particularly in drinkers and nonoverweight individuals (13).

Some studies have explored GGT and its role in the development hypertension. Saijo et al (14) found a connection between GGT and an increased level of arterial stiffness. Celik et al (15) found that regardless of the mechanism, young patients with prehypertension exhibit higher serum GGT levels compared with healthy subjects. More importantly, increased GGT levels are independently associated with impaired aortic elasticity in patients with prehypertension (15). Serum GGT levels can be an alternative indicator of arterial stiffness in hypertension patients. This conclusion was supported by Song et al (16) in a study that involved 1387 participants.

GGT AND CAD

Although CAD is one of the most common types of heart disease, it is difficult to predict the risk of CAD and intervene at an early stage. GGT has been confirmed to play a role in the occurrence and progression of CAD, especially in prognosis judgment.

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Elevated levels of serum GGT are involved in the pathogenesis of CAD

GSH is a tripeptide comprised of three amino acids: gamma-glutamic acid, L-cysteine and L-glycine. Its primary biological function is to act as a nonenzymatic reducing agent to help keep cysteine thiol side chains in a reduced state on the surface of proteins. GSH also prevents oxidative stress in most cells and helps trap free radicals that can damage DNA and RNA. The physiological role of GGT is to initiate the hydrolysis of extracellular GSH by cleaving the gamma-glutamyl amide bond of the tripeptide to cysteine and other thiol compounds, which are known to promote LDL oxidation by reducing Fe(III) to redox-active Fe(II) (17). Recently, catalytically active GGT has been found within atherosclerotic coronary plaques from autopsy studies and surgical endoarterectomies (18). Some researchers believe that serum GGT is partially adsorbed onto LDL lipoproteins, which can carry GGT activity inside the plaque (in proportion with serum GGT levels), in which free iron has also been described (19). GGT-mediated reactions catalyze the oxidation of LDL lipoproteins, likely contributing to oxidative events influencing plaque evolution and rupture (20). GGT has been considered to play a central role in the formation of the fibrous cap, apoptosis of cellular elements of the lesion, plaque erosion and rupture, enhanced platelet aggregation and thrombosis (19).

Some researchers have focused on the relationship between serum GGT level and coronary blood flow. Caliskan et al (21) confirmed that serum GGT level is independently associated with coronary flow reserve impairment in hypertensive patients. The investigators reported that serum GGT level was an independent marker of target organ damage in hypertensive subjects without concomitant risk factors. Sen et al (22) evaluated the relationship between elevated serum GGT activity and slow coronary flow and found that the mean thrombosis in myocardial infarction frame count showed a positive and moderate correlation with serum GGT activity. Serum GGT activity was the only independent predictor of the mean thrombosis in myocardial infarction frame count (22).

CAD prognosis can be predicted by measurement of serum GGT levels

It has been confirmed that elevated CRP levels are a predictor of adverse outcomes in patients with acute coronary syndromes and help to identify patients who may be at risk for cardiovascular complications (23). Emiroglu et al (24) performed a comparative analysis of serum GGT and high-sensitivity CRP (hs-CRP) in a trial involving 219 patients presenting with acute coronary syndrome (ACS) and 51 control subjects. Results of the analysis showed that serum GGT and hs-CRP levels were higher in ACS patients and that a moderate but significant correlation was present between GGT and hs-CRP (24). In another prospective study investigating the clinical significance of serum GGT levels during the early postmyocardial infarction period (25), researchers found a significant positive correlation between serum GGT and hs-CRP and homocysteine levels. Left ventricular (LV) end-diastolic diameter remained independently associated with serum GGT activity on day 5 following acute myocardial infarction. Although this study was limited by its small sample size, short-term follow-up period and a noncontrolled study design, the authors reported that serum GGT played a potential role in predicting LV dilation and dysfunction during the early postmyocardial infarction period. The study by Emdin et al (26) agreed with this conclusion. They reported that GGT level – similar to CRP and fasting glucose – was an independent risk factor in patients with established CAD in a study evaluating 474 subjects with angiographically documented CAD. Low serum GGT levels were helpful in identifying patients with the lowest risk of cardiac death (26).

Other studies have focused on the relationship between GGT and types of CAD. Dogan et al (27) found that GGT levels were higher in patients with significant stenosis compared with those without significant stenosis in a study that investigated the association between significant stenosis and major cardiac events (MACE) in 237 non-ST elevation ACS patients. MACE-free survival was slightly poorer in ACS patients with GGT levels in the upper tertile compared with those with levels in the lower tertile at 12 months (27). In another study that involved 425 patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (28), although the TIMI flow percentages were similar in the three GGT tertiles (32%, 45% and 42%), serum GGT activity was associated with in-hospital MACE. Breitling et al (29) reported that serum GGT level was associated with prognosis independent of a variety of established risk markers in patients with stable CAD in a study that included 1152 participants of an in-patient ACS rehabilitation program. The association appeared to be similar to that reported for primary cardiovascular disease, which should prompt additional studies of its clinical utility in cardiovascular patient care (29). In addition, serum GGT activity was found to be associated with higher occlusion rates of venous bypass grafts in a study investigating the relationship between serum GGT levels and saphenous vein bypass graft disease at least one year after coronary artery bypass graft surgery (30). GGT levels have also been confirmed to be an independent predictor of early mortality in STEMI patients without previously known diabetes who underwent mechanical revascularization (31).

GGT AND CARDIAC SYNDROME X

Cardiac syndrome X (CSX) is a condition in which patients with no physical findings of CAD experience angina. Although it is not clear what causes CSX, some recent studies have investigated the role of GGT. Demir et al (32) compared serum GGT levels between patients with CSX and asymptomatic healthy individuals. In this study, serum GGT activity in patients with CSX was confirmed to be higher than in healthy controls; moreover, GGT activity was further increased in patients with CSX who also had the metabolic syndrome. The relationship between serum GGT activity and carotid intima media thickness in patients with CSX was evaluated by Yagmur et al (33). Serum GGT activity in patients with CSX was shown to be as high as that in patients with CAD. A significant correlation was found between GGT activity and carotid intima media thickness measurements, but serum GGT activity did not correlate with serum CRP levels in patients with CSX. It was suggested that increased GGT levels play a role in the pathogenesis of the microvascular atherosclerotic process of CSX (33).

GGT AND HEART FAILURE

It has been shown that elevated serum GGT activity exists in the early stages of heart failure (HF), the final and common pathway of all cardiovascular diseases (34). In an evaluation of 1087 ambulatory patients with chronic HF, Ess et al (35) found the prevalence of elevated GGT to be 43% in men and 48% in women. GGT was independently associated with adverse outcomes in these patients. This finding further highlights the clinical importance of GGT in cardiovascular disease (35). In a prospective study involving 3494 men 60 to 79 years of age with no diagnosed HF or myocardial infarction followed-up for a mean period of nine years, in whom there were 168 incident cases of HF (36), elevated GGT was associated with significantly increased risk of incident HF in men <70 years of age but not in men ≥70 years of age. The relevance of serum GGT and disease severity in chronic HF was investigated by Poelzl et al (37), who found that serum GGT was associated with severity of HF as assessed by New York Heart Association class, LV ejection fraction and amino-terminal pro-B-type natriuretic peptide levels. Increased GGT levels are an independent predictor of death or heart transplantation. GGT may provide additional prognostic information, especially in patients with mild HF (37).

Other studies have focused on the mechanism of elevated serum GGT levels in HF patients to explore new methods of intervention in HF progression. Zheng et al (38) identified the role of GGT in reversing pathogenic K^+ channel remodelling in the diseased heart. They found that GSH_o elicits GGT- and reactive oxygen species-dependent transactivation of tyrosine kinase signalling that upregulates K^+ channel activity or expression via redox-mediated mechanisms. The signalling events stimulated by GGT catalysis of GSH_o may be a therapeutic

target to reverse pathogenic electrical remodelling of the failing heart (38). Higher central venous pressure has also been found to be related to serum GGT levels in HF patients, and abnormal liver function was attributed to increased serum GGT levels (39). However, further studies should be undertaken to elucidate the mechanism of elevated serum GGT levels in the progression of HF.

GGT AND OTHER CARDIOVASCULAR DISEASES

The relationship between serum GGT and acute pulmonary embolism (PE) has recently attracted some attention. Serum GGT was confirmed by Zorlu et al (40) to be associated with an increased risk for acute PE-related early mortality in a study evaluating 127 consecutive patients with confirmed PE. The authors reported that a high GGT level was associated with poorer hemodynamic parameters, and it appeared that GGT helped risk stratification in patients with acute PE. Nordenholz (41) confirmed this conclusion, but pointed out that serum GGT would need to be validated in a larger, more heterogeneous population before consideration as a stand-alone risk-stratifying marker of acute PE. Another study investigating the role of serum GGT in elderly patients with nonvalvular atrial fibrillation (AF) (42) indicated that serum GGT activity was significantly higher in patients with AF compared with those without AF. Serum GGT activity was independently associated with chronic nonvalvular AF. In addition, the significant correlation between GGT and acute glucose dysmetabolism (as indicated by admission glycemia and insulin resistance) can account, at least in part, for the prognostic role of GGT (31). Zhang et al (43) examined the relationship between LV diastolic function and GGT level in diabetic individuals. This study showed that metabolic parameters could affect diastolic function more than systolic functions, and that GGT may be an additional marker of diastolic dysfunction in diabetes patients with cardiovascular disease apart from known cardiovascular disease risk factors (43). Serum GGT may be a biological marker in the formulation of diabetes risk assessments (9).

SUMMARY

Although frequently used as an indicator of liver or biliary tract diseases, or alcohol consumption in clinical practice, serum GGT has been confirmed to be involved in cardiovascular disease mechanisms. Future studies, including more that examine molecular mechanisms, will help provide insight into the nature of cardiovascular diseases and lead to new preventive and treatment strategies.

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