

REVIEW PAPER

Gamma-Glutamyl Transferase: A Novel Cardiovascular Risk BioMarker

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Gamma-glutamyl transferase (GGT) is a second-generation enzymatic liver function test available for several decades, initially used as a sensitive indicator of alcohol ingestion, hepatic inflammation, fatty liver disease, and hepatitis. Longitudinal and cross-sectional investigational studies since 1990 have associated GGT with an increase in all-cause mortality, as well as chronic heart disease events such as congestive heart failure and components of the metabolic syndrome (abnormal body mass index and levels of high-density lipoprotein cholesterol, glucose, triglycerides, and systolic and diastolic blood pressure). In the upper reference range, GGT was found to be an independent biomarker of the metabolic syndrome, with a 20% per GGT quartile trend rise. Additionally, GGT was positively correlated with an 18% per quartile risk of cardiovascular events and a 26% per quartile increased risk of all-cause mortality. Furthermore, it may be considered a biomarker for "oxidative stress" associated with glutathione metabolism and possibly a "proatherogenic" marker because of its indirect relationship in the biochemical steps to low-density lipoprotein cholesterol oxidation. GGT is becoming an important addition to the multimarker approach to cardiovascular risk evaluation. It should be considered a valuable adjunct in stratifying patient risk and in assessing the aggressiveness of appropriate treatment, with hopes of preventing unnecessary cardiac events and deaths in future years. Prev Cardiol. 2010;13:36–41. ©2009 Wiley Periodicals, Inc.

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Gamma-glutamyl transferase (GGT) is a second-generation enzymatic liver function test (LFT) that became commercially available about 30 years ago and was used initially as a sensitive marker of hepatic inflammation. Originally called GGTP (gamma-glutamyl transpeptidase), it was felt to be the most sensitive LFT indicator of alcohol toxicity. It is in the class of hepatic enzymes similar to aspartic aminotransferase (AST), previously called serum glutamic oxaloacetic transaminase; alanine aminotransferase (ALT), previously called serum glutamic pyruvic transaminase; and alkaline phosphatase (ALP).

GGT is a glycoprotein with a molecular weight of 68,000 daltons, consisting of 2 proteins, the larger chain with a molecular weight of 46,000 daltons and the smaller one with a molecular weight of 22,000 daltons.

At higher than normal serum levels, liver function tests measure the severity of hepatic inflammation, cellular injury, or obstruction. ALT is found mainly in the liver and is elevated with hepatic inflammation or injury. AST is located in both hepatocytes and muscle cells and is elevated in the serum with hepatic cell involvement, skeletal muscle fiber inflammation, and myocardial cell injury. ALP is found in the hepatobiliary track and is markedly elevated with biliary track obstruction.

GGT is found not only in the liver but in other organ tissues, including the kidney,¹ lung, pancreas, and vascular endothelium, as well as in the extracellular fluid attached to α and β lipoproteins² and albumin carrier molecules.³ It is a sensitive indicator of hepatic cell inflammation and hepatic intracellular triglyceride accumulation as seen in obesity,⁴ nonalcoholic fatty liver disease (NAFLD),⁵ non-insulin dependent diabetes mellitus (NIDDM),⁶ and insulin resistance.⁷

BACKGROUND

The GGT enzymatic test has been available for several decades and was initially viewed as a sensitive indicator of ethanol ingestion. However, in 1990, the Tromso study⁸ from Scandinavia described basic distribution and population patterns of GGT. In 1993, Conigrave,⁹ working on alcohol-related



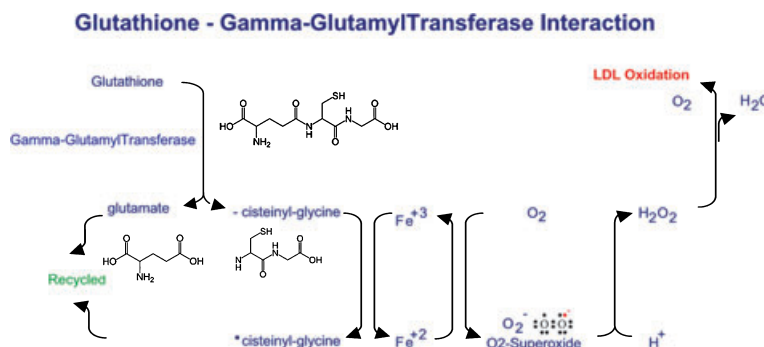


Figure 1. Steps in the gamma-glutamyl transferase enzyme reaction and its relationship to the oxidation of low-density lipoprotein (LDL) cholesterol.

research and associated testing, described an unexpected increase in GGT levels associated with cardiac mortality. Recent research described below has focused increasing attention on the usefulness of GGT as a predictor of cardiovascular disease.

At physiologic serum levels, GGT acts as a protein catalyst in the degradation of glutathione, the major thiol antioxidant in the body (Figure 1). Glutathione is a molecule consisting of glutamic acid, cysteine, and glycine, synthesized within the cell, and may be present both in the reduced state and in the oxidized dimer form by thiol bonding.

As an antioxidant, single glutathione molecules are formed and are metabolically inactive and require degradation. The oxidized form of glutathione is reduced by the action of glutathione reductase in preparation for recycling. GGT hydrolyzes this glutathione into glutamate and a cysteinyl-glycine dipeptide, and inside the cell, the amino acids are subsequently reused, producing additional reduced glutathione.

However, on the cellular membrane and in the extracellular space, the cysteinyl-glycine moiety can act as a strong reducing agent of iron, with the stepwise development of the super-oxide ion and hydrogen peroxide. Unintended oxidization of low-density lipoprotein cholesterol particles may occur, which is felt to participate in the formation of inflammatory atheroma within the vascular endothelial wall.¹⁰

An eloquent study by Drs. Paolicchi and Emdin¹¹ at the University of Pisa in 2004 specifically identified GGT in coronary atheroma removed at the time of surgical atherectomy (Figure 2). The enzymatically active GGT identification in the plaque was done by an azo-coupling reaction using gamma-glutamyl-4-methoxy-2-naphthylamide as a substrate for GGT activity, stained with fast garnet GBC as the chromogen. The images of GGT stained in an atheromatous plaque with a fibrous cap were felt significant in the direct participation of GGT and low-density lipoprotein cholesterol oxidation within that plaque. They felt the “pathogenic mechanism proposed for the role of GGT

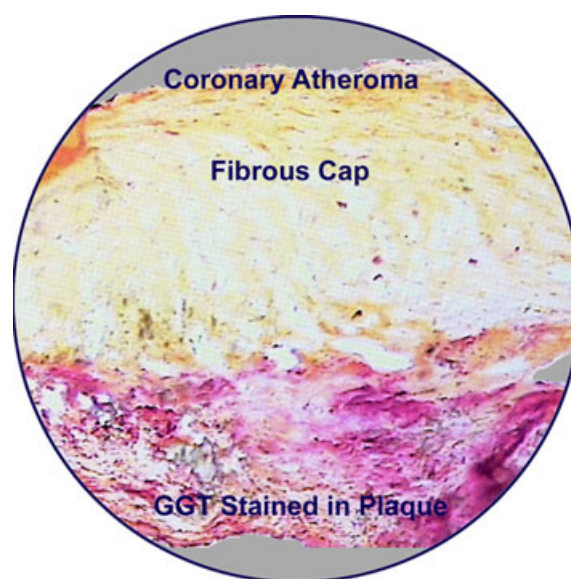


Figure 2. Photomicrograph of a coronary atheroma (20× magnification) identifying active enzyme within the plaque by an enzyme histochemical reaction to human gamma-glutamyl transferase (GGT), stained red with the diazonium salt fast garnet GBC, as the chromogen. Used with permission from Lippincott, Williams & Wilkins.

should be considered independent, complementary, and synergistic to conventional determinates.”¹¹

BIOMARKER FOR CARDIOVASCULAR RISK

To be a unique biomarker for cardiac and metabolic risk evaluation, GGT must meet certain stringent characteristics.¹² It must measure a single specific entity, either physiologic or pathologic, and offer additional information over presently used determinants. It must also add to the clinical assessment of a specific problem and correlate with known cardiovascular disease risk factors.¹³ Demographically, it must be applicable to both men and women of differing ages and varying ethnicities. It must be easily standardized, with both a high sensitivity and

specificity, and have automated testing readily available in most regions. GGT enzyme analysis has been available for many years, meets all of these strict measures, and thus would appear to pass accepted criteria as defined by Vasan,¹² as a biomarker for increased cardiovascular risk.

RECENT CLINICAL STUDIES

GGT levels were first associated with cardiovascular disease and all-cause mortality in a British Regional Heart Study by Wannamethee¹⁴ reported in October of 1995. This study evaluated 7613 British men over 11.5 years in England, Wales, and Scotland. The study plan included personal history questionnaires, history and physical exams, and laboratory screening for GGT, total cholesterol, high-density lipoprotein cholesterol, and non-fasting glucose. Increasing GGT levels were strongly associated with all-cause mortality, particularly in patients with ischemic heart disease, and a strong positive correlation was also noted with body mass index, total cholesterol, and diabetes mellitus^{15,16} (some of the present criteria for the metabolic syndrome).¹⁷ A lesser correlation was seen in relation to blood pressure, heart rate, and cigarette smoking. There was no correlation with acute cardiac events, cancer, or other causes of noncardiac deaths including alcohol ingestion.

A second important cross-sectional and longitudinal study reported by Ruttman¹⁸ in 2005 involved the Vorarberg Health Monitoring and Promotion Program in western Austria, with the participation of 163,944 adults and GGT evaluated as a risk factor for cardiovascular mortality. GGT was positively associated with significant risk factors for cardiovascular disease including body mass index,¹⁹ serum triglycerides, total cholesterol, systolic and diastolic blood pressure, and glucose (most of those criteria are now part of the metabolic syndrome). Other less positive correlates included ethanol ingestion and smoking, whereas physical activity, education and high-density lipoprotein cholesterol were negatively correlated with GGT. Using the Cox hazard ratio analysis and GGT values partitioned in quintiles, cardiovascular survival rates decreased significantly with each increasing group. Within the highest quintile, there was a 64% increase in all vascular-related deaths in men and 51% in women. A 162% increase in congestive heart failure was also identified in men within the highest grouping. This study concluded that GGT is an independent biomarker for cardiovascular mortality correlating with deaths from chronic heart disease (ischemic heart disease and congestive heart failure) but not acute cardiac events. Patients with higher GGT values had a more than 1.5-fold risk increase of total mortality from cardiovascular disease, and adults younger than 60 had an additional 2- to 2.6-fold increase in risk. Positive correlations in this group included body mass index, total cholesterol, blood

pressure, low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, triglycerides, glucose, ethanol ingestion, and cigarette smoking.

A cross-sectional paper published by Onat and colleagues²⁰ in October 2006 from the Turkish Adult Risk Factor Study showed that waist circumference is the major determinant in GGT activity and that a doubling of GGT increases the odds ratio of metabolic syndrome developing by 74% and of coronary heart disease developing by 45%.

A third large strictly longitudinal study reported by Kazemi²¹ in 2007 involved 283,438 patients over a 12-year period. This study evaluated both inpatients and outpatients seen at a general hospital who had GGT tests ordered at initial visit and were followed over time to relate GGT levels with cause of death. Using the Cox hazard ratio, an analysis of GGT for all-cause mortality, cancer-related deaths, and non-cancer-related deaths, including subsets of vascular, cerebrovascular, and ischemic heart disease, was performed. Significant relationships developed even in patients with relatively normal GGT values. In the highest quintile for all-cause mortality, a 100% risk increase was observed. These findings provided a strong predictive value of long-term survival even with GGT values within the considered reference range. GGT values were significantly associated with all-cause mortality, cancer-related deaths, non-cancer-related deaths, and vascular mortality. Younger patients evaluated in decreasing decade intervals had increasing mortality risk, with up to 3.3 times the risk if younger than 30. GGT levels found significantly above the normal cutoff were a gross predictor of hepatobiliary disease and death.

The most recent complete study, reported in January 2007, evaluated 3451 patients in the Framingham Offspring Study²² looking at cross-sectional correlation of GGT with multiple variables and longitudinal GGT correlation with the metabolic syndrome, coronary heart disease risk factors, onset of congestive heart failure, peripheral vascular disease, cardiovascular disease, or death. Participants were evaluated every 4 years over a 20-year span between 1971 and 1991. Body mass index ≥ 30 kg/m² was used as a proxy for abdominal circumference in the National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome.

Cross-sectional analysis disclosed significant positive GGT correlation, in decreasing order of significance, to triglycerides, male sex, and alcohol consumption (accounting for the most variation). Additional covariates included diastolic blood pressure, body mass index, age, smoking, low-density lipoprotein cholesterol, and fasting glucose. Although previously reported by other authors,^{23,24} including a report using the National Health and Nutrition Examination Survey III population,²⁵ no significant statistical interaction was seen between

Table I. Framingham Offspring Study: Longitudinal Study Results Summary

GAMMA-GLUTAMYL TRANSFERASE (GGT) VALUES						
GGT values (U/L), men	1–11	12–16	17–24	25–99	Normal, ≤50 U/L	
GGT values (U/L), women	1–6	7–9	10–13	14–88	Normal, ≤40 U/L	
QUARTILES	1ST	2ND	3RD	4TH	QUARTILE TREND	P VALUE
METABOLIC SYNDROME (MET S)						
AT 20 YEARS (968 PATIENTS)						
Met-S developed, %	n/a	n/a	n/a	n/a	28.0	
HR adjusted for age and sex	Ref	1.21	1.49	1.85	1.23	≤.001
HR adjusted for age, sex, and CRP	Ref	1.23	1.36	1.76	1.20	≤.001
CARDIOVASCULAR DISEASE (CVD)						
AT 20 YEARS (535 PATIENTS)						
CVD developed, %	10.5	12.1	16.7	23.8	15.5	
HR adjusted for age, sex, and CRP	Ref	1.28	1.53	1.88	1.23	≤.001
HR adjusted for all covariables ^a	Ref	1.26	1.40	1.67	1.18	≤.001
ALL-CAUSE MORTALITY (DEATH)						
AT 19.1 YEARS (362 PATIENTS)						
Mortality, %	6.3	7.4	12.2	16.6	10.5	
HR adjusted for age, sex, and CRP	Ref	1.20	1.65	1.94	1.26	≤.001
HR adjusted for all covariables ^a	Ref	1.21	1.67	1.95	1.26	≤.001
Abbreviations: CRP, C-reactive protein; HR, hazard ratio; n/a, not available; Ref, reference quartile. ^a Adjustment for all covariables included age, sex, CRP, body mass index, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, and alcohol consumption.						

GGT and C-reactive protein. This study did not report the percentage incidence of metabolic syndrome per GGT quartile, but it did permit calculation of the percentage of participants in whom the syndrome developed over the 2-decade study period.

As seen in Table I, longitudinal 20-year study results disclosed 28% of participants in whom the metabolic syndrome developed. After adjustment for age and sex, a 23% per GGT quartile increase was found, and after an additional adjustment for C-reactive protein, a 20% per GGT quartile trend was recorded regarding the metabolic syndrome. With still further adjustment for all additional identified covariables, including age, sex, C-reactive protein, body mass index, fasting glucose, triglycerides, systolic and diastolic blood pressure, alcohol consumption, and smoking status, a 9% per GGT quartile trend still remained (data not shown) over the 20-year study. The stepwise GGT quartile increase, adjusted for all covariables, unfortunately, was not reported. This was the first reputable study to demonstrate the separate correlation of GGT with the metabolic syndrome after all confounding variables were taken into account.

Over the same period, cardiovascular disease developed in 15.5% of participants, with an 18% per GGT quartile increase, and in relation to all-cause mortality, 10.5% of patients died during the study, with a 26% per quartile trend. This study reported GGT in the 4th quartile to be an independent predictor of development of the metabolic

syndrome, with a 1.76-fold risk increase in its incidence over 20 years.^{22,26}

These and other more recent articles regarding GGT published by experts in the field point to GGT as an important biomarker for prognostic cardiovascular risk evaluation. In 2007, Grundy,²⁶ in his editorial regarding the Framingham Offspring Heart Study, discussed GGT as another good biomarker for metabolic syndrome and cardiovascular risk. Even more recently, Emdin and colleagues²⁷ from the University of Pisa reported in their article regarding the additive prognostic value, along with C-reactive protein and fasting glucose, of GGT in coronary artery disease.

CLINICAL UTILIZATION

In a landmark consensus paper in 2003, Nagahavi, Libby,^{28,29} and others presented a 2-part risk assessment compendium entitled “From Vulnerable Plaque to Vulnerable Patient.” Risk detection was subdivided into tests and biomarkers regarding “the vulnerable plaque, the vulnerable blood, and the vulnerable myocardium.” The “vulnerable vessel” is included here to help better identify early occult vascular changes.

Evaluation of the “vessel at risk” would include clinical inflammatory markers such as high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A₂, and fibrinogen, while homocysteine could be used as a proxy for endothelial function.¹³ The GGT biomarker would fall under a new classification of “oxidative stress,” in view of its role in the

degradation of the antioxidant glutathione. It could likewise be considered a proinflammatory marker³⁰ in view of its generation of cysteinyl-glycine, which has an indirect effect causing low-density lipoprotein cholesterol oxidation in the presence of iron. Its independent correlation with the metabolic syndrome makes the biomarker valuable, along with blood glucose, insulin levels, and hemoglobin A_{1c} in evaluating patients at risk for diabetes or insulin resistance or who have diabetes or insulin resistance.

Measurements of the “plaque at risk” would include lipid profile evaluation, with low-density lipoprotein cholesterol concentration; low-density lipoprotein particle size measurement; small, dense low-density lipoprotein; and apolipoprotein B. The high-density lipoprotein (HDL) cholesterol measurement and high-density lipoprotein particle size determinations, especially HDL 2b, are considered part of plaque risk determination. Apolipoprotein A1 can also be grouped as part of this component.

Laboratory testing to evaluate the “blood clotting mechanism at risk” or the “hypercoagulable state” would include fibrinogen; lipoprotein(a), in view of its structural similarity to plasminogen; and possibly homocysteine.

Evaluation of the “myocardium at risk” includes creatine phosphokinase and, more importantly, the biomarker N-terminal prohormone brain natriuretic peptide to identify both ventricular and atrial myocardial cell stress.

CONCLUSIONS

The GGT enzymatic assay at abnormally high serum levels is an established liver function test for alcoholic toxicity, inflammation, fatty liver disease (hepatic steatosis), and hepatitis.

However, in the upper reference range, GGT has recently been found to be a strong independent biomarker for the metabolic syndrome (insulin resistance syndrome). A 20% per GGT quartile trend was seen in relation to the development of the metabolic syndrome.

GGT is also an independent risk marker for the development of cardiovascular disease, with an 18% per quartile increase in risk, and shows independent correlation for all-cause mortality, with a 26% per quartile increase over baseline values. It was positively correlated with age, sex, triglycerides, blood pressure, body mass index, low-density lipoprotein cholesterol, fasting glucose, ethanol ingestion, and smoking, as expected for increasing cardiovascular risk. Negative correlation included physical activity, education, and high-density lipoprotein cholesterol.

In addition, GGT can be considered a biomarker for oxidative stress associated with glutathione regulation and degradation and possibly a proatherogenic marker because of its indirect relationship in the biochemical steps leading to low-density lipoprotein oxidation.

Further academic studies will need to be done to evaluate GGT's overall importance, independent from high-sensitivity C-reactive protein and other presently accepted biomarkers and relative to the traditional risk factors used for predicting the development of the metabolic syndrome and cardiovascular disease. However, because of its wide availability and inexpensive cost for screening, identifying higher than expected GGT levels in otherwise healthy individuals should alert the physician to study those patients in more detail, with the hopeful outcome of preventing unnecessary cardiac-related events and deaths in future years.

GGT is a unique biomarker in the continuum of cardiovascular disease risk. GGT is thus a potentially valuable addition to the growing list of clinically available tests useful in initially stratifying patient risk associated with well-known cardiovascular conditions and should be considered in assessing the appropriate aggressiveness of treatment.

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