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Gamma-Glutamyl Transferase (γ -GT) – An old dog with new tricks?

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Abstract

Gamma-Glutamyl Transferase (γ GT) is a key transferase involved in the transpeptidation of functional gamma-glutamyl groups to various receptor moieties. It performs important roles in antioxidant defence mechanisms, particularly glutathione recycling, xenobiotic metabolism, but analogously may also have a pro-oxidant role.

γ GT is very sensitive for diagnosis of liver injury, although it has poor specificity for particular aetiologies. It has been used to reflect temporal changes as a form of monitoring depending on aetiology.

Given its cellular role in antioxidant function, it has been investigated as a surrogate biomarker of oxidative stress. It has also been found to be a predictor of mortality across a spectra of non-hepatic disease pathologies, from metabolic and cardiovascular risk to chronic kidney disease and neoplasia. Similarly, it also remains of interest to the insurance industry given an apparent ability to predict mortality, in addition to an historical interest from law enforcement as a marker of chronic alcohol ingestion.

Here, we review some of the unique characteristics of this important enzyme, previously considered as a mere specific marker of liver dysfunction, but now with clear extra-hepatic implications and novel applications and utility.

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Keywords

gamma glutamyl transferase (γ GT); Glutathione; Glutamyl Cycle; Cholestasis; prognostication

Introduction

Gamma- Glutamyl Transferase (γ GT) is a key transferase involved in the transpeptidation of functional gamma-glutamyl groups to receptor molecules. Biologically, γ GT is very sensitive for diagnosis of liver injury, although enzyme induction can lead to loss of specificity for damage and it has poor specificity for particular aetiologies. More recent evidence has suggested that it also plays an important role in antioxidant defence and xenobiotic metabolism, as well as offering tantalising associations across a continuum of disease states including cardiovascular disease and cancer. In this mini review we explore the structure and function of γ GT, some of the historic applications of γ GT, as well as its evolution beyond a simple marker of cholestasis. We have summarised some of the key aspects of γ GT's unique physiology in table 1, but we are keen to suggest readers may wish to access a number of additional insightful recent reviews on the topic.^{1,2}

γ GT biology

Gamma glutamyl transferase (γ GT) is a glycosylated microsomal enzyme that catalyses the transfer of a gamma-glutamyl group to acceptor peptides and L-amino acids, particularly cysteine.^{3,4} γ GT is relatively ubiquitously expressed in human tissue and cell types, except within myocytes, and with some variability in expression profiles between cell types. It is most abundant on the luminal surfaces of cells with secretory or absorptive properties but can also be found on the basolateral surfaces of renal epithelial cells.⁵ Alternate gamma-glutamyl targets include γ GT1 substrates, including Glutathione di-sulfide (GSSH), leukotriene C4 (LTC4)⁶ and S-nitroso-glutathione⁷ and GSH-xenobiotic adducts. As such, γ GT plays a prominent role in homeostasis of glutathione production and recycling, inflammatory and nitric oxide signalling, as well as oxidative stress amelioration.

γ GT and Glutathione

Glutathione exists as a tripeptide, γ -L-glutamyl-L-cysteinylglycine, present in all mammalian tissues, with the highest intracellular concentrations found in the liver.⁸ Here, as the most abundant non-protein thiol, it is responsible for oxidative stress mitigation. It exists in a thiol-reduced state (GSH), as the most prominent form (>98% of total), and as a disulfide-oxidised (GSSG) variant.⁹ Within eukaryotic cells, GSH resides principally in the cytosol (80–85%), with 10–15% in the mitochondria, whilst the endoplasmic reticulum has a minute reservoir of GSH. GSH principally is derived from hepatocytes, with most being excreted into plasma and bile.¹⁰ GSH is unique in its structure whereby the gamma-carboxyl portion of glutamate links to cysteine, rather than traditional α -carboxyl dipeptide formation. It is this unique characteristic that means this bond can only be hydrolysed by γ GT.

Another fundamental aspect of GSH homeostasis relates to cysteine cycling, which is required for de-novo intracellular GSH synthesis, a process enzymatically facilitated by γ GT. γ GT also coordinates the transfer of the gamma-glutamyl moiety of glutathione S-compounded to mercapturic acid, thereby releasing cysteinyl-glycine.¹¹ Importantly, cysteinyl glycine may interact with free iron species, thereby inducing the Fenton reaction and consequent superoxide production, a potent ROS, which may have pathogenic role in a number of human diseases.¹²

γ GT Induction

It has been consistently reported that serum γ GT increases in patients taking anticonvulsant drugs. A number of older anticonvulsant therapies are well recognised as enzyme -inducing moieties including phenytoin and phenobarbitone, which are again associated with deranged serum γ GT levels. There appears to be a synergistic effect on modulation of alcohol and ingestion of phenytoin in incrementing serum γ GT levels. In another study by Herzberg¹³, 40% of patients exposed to commonly used medications including α -methyldopa, quinidine, digoxin, diazepam and furosemide demonstrated a sustained rise in γ GT which suggests induction of hepatic microsomal enzymes by these commonly prescribed compounds. Evidence extrapolated from some studies demonstrated that serum γ GT incremented following a reduction in hepatic glutathione secondary to drug induction.¹⁴ This would indirectly support the supposition that γ GT mediates hepatic glutathione homeostasis. Interestingly, phenobarbital (a potent enzyme inducer) paradoxically increases both γ GT and glutathione. However, a trial combination of cysteine and phenobarbital resulted in a nonsignificant decrease in γ GT relative to control. This infers that γ GT undergoes induction when enzyme-inducing drugs decimate hepatic glutathione levels; γ GT induction may therefore subsequently result in higher than normal glutathione as a consequence. As a corollary, if glutathione does not fall, γ GT is not induced, which provides important insight into how this might be exploited translationally.

γ -Glutamyl Cycle

The γ -glutamyl cycle comprises of six enzymatically catalysed reactions that maintain glutathione homeostasis, which is summarised in figure 1. Within the gamma-glutamyl cycle, inherited genetic defects have been described in four enzymes: γ -glu-cysH Synthetase (γ -GC synthetase), GSH synthetase, 5-oxoprolinase and γ -glutamyl transpeptidase.¹⁵ Impaired GSH-synthetase and γ -GC synthetase functionality causes relative GSH deficiency. GSH synthetase deficiency is characterised by excess production of 5-oxoproline, which is manifested biologically as metabolic acidosis, 5-oxoprolinuria, haemolytic anaemia and neuromuscular disorders.¹⁷¹⁶ In patients with isolated γ -GC synthetase deficiency, haemolytic anaemia predominates, with or without hepatosplenomegaly. Importantly, isolated erythrocytic GSH-synthetase deficiency results in haemolytic anaemia but not 5-oxoprolinuria. Treatment is principally focused on acidosis correction, high concentrate supplementation of vitamins C and E and avoidance of precipitating haemolytic crises.¹⁵

γ GT as a liver function test

γ GT has been adopted as a liver function test since the 1960s. A seminal paper by Szczeklik¹⁷ demonstrated mean values in differing aetiologies of liver disease, highlighting variation in serum γ GT over time, and contrasting with other enzymatic trends including aldolase, phosphohexose isomerase and aspartate and alanine transferases. γ GT demonstrates high sensitivity for liver damage, being abnormal in majority of patients with liver disease irrespective of pathogenesis, however, extremes of upper limits are most commonly seen patients with cholestasis. Conversely, there is an inherent lack of specificity in γ GT, especially given other contributing diseases and conditions including pancreatitis, diabetes mellitus, obesity, excessive alcohol, enzyme-inducing drugs.¹⁴ An interesting observation in patients with chronic active hepatitis, was that γ GT tended to normalisation in remission and in those undergoing treatment, however, this never reached statistical significance, but may provide a useful insight into treatment response.¹⁸

Importantly, while the normal reference range for γ GT remains relatively consistent across age, there is inherent male – female variation in serum concentrations. Additionally, there are a number of demographic, physiological and inducible factors which affect γ GT so there is heterogeneity in defining the reference interval. The standard reference thresholds for γ GT in adult humans as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) are presented in table 2.¹⁹

There have been incident case reports of isolated high serum gamma-glutamyl transferase levels in the absence of other predisposing factors within an extended Italian familial series. This condition has an autosomal dominant mode of inheritance and does not confer any disease specific risks.²⁰

Conversely, there is a spectrum of related cholestatic conditions which manifest as low – normal γ GT, collectively termed *low gamma-GT familial intrahepatic cholestasis*, with disease severity which may range from mild to severe.²¹ These forms of inherited cholestatic disease appear to be inherited in an autosomal recessive manner. There are a number of other disease variants within this continuum, however, it beyond the scope of this article to cover in more detail.

Diagnostic utility in liver disease

After perfecting the methodology for measuring serum γ GT,²² Orłowski evaluated the diagnostic potential of γ GT in ~100 conditions felt likely to alter serum levels.²³ In a mixed cohort, patients with alcohol-related liver disease (ArLD), viral hepatitis, carcinomatosis and malabsorption were compared with those with no hepatic or renal pathology. γ GT was markedly elevated in hepatobiliary disease as well as ArLD and carcinomatosis, whilst transaminases and alkaline phosphate remained within normal limits.²⁴ The authors concluded that serum γ GT may therefore be useful in the clinical assessment of ArLD and primary and secondary forms of hepatic neoplasia.

Whilst γ GT is relatively ubiquitously expressed across tissues as previously described, its principle utility has been as part of the extended panel of liver function tests, including as a

composite of a number of non-invasive algorithms of liver fibrosis assessment.²⁵ It is well established as a very sensitive marker of hepatobiliary disease, with lower specificity than aspartate aminotransferase (AST) and alanine aminotransferase (ALT) for diagnosis of liver disease²⁶, however, it is more sensitive than ALT and AST in anicteric, non-alcohol related parenchymal disease. Despite the introduction of a standardised measurement methodology for γ GT, there have not been more contemporaneous studies to determine if new diagnostic reference thresholds should be derived. A broad clinical approach to determining the cause of an elevated γ GT is provided in figure 2.

Alcohol-related Liver Disease

In 1976, the Blennerhassett Committee recommended the identification of high-risk individuals among those persons convicted of driving under the influence of alcohol.²⁷ There was increasing interest in prospectively identifying high-risk offenders and supporting assessment by clinicians from the Department of Transport in determining evidence of alcohol dependence. There was widespread enthusiasm in the clinical utility of γ GT as a prospective biomarker of problem alcohol ingestion. Given its enzymatic activity is not considerably raised following a single bout of drinking, it was seen to represent an obvious candidate.²⁸

This premise was applied across a number of cohort studies in Tayside, Scotland. A quarter of drivers convicted of drink driving had abnormal γ GT activity at time of arrest. Dunbar and colleagues surmised that overall γ GT activity demonstrated that blood ethanol level in isolation is poorly predictive of wider-alcohol related issues among drunk drivers (other than those associated with driving under the influence). Serial γ GT levels also suggested that up to a 1/3 of these persons may be problem drinkers.²⁹ They did, however, note a strong association between raised γ GT activity and accidents in older offenders. Among young drivers the traditional association between blood alcohol concentration and accidents was strongly associated. Focusing solely on measured blood alcohol concentration may therefore disguise a relation between chronic, rather than acute, alcohol abuse and accidents.³⁰ Whilst γ GT proved very sensitive for chronic alcohol use, its specificity was relatively poor, with 17% of persons having abnormal levels in the context of no identifiable cause. Despite its relative sensitivity, these limitations continue to limit γ GT as a reliable and definitive biomarker of alcohol related disease. Given the historical nature of these studies, there would likely be significant interest in revisiting the wider applicability of γ GT in chronic alcohol use, especially where it might be combined with novel serum and urine alcohol metabolites.

Cholestasis

γ GT has been reported as a marker of biliary disease, in part owing to its association with alkaline phosphatase, another indirect biochemical marker of cholestasis. This association was demonstrated by Whitfield and colleagues³¹ in a large cohort of patients with liver disease and healthy controls. Average serum activities of γ GT and alkaline phosphatase (ALP) were three to six times greater in biliary disease compared to parenchymal aetiologies. In mixed parenchymal and biliary diseases, the ratios of mean γ GT to ALP were approximately equivalent. Within this cohort, they also noted that γ GT elevations often

resolved corresponding to overall liver recovery, whether primary biliary or hepatocyte in origin.

Similar findings were subsequently reported by Cushieri and Baker¹⁸, whereby patients with extrahepatic biliary obstruction had significant elevations of γ GT and ALP, which resolved on removal of the offending lesion. They noted an appreciable lag time in reduction of γ GT, particularly in cases of significant jaundice pre-procedure.

General Prognostication

Beyond the interest in using γ GT to identify those at risk of alcohol-related vehicle accidents, there is increasing curiosity around the utility of γ GT in risk stratification relating to cardiovascular disease and malignancy. Clearly, this is of significant interest to clinicians and healthcare providers, however, additionally, it is of enormous interest to the insurance and life assurance industries.

Evidence from a number of epidemiological studies suggest that increased serum levels of γ GT are associated with increased cardiovascular risk, including addition of the various components of the metabolic syndrome (metS). Similarly, novel cardiovascular predictive determinants including hsCRP, fibrinogen and F2-isoprostanes also demonstrate strong correlation with γ GT.³²

There has been significant dissonance regarding the mortality effect seen in those with increased γ GT in cardiovascular disease. Parallel epidemiological studies were insufficient to delineate whether serum γ GT simply reflected increased cardiovascular disease risk determinants, or, whether γ GT had prognostic propensity beyond these individual risk strata.³² The Framingham heart study was developed from the Framingham Offspring Study in 1971. Within this cohort elevated γ GT was associated with fatal and non-fatal incident cardiovascular events and predicted development of the metS. This association was apparent even on correcting for additional variables including CRP, and additional risk factors when temporally modelled as covariates including fasting glucose and the other individual components of the metS.

Interestingly, moderate to high levels of serum γ GT (50th-90th percentiles) has been demonstrated to significantly associate with the incidence of heart failure in a Finnish cohort.³³ Similarly, γ GT appears to have a mechanistic role in reversing the down-regulation of K⁺ channels in the myocardium post myocardial infarct and further scavenging ROS, which may aid cardiac remodelling.

Another area of increased interest is individual cancer risk stratification. Whilst there are relative predictors for cardiovascular disease (metabolic syndrome, hyperlipidaemia, diabetes), cancer risk profiling usually relies on clinical or family history and is generally less robust by underwriting standards. A number of clinical studies have attempted to model for cancer risk using laboratory markers and physical attributes, however, they often only demonstrate univariate risk factors. A large study by Palmier and Lanzrath³⁴ utilising 1.25 million insurance applicants who were matched to claims records, demonstrated that γ GT positively correlated with cancer mortality across most modelled ranges, albeit the apparent

risk appeared to plateau at higher values. Alkaline phosphatase levels and relative risk appear to positively correlate with γ GT in this cohort

Conclusion

γ GT is an enzyme of many parts, vital to maintaining oxidative stress and signalling homeostasis. Once a mainstay of the liver function test panel, which in many areas it was discontinued as a cost-saving measure. It is now making a resurgence as a sensitive gateway test to early detection of chronic liver disease and as a prognostic marker for cardiovascular disease. These novel insights clearly represent exciting new avenues of research for this figurative “old dog”.

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List of Abbreviations:

| | |
|--|-------------------------------------|
| γGT | gamma glutamyl transferase |
| GSSH | glutathione disulfide |
| LTC4 | leukotriene C ₄ |
| GSH | glutathione |
| γ-GC synthetase | γ -glu-cysH synthetase |
| ROS | reactive oxygen species |
| ArLD | alcohol-related liver disease |
| AST | aspartate transaminase |
| ALT | alanine transferase |
| ALP | alkaline phosphatase |
| MetS | metabolic syndrome |
| hsCRP | high-sensitivity c-reactive protein |

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Key Points

- An important enzyme for transpeptidation
- Sensitive biomarker for many liver pathologies
- Not specific for any individual liver disease or of direct liver injury
- γ -GT increases in response to oxidative stress and glutathione depletion
- Indirect biomarker for cardiovascular and metabolic risk

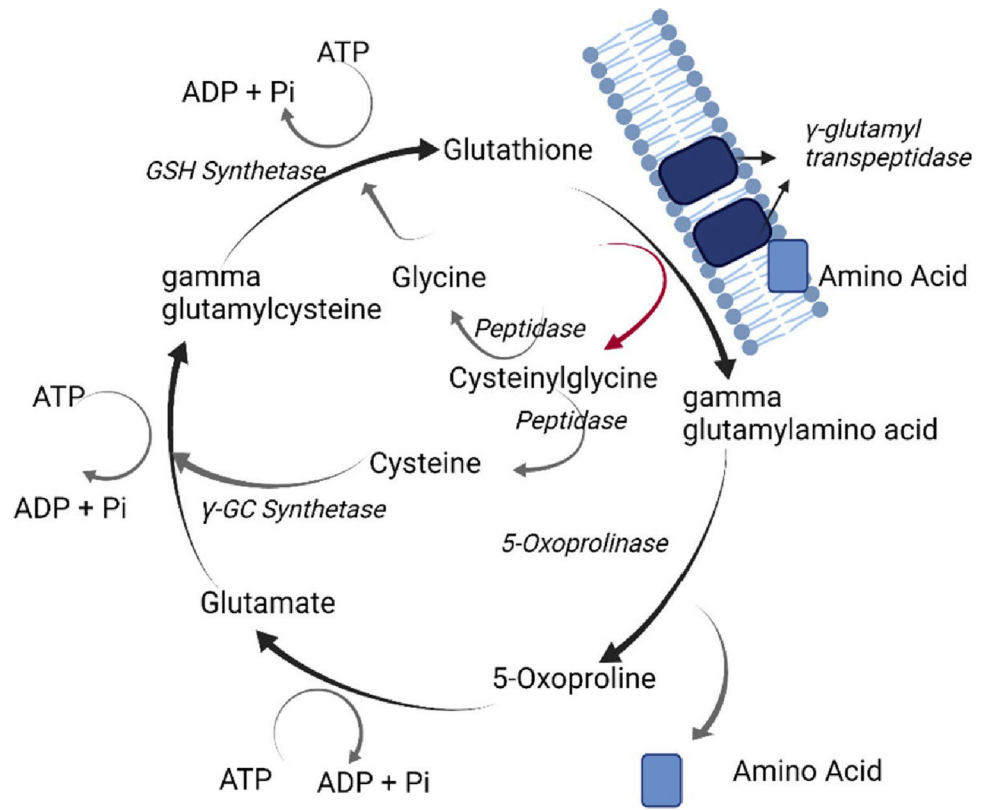


Fig 1:
Overview of gamma glutamyl cycle

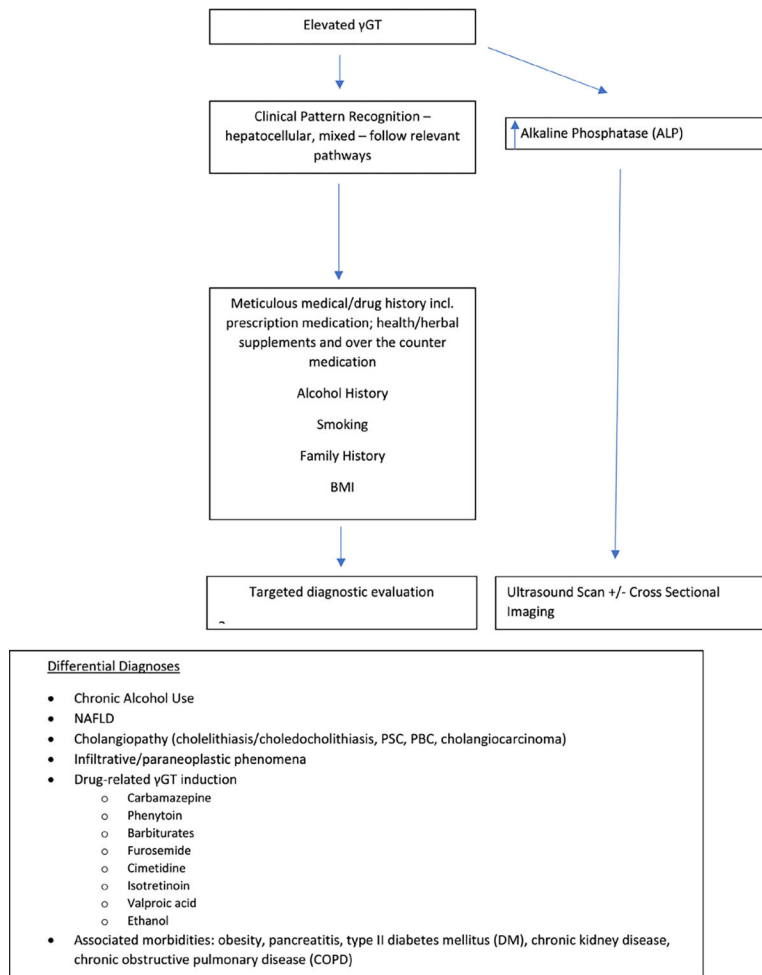


Fig 2:
Suggested approach to elevated γ GT

TABLE 1

Physiological associations of γ GT in disease

| Organ/Tissue System | Physiological associations of γ GT |
|-----------------------|--|
| Cardiovascular | <ul style="list-style-type: none"> Evidence of co-localisation of γGT with typical foam cells and CD68+ macrophages, in addition to LDL in atherosclerotic deposits. Increased incidence of congestive cardiac failure in those with higher serum values of γGT. May be reflective of adaptative sequelae post-myocardial infarct |
| Lung | <ul style="list-style-type: none"> Incompletely understood γGT produced by type II pneumocytes and secreted into epithelial lining fluids (ELF); which may have a pathogenic effect. Increased levels of ELF γGT are found in cystic fibrosis (CF) and likely reflect secretion from neutrophils within chronically inflamed airways. |
| Neoplasia | <ul style="list-style-type: none"> Biologically plausible that γGT expressive tumours would have survival advantage in mitigating levels of oxidative stress in high cellular turnover state γGT may protect certain cell lines from pro-oxidant chemotherapeutic regimes |
| Neurological | <ul style="list-style-type: none"> Animal models of inflammatory CNS disease states implicate γGT and GSH pathways γGT appears to have pro-oxidant signature, whereby blockade appears to ameliorate inflammatory effect. |
| Skeletal | <ul style="list-style-type: none"> May behave as a damage associated molecular pattern (DAMP), inducing RANKL and causing osteoclastogenesis |
| Renal | <ul style="list-style-type: none"> Ischaemia/perfusion deficit to renal tubules results in increased γGT activity and reduced GSH concentrations. Injurious effect of γGT-related cell toxicity likely related to membrane lipid peroxidation. |

Table 2:Proposed IFCC γ GT standard ranges

| <i>Gender</i> | <i>Upper reference limit*</i> | <i>90% confidence intervals</i> |
|---------------|-------------------------------|---------------------------------|
| <i>Women</i> | 38 (U/l) | (37–39 U/l) |
| <i>Men</i> | 55 (U/l) | (53–58 U/l) |

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