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Metabolism and Target Organ Damage

Review

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Concise review: gamma-glutamyl transferase - evolution from an indiscriminate liver test to a biomarker of cardiometabolic risk

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Abstract

This concise review article critically examines the recent medical literature regarding gamma glutamyl transferase (GGT) with a special emphasis on newly proposed indications for GGT use, including cardiovascular risk assessment.

GGT is a ubiquitous glycosylated protein embedded in the outer surface of cell membranes, which catalyzes the transfer of glutamyl groups from various substrates and plays a key role in the antioxidant/pro-oxidant balance. In the past, the enzyme was considered a non-specific liver test. Current evidence supports the role of GGT in the assessment of portal hypertension in cystic fibrosis, porto-sinusoidal vascular disease, malignant mesothelioma, and incident type 2 diabetes and as a biomarker of cardiometabolic risk and cardiovascular disease.

Several specific points including the use of GGT in hepatology as a sensitive but poorly specific test and the association of GGT with metabolic syndrome, nonalcoholic fatty liver disease and its fibrotic stages, cardiometabolic risk, chronic kidney disease, neurodegenerative disorders and dementia, idiopathic pulmonary arterial hypertension, and Corona Virus Disease 2019 (COVID-19) are addressed based on the most recent research in these fields. Putative mechanisms linking GGT with increased metabolic stress and the effects of various therapeutic interventions on GGT values are also discussed.

We conclude that GGT has evolved from an indiscriminate liver test and an index of alcohol consumption to a biomarker of cardiometabolic health. The proper interpretation of GGT values (i.e., of hepatic *vs.* extrahepatic origin) is deeply affected by the clinical and epidemiological context. We propose that GGT may be utilized in public health campaigns, in the research arena, and in clinical practice to identify those individuals who can benefit most from the proactive preventive and therapeutic approaches, given that they are at high cardiometabolic risk.

Keywords: Cardiometabolic risk, chronic kidney disease, COVID, incident type 2 diabetes, insulin resistance, liver fibrosis, metabolic syndrome, NAFLD, portal hypertension

BACKGROUND AND AIMS

In ancient Middle Eastern cultures, the liver was believed to be the site of life itself, just as the heart was so considered in the Western society of the time[1]. Interestingly, modern science has indeed re-confirmed a strong nexus between the most common hepatic disorder, nonalcoholic fatty liver disease (NAFLD), and increased cardiometabolic risk[2]. Many years ago, medical students were taught that gamma glutamyl transferase (GGT) would be used to diagnose many liver diseases, making this laboratory test somewhat indiscriminate. Although GGT activity elevation is the most sensitive marker of hepatobiliary disease, hepatologists would discourage the routine use of the GGT test, owing to economical cost issues and the fact that it cannot by itself indicate a specific liver disease[3].

According to old paradigms, patients with chronic liver disease used to be spared and possibly protected from cardiovascular events[4]. However, that view was based on chronic liver disease occurring, at that time, mainly owing to viral infections against which no effective antiviral therapy was available. Contrary to the old views, it is becoming increasingly clear that chronic liver disease within the NAFLD spectrum increases the risk of adverse cardiovascular events[1,2].

Paralleling this paradigm shift, it has also become evident that a change in GGT activity is associated with a much larger disease spectrum than previously thought and that, rather than being a limitation, this attribute could offer new diagnostic opportunities for clinicians and researchers alike.

With this background, the present concise review article critically recapitulates the recent advances in our understanding of the normal biology of GGT and its significance in disease states. These comprise both hepatic and extrahepatic conditions, including portal hypertension in cystic fibrosis, porto-sinusoidal vascular disease, malignant mesothelioma, incident type 2 diabetes (T2D), cardiovascular disease risk, metabolic syndrome, fibrosing NAFLD, chronic kidney disease (CKD), neurodegenerative disorders and dementia, idiopathic pulmonary arterial hypertension, and Corona Virus Disease 2019 (COVID-19). Additionally, putative mechanisms linking GGT with increased cardiometabolic stress and the effects of various therapeutic interventions on GGT values are also discussed.

Rather than trying to perform a systematic review, in this appraisal, we analyze recently published studies on GGT. Special emphasis is given to data showing a trajectory of change in GGT use from an indiscriminate liver test to a biomarker of cardiometabolic risk and disorders, oxidative stress, and insulin resistance over the last few years. The studies were identified based on the authors' agreement and integrated both with cross-references of retrieved articles and with other publications identified from the authors' bibliographic archives.

STRUCTURE AND FUNCTION OF GGT

GGT, an evolutionarily conserved cell surface glycoprotein, is anchored in the cell membrane via its N-terminus, while the catalytic activity resides within the extracellular protein domain[5]. In humans, GGT is synthesized as a 569 amino acid enzymatically inactive pro-peptide[6] which undergoes activation by autocleavage into two subunits. N-glycosylation is essential for proper folding, autocleavage, and activation of human GGT[7,8]. Data on the crystal structure of human GGT have been reviewed elsewhere[9]. GGT is most abundant on the luminal surfaces of cells with secretory or absorptive properties that line glands and ducts throughout the body, such as the kidneys and the biliary system, with the highest level of GGT activity detected in the kidney[10]. This typical localization of GGT led to the suggestion that the enzyme is involved in the transport of amino acids via a sequence of reactions called the "gamma-glutamyl cycle" - a view that is not supported by current evidence. However, GGT may be important for the accessibility of the amino acid cysteine by the cells. The enzyme is also expressed on the basolateral surfaces of renal epithelial cells.

GGT removes the γ-glutamyl group from a wide range of extracellular substrates including proteins by cleavage of γ-carboxyl bonds of glutamate in these compounds. The γ-glutamyl moiety may be transferred to other acceptors (water or amino acids), leading to the release of glutamate or the formation of new γ-glutamyl compounds. The principal physiological substrate of GGT is glutathione [γ-glutamyl-cysteinyl-glycine (G-SH)]. The enzyme does not attack the alpha-carboxyl bond of glutamate in peptides or proteins[11,12].

The most important physiological function of GGT is the participation of the enzyme in G-SH and cysteine homeostasis. This function is supported by findings that GGT deficiency, either clinical or experimental (GGT knockout mice), is associated with glutathionuria because of the absence of GGT activity on the apical surface of the cells in the proximal tubules of the kidneys and reduced content of cysteine in plasma and cells[13].

Cells pump out G-SH (G-SH translocation) to regulate intracellular concentration and provide G-SH for extracellular reactions. The G-SH breakdown by GGT in the extracellular space increases the availability of cysteine, which is taken up by cells and used as an essential precursor for the *de novo* intracellular synthesis of G-SH[9].

Cysteine is a semi-essential amino acid and a rate-limiting substrate for intracellular synthesis of G-SH (glutamate and glycine are also taken up by the cells, but they may be supplied by the products of glycolysis or citric acid cycle as well). The G-SH cleavage by GGT leads to the production of cysteinyl-glycine dipeptide, which retains the thiol group and is a more reactive and stronger reducing agent than G-SH[14].

Cysteinyl-glycine dipeptide reduces iron from Fe^{3+} to Fe^{2+}, enabling the production of reactive oxygen species (ROS) including super-oxide (O^{2-}) and hydrogen peroxide (H_2O_2)[15,16]. ROS have multiple cellular targets and promote (per)oxidation of various cellular constituents and low-density lipoproteins[17]. Considering the role of ROS in the pathophysiology of various diseases, the increased levels of these species associated with GGT action may represent an important mechanism for the involvement of GGT in increasing cardiometabolic risk [Figure 1]. In this regard, GGT may be considered a biomarker of antioxidant inadequacy - having a role in the increased production of reactive species (particularly in the presence of free iron) - and low antioxidant defense (depleted G-SH), especially in the liver[18].

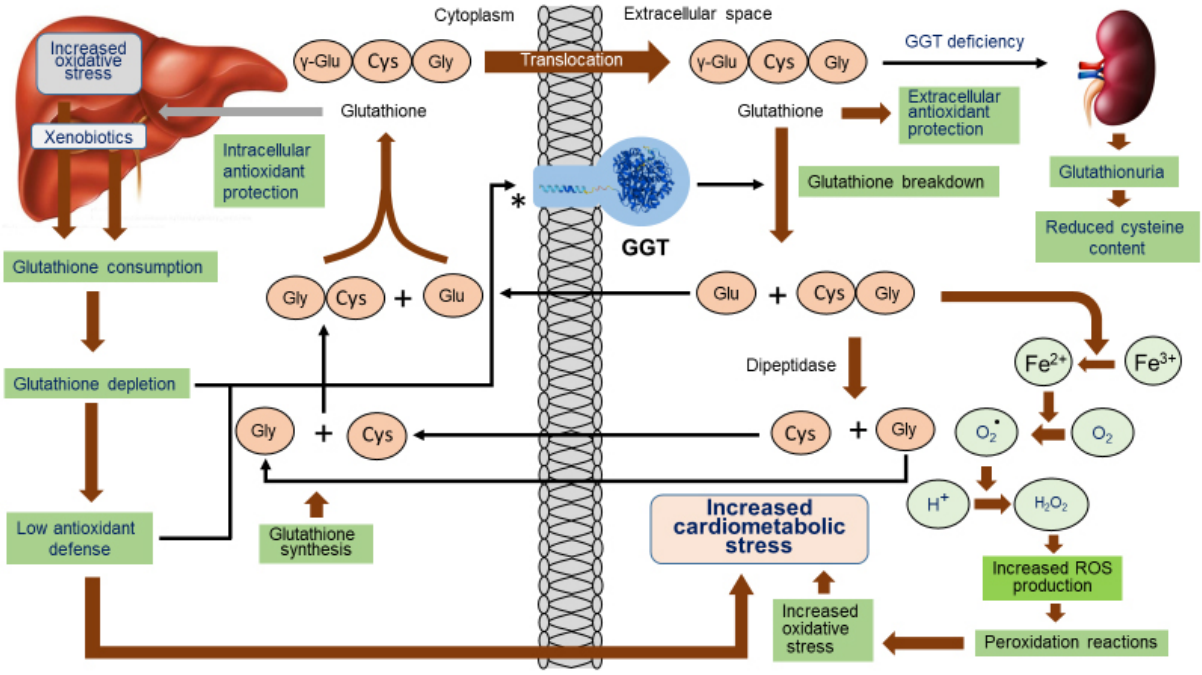

Figure 1. Gamma-glutamyl transferase (GGT) and increased cardiometabolic stress. The glutathione breakdown initiated by GGT action and synthesis of G-SH is shown. In the presence of ferrous iron (Fe^{2+}), cysteinyl-glycine - a product of GGT action—initiates a series of reactions leading to the generation of reactive oxygen species and increased oxidative stress. The G-SH consumption due to increased oxidative stress or xenobiotics leads to low antioxidant defense, which contributes to increased oxidative and cardiometabolic stress. The scheme supports the view that GGT elevation may be a marker of antioxidant inadequacy. Cys: Cysteine; GGT: gamma-glutamyl transferase; Glu: glutamate; Gly: glycine; ROS: reactive oxygen species. The asterisk next to the cell membrane domain of GGT shows cellular stimuli promoting GGT elevation in the setting of glutathione depletion and low antioxidant defense.

Cysteinyl-glycine dipeptide undergoes further breakdown by enzyme dipeptidase to produce free cysteine and glycine, and all three amino acids are taken up by cells and used to re-synthesize G-SH, a molecule that plays an important role in protecting cells from oxidative stress resulting from normal cell metabolism[19]. Probably the best-known biological function of GGT is its key role in maintaining cysteine homeostasis, thereby protecting tissues from oxidative stress[9]. Evidence for this function comes from both experimental and clinical studies[19]. Rats fed with low-protein diets (which are particularly poor in sulfurated amino acids) will exhibit increased hepatic G-SH and GGT activity, with both returning to baseline values when methionine is added to the low-sulfur diet[19]. Moreover, GGT-knockout mice (that can be rescued by supplementing drinking water with N-acetylcysteine) will exhibit a plasma cysteine concentration 80% lower than their wild-type counterparts[13]. These animals failed to grow normally, developed cataracts, exhibited increased levels of oxidative DNA damage, and were prone to developing oxygen-induced lung injury and died prematurely owing to cysteine deficiency, reduced intracellular GSH, and increased oxidative stress[9,19]. Along the same lines, patients with recessively inherited GGT deficiency also had glutathionuria, which results from the absence of GGT activity on the apical surface of renal proximal tubules[9,19].

Collectively, the above studies show that GGT also plays an important adaptive role in organs wherein it was not believed to be clinically relevant, such as the lung[19]. Contrary to the physiological functions, GGT and G-SH (especially in the presence of pro-oxidants such as iron and copper) can also become potentially harmful through possible pro-oxidant and carcinogenic effects occurring via free radical formation, peroxidation of lipids, and, eventually, mutagenesis[19]. The role of GGT in carcinogenesis and particularly

the changes in methylation status, changes in GGT mRNA type and GGT isoforms in hepatocarcinogenesis, and the potential role of GGT in chemotherapy-resistant cancers have been reviewed elsewhere[19].

NOVEL ETIOLOGIES OF RAISED GGT VALUES

The classic view stemming from the mid-1960s considered GGT as a marker of different types of liver disease such as hepatitis C, cholestatic syndromes, alcohol-related liver disease, porphyria cutanea tarda (which is not rarely associated with alcohol abuse), drug-induced liver injury, and nonalcoholic steatohepatitis (NASH)[19,20] which typically belongs to the *"alcohol-like liver disease in nonalcoholics"* disease spectrum[21]. Additionally, GGT was extensively used to follow up on the progression of alcohol-related liver disease and assess alcohol abstinence among those with long-lasting alcohol consumption[20].

Although not entirely known, the mechanism(s) of elevation of GGT activity in patients with chronic liver disease of various etiologies may involve not only a passive release of the enzyme from the injured cells but also an accelerated release kinetics due to either increased intracellular synthesis or enhanced release into the bloodstream of GGT molecules expressed on cell surface[19].

How should an isolated GGT elevation be worked out in seemingly healthy individuals? Most experienced clinicians would generally agree that patient reassurance and follow-up are indicated, and extensive diagnostic workup is not warranted[3,22]. Conversely, raised GGT values are generally considered to be sensitive for detecting hepatobiliary disease whenever associated with other abnormal liver tests[23]. For example, GGT measurement may help to determine a hepatic origin of an "isolated" elevation of alkaline phosphatase activity[3]. However, GGT is poorly indicative of specific etiologies[24]. In this regard, recent studies have contributed to widening the spectrum of (hepatic and extrahepatic) conditions that can be associated with raised GGT serum levels. These studies expand the historical role of GGT as a marker of alcohol consumption[19] and support this enzyme as a correlate of mortality owing to a variable gamut of extrahepatic diseases ranging from cardio-nephro-metabolic conditions to cancer. This has raised the interest among insurance companies, given the ability of GGT to serve as a correlate of an increased risk of mortality[24].

Portal hypertension in cystic fibrosis

Cipolli *et al.* followed a cohort of 577 patients diagnosed with cystic fibrosis through newborn screening over 28 years with yearly examinations for portal hypertension up to an age of 18.5 years[25]. They found that raised liver enzymes, particularly GGT [hazard ratio (HR): 5.71; 95%CI: 3.11-10.47], alanine aminotransferase (ALT)/GGT (HR: 5.56; 95%CI: 2.82-10.98), and alkaline phosphatase (ALP)/GGT (HR: 5.74; 95%CI: 2.78-11.86) were associated with the development of portal hypertension[25]. Such findings are consistent with the study by Görtzen *et al.*, who reported that GGT was the only independent correlate of splanchnic vein thrombosis among 126 patients with myeloproliferative neoplasms[26].

Porto-sinusoidal vascular disease

Pugliese *et al.* retrospectively evaluated liver biopsies in 29 patients (4.5% of those submitted to liver biopsy over an approximately five-year period at their institution) who had isolated, persistently raised, GGT ≥ 2 upper normal value[27]. Analysis of histological specimens disclosed that 13 patients (45%) had porto-sinusoidal vascular liver disease (PSVD) typically associated with nodular regenerative hyperplasia, defined by abnormal hepatocyte plates, nodular transformation, and markedly dilated portal and centro-lobular veins[27]. PSVD is a novel disease entity comprising non-cirrhotic portal hypertension and various histological patterns including nodular regenerative hyperplasia[28]. In the study by Pugliese *et al.*, five patients (17.2%) had liver biopsy findings compatible with NASH, three (10.3%) with hepatic sarcoidosis,

and in two patients, the liver histology disclosed congenital hepatic fibrosis, and non-specific findings were found in six (21%) patients[27]. The limited availability of published data on liver biopsies among patients with isolated elevated GGT values in general, the retrospective study design, and the limited number of patients included in this study[27] probably make it premature to abandon the more prudent and largely endorsed approach to submit these patients to follow-up evaluation over time[3,22].

Pleural malignant mesothelioma

Foddis *et al.* evaluated the diagnostic accuracy of specific GGT fractional enzymatic activity patterns in pleural malignant mesothelioma in blood samples of 175 workers at risk (i.e., previously exposed to asbestos), 157 (non-exposed) healthy subjects, and 37 patients with pleural malignant mesothelioma by using a molecular exclusion chromatographic method[29]. A specific profile of GGT fraction activity (i.e., increase in big-GGT and medium-GGT) was found to be significantly associated with pleural malignant mesothelioma[29]. This innovative approach needs further evaluation by additional studies. However, a study by Greb *et al.* in patients with pleural malignant mesothelioma reported that adding GGT did not improve the established Multimodality Prognostic Score comprising pre-chemotherapy tumor volume, histological analysis, baseline C-reactive protein, and post-chemotherapy tumor progression[30].

GGT and T2D

Since the early 2000s, a consistent body of literature has supported the association of GGT with insulin resistance and the risk of developing T2D[19].

In a pioneering study, Lonardo *et al.* reported on insulin resistance (evaluated with homeostasis model of insulin resistance (HOMA-IR) and defined by a cut-off value of HOMA-IR ≥ 2.26) in 99 individuals with hepatic steatosis due to variable etiologies consisting of: (a) familial heterozygous hypobetalipoproteinemia, an inherited disorder characterized by low plasma levels of apolipoprotein B (apoB) and low-density lipoprotein cholesterol (LDL-C), < 5th percentile for age and sex, and hepatic steatosis owing to impaired capacity of the hepatocyte to export lipids into the bloodstream; (b) NAFLD; and (c) hepatitis C virus (HCV) infection by different viral genotypes which are associated with different hepatosteatogenic pathomechanisms[31]. The cases were compared to 42 hepatosteatosis-free healthy controls. Data show that HOMA-IR, at age and body mass index (BMI)-adjusted multivariate analysis, correlated with hepatic steatosis ($P = 0.016$) and GGT ($P = 0.016$). Importantly, GGT and insulin resistance were closely correlated [Figure 2].

If GGT is a true marker of insulin resistance, it can logically be anticipated that GGT (a surrogate marker of NAFLD) could predict the future occurrence of T2D. Evidence supporting this notion was provided by a meta-analysis by Ballestri *et al.*, which included 20 studies with a total of 117,020 patients assessed over a median follow-up of five years (range from 3 to 14.7 years)[32]. In this study, NAFLD was indeed associated with an increased risk of incident T2D with a pooled relative risk (RR) of 1.97 [95% confidence interval (CI): 1.80-2.15] for ALT, 1.58 (95%CI: 1.43-1.74) for aspartate aminotransferase (AST), 1.86 (95%CI: 1.71-2.03) for GGT (upper *vs.* lower quartile or quintile), and 1.86 (95%CI: 1.76-1.95) for ultrasonography[32]. Likewise, Chen *et al.*, based on a large study population (over 132,000 adults followed for almost six years) without T2D at baseline, found that NAFLD, ALT, AST, GGT, and ALP were associated with the risk of new onset T2D in both sexes with hazard ratios (HRs) of 2.08, 1.27, 1.23, 1.58, and 1.37, respectively, in men, and 2.65, 1.56, 1.18, 1.48, and 1.44, respectively, in women[33].

Klaassen *et al.* provided further evidence for a close association of GGT with incident T2D in a more clinically complex setting[34]. The authors followed a series of 500 subjects (56% men; age, 50 ± 12 years) who were T2D-free at baseline and were submitted to renal transplantation over a 9.6-year median period

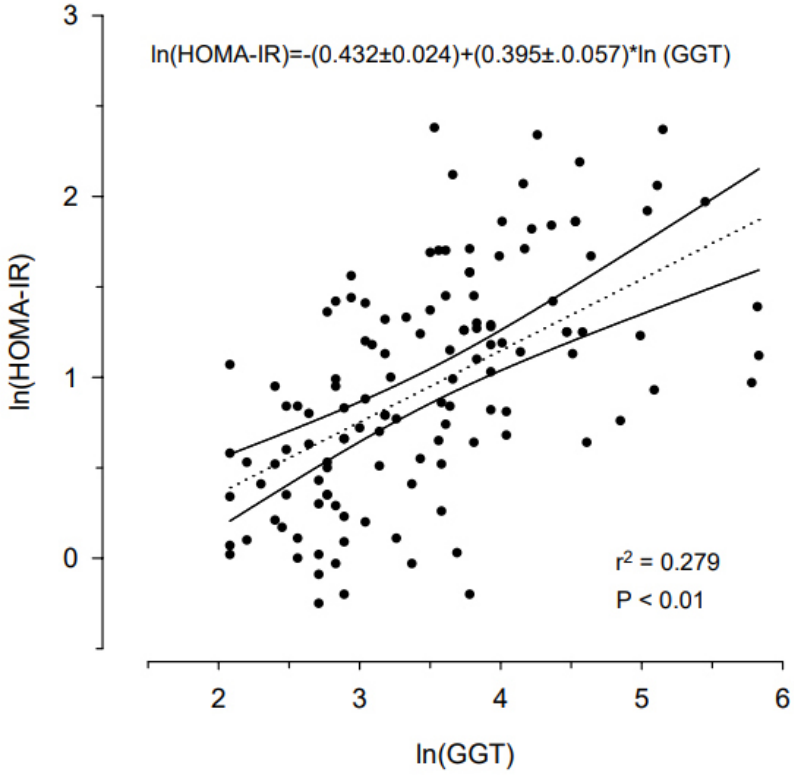

Figure 2. Relationship between HOMA-IR and GGT. Association of (logarithmically transformed) HOMA-IR and (logarithmically transformed) GGT as estimated by regression analysis ($r^2 = 0.279$, $P < 0.01$). Reprinted with permission from[31].

[interquartile range (IQR): 6.2-10.2 years]. This study showed that elevated serum activities of ALT and GGT in the subclinical range were strongly associated with incident post-transplant T2D in renal transplant recipients.

Of note, while confirming that NAFLD, diagnosed either by ultrasonography or liver enzymes, predicted incident T2D, another meta-analysis by Lallukka and Jarvinen[35] found that NAFLD associated with specific genetic traits was not associated with excess risk of incident T2D. Whether those genetic polymorphisms predisposing to NAFLD[36] are also associated with lower GGT values compared to "metabolic NAFLD" in adults remains to be investigated. However, a study conducted on German children found that serum ALT activities were significantly different among carriers of different patatin-like phospholipase domain containing 3 (PNPLA3) genotypes (ANOVA, $P = 0.022$). The *PNPLA3* gene encodes for the membrane bound PNPLA3 enzyme, which is mainly expressed in the liver (where it is involved in hepatic steatosis) and adipose tissue (where it mediates acylglycerol hydrolysis). However, carriers of the PNPLA3 p.148Met/Met variant did not show any variations in AST or, importantly, GGT serum activities[37].

Adding momentum to this consistent line of research, Zhao *et al.* investigated the dose-response risk of incident T2D as a function of GGT serum activity at baseline, assessed with the evaluation of 15,464 Japanese participants followed for up to 13 years[38]. The study found that the risk of incident T2D increased by 4% for every 1 IU/L increase in the baseline serum GGT (when GGT was < 24 IU/L). Hua *et al.* aimed to explore the role, if any, of ethnicity and other potential confounding factors in the association of GGT with incident T2D, by prospectively evaluating a large sample of 6928 adults of Hispanic/Latino background who were free of T2D or hepatitis virus and did not drink excess alcohol at study entry, over a six-year follow-

up[39]. The highest quartiles of ALT and GGT (compared to the lowest quartile) were associated with an increased risk of developing incident T2D [risk ratio (RR): 1.51; 95%CI: 1.03-2.22; *P*-trend = 0.006 for ALT; RR: 2.39; 95%CI:1.60-3.55; *P*-trend = 0.001 for GGT]. Interestingly, higher GGT values were associated with an increased risk of incident T2D even among individuals with ALT or AST below the median levels. The associations of ALT and GGT with incident T2D were similar among most individuals of Hispanic heritage except for subjects of Dominican ancestry (*P* for interaction < 0.05)[39]. Based on these findings, the authors concluded that assessment of liver enzymes could identify individuals at a high risk of incident T2D who may benefit from T2D prevention interventions.

One of the most recently published studies evaluating the risk of incident T2D in relationship with GGT levels showed an increased incidence rate and risk of T2D in parallel with cumulative exposure to high GGT values. The study by Park *et al.* included 346,206 Korean subjects free of T2D who were followed over a mean of 9.2 ± 1 years[40]. In this study, the relationship between the number of exposures (ranging from 0-5 exposures) to high GGT (defined as those in the highest quartile of GGT activity) and the risk of developing T2D was assessed. After adjustment for confounding factors, subjects with five consecutive high GGT levels (exposures) were at increased risk of incident T2D with a HR of 2.60 (95%CI: 2.47-2.73) in men and a HR of 3.05 (95%CI: 2.73-3.41) in women, compared to subjects who had never had high GGT levels[40].

Finally, Wang *et al.* assessed the relationship between trajectories of change in GGT activity and incident hyperglycemia among 4547 individuals followed for three years[41]. Adjusted HRs of hyperglycemia for the high-increasing and low-increasing classes (of GGT activity) were 1.341 (CI: 1.076-2.051) and 1.264 (CI: 1.048-1.525) when compared to the stable class. Additionally, a steeper GGT slope more effectively predicted incident hyperglycemia than the absolute GGT value, and this finding was more evident among men than women[41].

In aggregate, recent studies further support the association between elevated GGT activity and the risk of incident T2D and lay the foundations for monitoring and lowering GGT levels as a reasonable public health target for T2D prevention. Specific interventions to be considered thus far are discussed later in this review (Section 10).

GGT, METABOLIC SYNDROME, NAFLD, AND FIBROSIS

Bertoli *et al.* studied the relative contribution of visceral (VAT) and subcutaneous (SAT) adipose tissue to cardiometabolic disease by dissecting abdominal adipose tissue in VAT and SAT with ultrasonography and assessed the specific association of these types of adipose tissue with metabolic syndrome and its constitutive features including hyperuricemia and raised liver enzymes compared to adipose tissue assessed by waist circumference[42]. Based on the cross-sectional evaluation of 2414 Italian adults, they found that VAT had the strongest association with high triglycerides, high ALT, and high GGT levels; in addition, compared to waist circumference, VAT was associated more strongly with high ALT and high GGT levels and similarly associated with hyperglycemia and hyperuricemia[42]. Given that visceral obesity (hence, expanded and inflamed VAT) may be envisaged as the "pace-maker" of metabolic syndrome[43,44], this study lends further support to GGT as an enzyme of major metabolic significance.

Along the same lines, Chen *et al.* performed a community-based study of 1566 Taiwanese patients with NAFLD who were divided into four groups based on ALT and GGT activity values: normal GGT/normal ALT (n = 1217), elevated GGT/normal ALT (n = 101), elevated ALT/normal GGT (n = 147), and elevated GGT and ALT activities (n = 101)[45]. Additionally, 1147 controls (normal ALT, GGT, and abdominal ultrasonography) were included. Data show an association of GGT with high sensitivity C-reactive protein,

lower adiponectin, T2D, and CKD. Compared to controls, a progressive increase in the risk of metabolic syndrome was found among subjects with normal GGT [odds ratio (OR) = 1.71], isolated elevation of GGT (OR = 3.06), isolated elevation of ALT (OR = 4.00), and elevation of both GGT and ALT activities (OR = 4.17). At linear regression analysis, a positive association between GGT or ALT values and the extent of hepatic steatosis and liver fibrosis stage was found[45]. This study supports the biologically plausible possibility that, in patients with NAFLD, raised GGT values are associated with metabolic syndrome, severity of hepatic steatosis, and fibrosis. Expanding these findings to morbid obesity, Coccia *et al.* evaluated 90 patients undergoing bariatric surgery and intraoperative liver biopsy[46]. Of these, 77 non-diabetic individuals underwent oral glucose tolerance tests and calculation of the Oral Glucose Insulin Sensitivity index (OGIS). Data show that ALT (P = 0.03), GGT (P = 0.008), triglycerides (P = 0.04), and HOMA-IR (P = 0.05) increased in parallel with the stage of liver fibrosis assessed histologically[46].

A population-based study conducted in Northern Italy (the Bagnacavallo Study)[47] shed some doubt on the true diagnostic accuracy of GGT in identifying liver fibrosis in a non-hospital-based setting. Foschi *et al.* evaluated 2159 subjects, with approximately a third of whom (636 subjects; 29%) undergoing transient elastography - a surrogate non-invasive marker of liver fibrosis - for assessing liver stiffness[47]. Data show that the mean change in liver stiffness associated with an increase from the 5th to 95th internal percentile of various markers, notably including logarithmically transformed GGT, was ≤ 1 kPa and, therefore, of arguable clinical significance[47]. The authors[47] suggested that the so-called "spectrum bias" may have accounted for their findings, i.e., the substantial variability in the performance of a given diagnostic test as a function of the variable prevalence of the underlying disease[48].

Kozakova *et al.* studied 825 healthy European adults at low to below average 10-year cardiovascular risk and free of metabolic syndrome and liver disease and a control group of 154 apparently healthy non-obese subjects at low to below average CV risk and free of metabolic syndrome and liver disease[49]. Data show that GGT levels were directly and independently associated with the diameter and stiffness of large arteries. Additionally, subjects with pre-hypertension had significantly higher GGT levels and arterial stiffness than normotensive controls, and pre-hypertensive individuals who developed hypertension over a three-year follow-up period had significantly higher baseline GGT levels than those in whom no such blood pressure variation was registered[49]. This study suggests the use of GGT to detect individuals at risk of incident arterial hypertension and macrovascular hypertensive arteriopathy. However, it remains to be ascertained whether interventions resulting in GGT lowering would halt the progression of vascular disease.

Zinterl *et al.* conducted a cross-sectional study of the associations of peak oxygen uptake (VO_{2peak}) with liver fat content (LFC) assessed by magnetic resonance imaging proton density fat fraction, GGT, and aminotransferase measurement in a sample of 2151 German adults from two population-based cohorts[50]. Significant inverse associations of VO_{2peak} with LFC and serum GGT (but not with serum aminotransferase levels) were found, such that 1 L/min lower VO_{2peak} was associated with a 1.09% (95%CI: 0.45-1.73; P = 0.002) higher LFC and a 0.18 μkatal/L (95%CI: 0.09-0.26; P < 0.001) higher GGT serum activity[50]. Zinterl *et al.* suggested that attempts to improve VO2 peak may reduce LFC and GGT levels[50]. However, this hypothesis remains to be proven by specific randomized controlled trials. Of note, the study supports the notion that raised GGT values may be a marker of sedentary behavior. Therefore, the recent attempts to introduce GGT as a parameter for stratifying dysmetabolic patients may improve our personalized medicine approach to metabolic disorders and NAFLD[51-53].

Pennisi *et al.* applied competing risks modeling to conduct a retrospective analysis of data from two multicenter subsets of patients with NAFLD prospectively recruited in Italy and other countries in whom

the assessment of liver fibrosis had been conducted either histologically (study cohort n = 2135 patients) or non-invasively (validation cohort n = 2790 patients)[54]. Data show that, among patients with more advanced hepatic fibrosis (i.e., F3-F4 stages), older age, obesity, thrombocytopenia, and higher GGT activity (transformed in log scale) were independent correlates of the risk for liver-related events (defined as ascites, variceal hemorrhage, encephalopathy, jaundice, or hepatocellular carcinoma)[54]. Taken in the context of previous investigations, this study suggests that GGT interpretation should best be flexible based on the patient population under consideration. In the specific setting of individuals with advanced chronic liver disease, raised GGT levels do predict complications of cirrhosis rather than cardiovascular events.

Compared to NAFLD, our understanding of the role of GGT in diagnosing metabolic-associated fatty liver disease (MAFLD) is more limited owing to the paucity of published studies. With this background, two recent studies suggest that GGT plays a role in the diagnosis of MAFLD. In the study by Liu *et al.*, which included 229 participants (97 with MAFLD and 132 non-MAFLD controls), GGT was found to be an independent risk factor for MAFLD (OR: 1.055; CI: 1.032-1.078; $P < 0.001$)[55]. Consistent with this pioneering study, Guan *et al.*, in their population-based study enrolling 204,394 individuals (71,756 with MAFLD), found that GGT was significantly associated with the diagnosis of MAFLD with an OR of 1.002 (CI: 1.002-1.002; $P < 0.001$)[56]. These interesting findings need to be confirmed in non-Asian populations.

GGT AND CARDIOMETABOLIC RISK

The epidemiological evidence linking GGT with cardiometabolic risk in studies performed before 2016 has been recently reviewed[57]. The points raised by this review are summarized in Figure 3.

More recent epidemiological studies are summarized in Table 1[58-60]. The association of GGT with the risk of atrial fibrillation (AF) or heart failure has also been reported and reviewed elsewhere[20]. The best evidence with respect to the association between GGT and the risk of AF comes from a meta-analytic review by Liu *et al.*, who elaborated on five prospective studies with a total of 282,615 participants and 7062 AF events[61]. Data show an adjusted RR of 1.10 (95%CI: 1.06-1.14) for incident AF per one standard deviation change in log baseline GGT value[61]. Notably, GGT but not aminotransferases (for ALT, RR: 1.04; 95%CI: 0.90-1.20; P = 0.607; for AST, RR: 1.05; 95%CI: 0.96-1.15; P = 0.268) was associated with the risk of AF.

Studies in the early 2010s consistently demonstrated that raised GGT serum activities at baseline were associated with a higher risk of subsequent incident heart failure[62-64]. A more recent population-based longitudinal cohort study that assessed GGT variability (a calculated index assessing the coefficient of variation, standard deviation, and variability independent of the mean) in 119,201 individuals found that higher GGT variability was strongly associated with a significant increase in the incidence of hospitalized heart failure, particularly among dyslipidemic subjects[65]. This study suggests that higher variability of GGT levels is a potential biomarker of the risk of incident heart failure requiring hospitalization and, therefore, a potential tool for preventing this condition.

PATHOPHYSIOLOGICAL MECHANISMS OF THE ASSOCIATION OF GGT WITH CARDIOMETABOLIC RISK

Whether GGT plays a direct role in atherogenesis and its clinical correlates or its elevated levels are only an epiphenomenon of concomitant cardiovascular risk factors remains incompletely elucidated.

The putative pathophysiological mechanisms of the association between elevated GGT activity and cardiometabolic risk have recently been reviewed[66]. These may be classified into two categories. Elevated GGT serum activities are linked with multiple cardiometabolic risk factors such as metabolic syndrome,

Table 1. Gamma-glutamyl transferase and cardiometabolic risk[58-60]

Author (year)	Type of the study/origin	Number (age; sex)	Follow-up	GGT cut-off	Outcome/risk estimate*	Interpretation
Kunutsor *et al.* (2015)[58]	Prospective cohort; Groningen, Netherland	6969 (mean age: 48 ± 12 years; range 28-75 years; women: 52%)	Median: 10.5 years	1 SD increment in log scale	Cardiovascular disease: adjusted HR = 1.24 [1.12-1.37] Cardiovascular disease: adjusted HR = 1.18 [1.06-1.30] after adjustment for CRP	Positive association; no improvement in the risk prediction by GGT**
Ndrepepa *et al.* (2016)[59]	Observational Munich, Germany	5501 patients with CAD [median age: 67.6 (59.1-75.1); women: 24.5%]	3 years	1 SD increment in log scale	All-cause mortality: adjusted HR = 1.30 [1.18-1.44] Cardiac mortality: adjusted HR = 1.21 [1.06-1.39] Non-cardiac mortality: adjusted HR=1.42 [1.23-1.63]	Positive association with mortality; improvement in risk prediction by GGT
Kim *et al.* (2022)[60]	Population-based (Korean National Health Insurance Service) Asian population (South Korea)	4,056,423 (848,498 with metabolic syndrome) (mean age: 47.0 ± 14.1 years in subjects without SCD and 62.0 ± 13.2 years in subjects with SCD; women: 45% in subjects without SCD and 28.9% in subjects with SCD)	8,162,351 (Q1) 8,789,346 (Q2) 8,184,478 (Q3) 8,209,202 (Q4) (person/years)	Q2, Q3, Q4 *vs.* Q1(reference)	Sudden cardiac death: adjusted HR=1.055 [1.000-1.112] for Q2 *vs.* Q1 Adjusted HR=1.158 [1.098-1.222] for Q3 *vs.* Q1 Adjusted HR=1.519 [1.437-1.605] for Q4 *vs.* Q1 metabolic syndrome: 9.4% *vs.* 44.1% for Q1 *vs.* Q4	Positive association between GGT and sudden cardiac death and metabolic syndrome; GGT variability (increase) associated with an increased risk of sudden cardiac death

CAD: Coronary artery disease; GGT: gamma-glutamyl transferase; HR: hazard ratio; Q: quartile; SCD: sudden cardiac death. *Risk estimates are hazard ratios with 95%CI. **No significant increase was found in C statistic after the inclusion of GGT in the multivariable model.

T2D, insulin resistance, NAFLD/NASH, subclinical systemic inflammation, telomere length, and oxidative stress, and all of them negatively affect the patient's cardiometabolic profile and outcome. This makes GGT a correlate of increased cardiometabolic risk. On the other hand, GGT might also exert a direct local pro-oxidant action contributing to plaque instability, rupture, and thrombosis and related clinical events. GGT activity (even when in the normal range) exerts pro-oxidant activity and catalyzes the oxidation of low-density lipoprotein (LDL) within atherosclerotic plaque, promoting atherosclerosis progression (build-up) and plaque instability[16,67]. Mechanisms of increased cardiometabolic risk related to GGT action are schematically illustrated in Figure 1.

Future prospective studies are needed to evaluate precise molecular pathophysiological mechanisms of GGT involvement in atherogenesis and cardiovascular events as well as to assess the impact of GGT-lowering therapies on these clinical outcomes.

GGT AND CKD

CKD is a common outcome of most cardiovascular risk factors and *per se* an important precursor of cardiovascular disease[68]. The latest evidence supporting

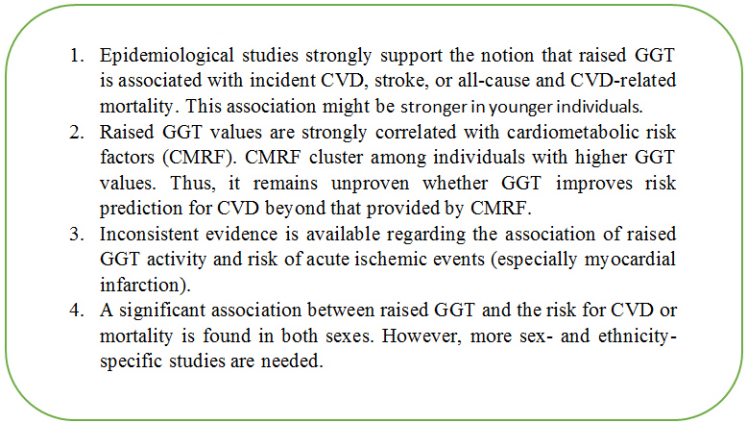

Figure 3. An overview of epidemiological evidence (studies published before 2015) linking raised GGT values with cardiovascular events and mortality[57].

the notion that NAFLD is the main factor for incident CKD comes from a recent meta-analysis of 13 studies with a total of 1,222,032 individuals (28.1% with NAFLD). This study demonstrated that those with NAFLD, compared to NAFLD-free controls, were at an increased risk of incident CKD (HR: 1.43; 95%CI: 1.33-1.54; I^2 = 60.7%) independent of major conventional risk factors of CKD (such as age, sex, obesity, arterial hypertension, and T2D). These findings were not affected by sensitivity analyses, and no significant publication bias was revealed by funnel plot analysis[69].

The association of GGT with both cardiometabolic risk factors and cardiovascular events (as discussed in Sections 5 and 6) and the close association between GGT and cardiovascular risk may sustain the argument that GGT and CKD are related. However, recent studies do not fully support this notion. Fan *et al.* conducted a meta-analytic review of eight studies with a total of 116,011 participants[70]. The study reported that subjects with the highest GGT serum activity did not exhibit a significantly higher risk of CKD [risk ratio (RR): 1.14; 95%CI: 0.99-1.31] compared to subjects with the lowest GGT activity. Although the pooled RR for the highest *vs.* the lowest GGT activity categories did show a 30% increased risk in studies of subjects from Asian countries (RR: 1.31; 95%CI: 1.06-1.60), it remained non-significant in studies of subjects from Western countries (RR: 1.04; 95%CI: 0.88-1.23) and sex-stratified analysis for both women (RR: 0.95; 95%CI: 0.84-1.07) and men (RR: 1.08; 95%CI: 0.86-1.36)[68]. In the study by Fan *et al.*, CKD was defined based on an estimated glomerular filtration rate (eGFR) cut-off of < 60 mL/min per 1.73 m^2 for more than three months or the presence of albuminuria[70]. It is uncertain what the findings could have been if analyses had been performed using the eGFR criterion alone. Additional ethnicity-specific data are eagerly awaited to understand these conflicting findings.

GGT, NEURODEGENERATIVE DISORDERS, AND DEMENTIA

Increased oxidative stress - due to excessive production of reactive species or insufficient antioxidant defense - is an important player in the pathophysiology of neurodegenerative disorders, damage to brain cells, and dementia[71].

A recent study from the Korean National Health Insurance Service (NHIS) database analyzed the association between GGT and Parkinson's disease. Subjects with heavy alcohol consumption, hepatobiliary and pancreatic disorders, and a previous history of Parkinson's disease were excluded, and the association between baseline GGT and incident Parkinson's disease was assessed over seven years. Parkinson's disease developed in 20,895 of 6,098,405 subjects (0.34%). Men and women in the upper quartile of GGT activity

had a 28% lower and 30% higher adjusted risk for developing Parkinson's disease, respectively, compared with the lower (reference) GGT quartile. Obesity and metabolic syndrome increased the risk for Parkinson's disease in both sexes[72]. A retrospective analysis of the Korean NHIS 2004-2016 datasets assessed the risk of incident dementia (all-cause dementia, Alzheimer's disease, and vascular dementia) according to GGT sex-specific quartiles and variability in individuals ≥ 40 years of age without dementia at baseline (n = 6,046,442) over a mean follow-up of 6.32 years. The fully adjusted risk for incident dementia was 3.4%, 9.0%, and 21.2% for GGT Quartiles 2, 3, and 4 *vs.* Quartile 1, respectively. The association between GGT variability quartiles and dementia risk remained significant even after adjusting for log-transformed baseline GGT values. The risk was highest in the group with a high baseline GGT level and highest GGT variability (27.3%)[73]. Consistently, another recent study conducted on 2943 Chinese women showed that the prevalence of mild cognitive impairment increased from 8.4% among women in the first GGT tertile to 21.4% among women in the fourth GGT quartile with a higher prevalence in the presence of obesity, sleep deprivation, hyperuricemia, or menopause[74].

Although supported by epidemiological evidence, the causality between elevated GGT levels and the risk of dementia remains unproven. A recent Mendelian randomization study assessed the association between GGT and Alzheimer's disease using summary statistics for single nucleotide polymorphism (SNP)-Alzheimer's disease associations obtained from the International Genomics of the Alzheimer's Project of 17,008 individuals with Alzheimer's disease and 37,154 controls[75]. Overall, 26 SNPs significantly associated with GGT in a previous genome-wide association study on liver enzymes were assessed. The odds ratio for Alzheimer's disease was 1.09 (95%CI: 0.98-1.22; P = 0.10) per one standard deviation of genetically elevated GGT[75], indicating no causality in the association between GGT and the risk for Alzheimer's disease. More studies are needed to assess the association between elevated GGT and the risk of neurodegenerative disorders and dementia.

GGT AND PULMONARY ARTERIAL HYPERTENSION

Increased oxidative stress plays a crucial role in the development and progression of pulmonary hypertension. In patients with pulmonary arterial hypertension, increased lipid peroxidation, reduced GSH, and low vitamin E concentrations have been reported[76].

A recent study compared serum GGT levels in 338 consecutive adult patients with idiopathic pulmonary arterial hypertension who underwent genetic counselling for bone morphogenetic protein receptor type 2 (BMPR2) and 338 age- and sex-matched healthy subjects[77]. Increased GGT levels were more frequent among cases than controls; moreover, increased GGT levels correlated with BMPR2 mutation, hemodynamic dysfunction, and poor outcomes in male patients with idiopathic pulmonary arterial hypertension[77].

A retrospective analysis of 731 incident cases of pulmonary arterial hypertension showed that GGT, AST to ALT ratio, and neutrophil to lymphocyte ratio (NLR) were reliable prognostic biomarkers at baseline and follow-up, with predictive power comparable to the gold standard for risk stratification of patients with pulmonary arterial hypertension[78]. Elevated GGT levels in patients with pulmonary arterial hypertension may reflect an increased burden of oxidative stress or liver dysfunction developing in the setting of the disease[79]. However, further studies are needed to assess whether GGT plays a mechanistic role in the pathophysiology of idiopathic pulmonary hypertension or the risk stratification of patients with this disease.

EFFECTS OF TREATMENT ON GGT VALUES

Interventions addressing GGT outcomes in the setting of various treatment options in patients with NAFLD and NASH are summarized in Table 2[80-85].

Collectively, these studies demonstrate that various interventions have proven effective in reducing serum GGT levels, including lifestyle changes, drugs, and metabolic surgery. Therefore, these or other approaches should best be evaluated by future randomized controlled trials, especially in subjects at increased risk of incident T2D and cardiovascular events.

GGT AND CORONA VIRUS DISEASE 2019 (COVID-19)

A recent literature review by Bertolini *et al.* reported elevated GGT levels in 13%-54% of patients with COVID-19 (weighted average: 23%)[86]. The pathophysiological mechanisms underlying elevated GGT levels among patients with COVID-19 remain poorly characterized, but potential contributors may include direct viral infection of hepatobiliary tissue, the host's inflammatory response to the viral infection, drug-induced liver injury, and pre-existing liver disease in a poorly defined proportion of patients[84]. Irrespective of the mechanism involved, it is of concern that raised GGT independently predicted in-hospital mortality, as shown in a study on 802 participants[87]. These data confirm a pioneering smaller study conducted in Wuhan, China[88], which reported that elevated GGT levels were common among patients with severe COVID-19 and positively associated with a prolonged hospital stay and severity of disease. However, by focusing only on COVID-19 patients without previous liver disease, Ponziani *et al.* found that GGT elevation was present in 13.6% of 515 patients with proven SARS-CoV-2[89]. Moreover, they found that the values of liver tests initially increased during hospitalization and improved over time, finally reaching values in the same order of magnitude as they were at the baseline. According to this study, liver test abnormalities at the baseline were indeed associated with increased risk of intensive care unit admission (OR: 2.19; 95%CI: 1.24-3.89; $P = 0.007$) rather than with mortality (OR: 0.84; 95%CI: 0.49-1.41; $P = 0.51$)[87].

The preferential increase in GGT activity in severe cases of COVID-19 remains incompletely investigated. However, postmortem studies have provided evidence on the liver tropism of SARS-CoV-2, including viral RNA detection in 69% of liver autopsies and isolation of SARS-CoV-2 from liver tissue[90]. Furthermore, other studies have shown that angiotensin-converting enzyme 2 - the host receptor for SARS-CoV-2 - is expressed in epithelial cells (cholangiocytes) of the bile duct[91]. Thus, a direct virus-related injury to cholangiocytes may cause cellular injury-related GGT release and inflammation-related biliary obstruction, both favoring preferential GGT elevation in circulation in severe cases of COVID-19.

CONCLUSION

GGT is a ubiquitous glycoprotein located on the outer surface of cell membranes, which catalyzes the transfer of glutamyl groups between various substrates and regulates antioxidant homeostasis. First introduced in clinical practice in the mid-1960s and early 1970s as an indiscriminate biomarker of various liver diseases, cholestasis, and exposure to alcoholic beverages, GGT is presently abandoned in many areas of the world due to cost-benefit issues[24].

However, GGT, together with BMI and triglycerides, is integrated into the fatty liver index (FLI) equation - an established non-invasive surrogate index of NAFLD originally developed by Bedogni *et al.*[92]. FLI also predicts NAFLD's extrahepatic complications including cardiometabolic risk, atherosclerosis, T2D, CKD, extrahepatic cancers, and mortality[93], further supporting a role for GGT as a cardiometabolic biomarker. Interestingly, new fields for GGT use have emerged, and GGT testing is increasingly being evaluated in diseases such as portal hypertension in cystic fibrosis, PSVD, and malignant mesothelioma and as a

Table 2. Effect of various lifestyle changes, pharmacological and non-pharmacological therapeutic interventions, and surgery on GGT serum values[80-85]

Author	Type of study/origin	Method	Interventions	Findings	Interpretation
Du *et al.* (2014)[80]	Meta-analysis of 5 randomized trials/2 from USA; 1 each from Romania, Singapore, and Turkey	147 patients with NAFLD/NASH	Pentoxifylline *vs.* placebo	Pentoxifylline reduced: body weight ($P = 0.04$); ALT ($P < 0.00001$); AST ($P = 0.0006$) glucose ($P = 0.0008$); tumor necrosis factor-α ($P = 0.007$); NAFLD activity score ($P < 0.00001$) and improved lobular inflammation ($P < 0.0001$). No significant effect on: body mass index ($P = 0.28$); total cholesterol ($P = 0.80$); triglyceride ($P = 0.98$), alkaline phosphatase ($P = 0.29$, GGT ($P = 0.39$) and interleukin-6 ($P = 0.38$); steatosis grade ($P = 0.11$); ballooning ($P = 0.10$) and fibrosis ($P = 0.50$)	Pentoxifylline therapy results in weight loss, improved liver tests, and to a limited extent, histological findings in patients with NAFLD/NASH
Franzini *et al.* (2017)[81]	Observational/ Italy	29 patients with T2D (22 women and 7 men) undergoing bariatric surgery. NAFLD was assessed histologically	5-hour mixed meal test before (T0), 15 days (T15), and 1 year after surgery (T365)	Laparoscopic sleeve gastrectomy but not Roux-en-Y gastric bypass reduced total GGT activity by 40% ($P = 0.007$) after T15, Reduction of total GGT; b-GGT by ≥ 60%; m-GGT by ≥ 50%, in all patients at T365. Higher levels of total, b-, s-, and m-GGT fractions at T0 in patients with biopsy-proven steatohepatitis ($n = 10$) compared with patients with low-grade steatosis. After adjustment, b-GGT was the only fraction related to insulin sensitivity	Laparoscopic sleeve gastrectomy reduced GGT NASH patients exhibit higher GGT values than those with simple steatosis Fraction b-GGT is specifically associated with insulin sensitivity
Laine *et al.* (2017)[82]	Randomized/France	274 non-diabetic dysmetabolic iron overload syndrome patients (119 iron-depleted and 114 controls were men) with hepatic iron > 50 μmol/g at magnetic resonance imaging	Bloodletting associated with lifestyle and diet advice ($n = 146$) *vs.* lifestyle and diet advice ($n = 128$)	Iron depletion (serum ferritin levels < 50 μg/L at 1 year) did not reduce GGT activity (54 ± 138 vs 49 ± 35 IU/L) ($P = 0.72$)	Iron depletion did not improve hepato-metabolic outcomes in subjects with non-diabetic dysmetabolic iron overload syndrome
Ma *et al.* (2021)[83]	Retrospective/China	1,048 NAFLD patients (Men 744; Women 304). 60.7% with abnormal GGT and 73.2% with abnormal ALT levels. NAFLD was diagnosed based on either ultrasonography or MRI.	Lifestyle modification and pharmaceutical interventions	Cumulative normalization rate of GGT was lower than that of ALT (38% *vs.* 62%, $P < 0.001$). Greater weight loss correlated with higher cumulative normalization rates of GGT and ALT. Independent correlates of GGT normalization were weight loss, ALT normalization, lower triglyceride, and HOMA-IR values. Elevated baseline GGT correlated inversely with GGT normalization	The normalization of GGT is less frequent than ALT in patients with NAFLD and concomitant GGT and ALT elevation Control of weight and insulin resistance was associated with GGT normalization
Malik *et al.* (2021)[84]	Meta-analysis (4 clinical trials/France)	270 patients (M/F ranged from 100/0 to 49/44 across the various treatment groups).	Elafibranor - a PPAR alpha and delta dual agonist ($n = 201$) *vs.* placebo ($n =$	Elafibranor reduced: GGT ($P < 0.001$), ALT ($P = 0.01$), total cholesterol ($P = 0.01$),	PPAR-alpha/delta dual agonist, elafibranor, improved metabolic parameters in

		Mean age ranged from 49 (± 9) years (Elafibranor) to 52.4 (11.9) years (Placebo arm).	69)	triglycerides ($P < 0.01$), ALP ($P < 0.01$) and low-density lipoprotein ($P = 0.003$). No significant impact on: HOMA-IR ($P = 0.26$) and AST values ($P = 0.53$)	dyslipidemic patients
Pastori *et al.* (2022)[85]	Meta-analysis of 22 studies: 16 with interventional, five with cross-sectional study and one with combined cross-sectional-and- interventional design/The majority of studies were from Europe[11] and the others from Japan, USA and Korea.	2,345 patients (% of women varied from 45.7% to 60.7% across the various studies) with NAFLD diagnosed histologically or based on imaging studies	Statin therapy *vs.* no statin therapy	GGT, ALT and AST at baseline were elevated in 15 of 16 interventional studies. Statin therapy reduced GGT by 19.93 U/L (-25.57%), ALT by 27.2 U/L (-35.41%) and AST levels by 18.82 U/L (-31.78%) in interventional studies. Statin therapy did not reduce GGT and AST values in cross-sectional studies	Statin therapy reduced ALT, AST and GGT values in patients with NAFLD The meta-analysis suggested that statin therapy is safe in patients with NAFLD

ALP: Alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; HOMA-IR: homeostasis model of insulin resistance; MRI: magnetic resonance imaging; NAFLD: nonalcoholic fatty liver diseas.

surrogate marker of (fibrosing) NAFLD and insulin resistance. There is solid pathophysiological evidence for an association (or involvement) of GGT with the risk of incident T2D, metabolic syndrome, cardiovascular disease, atrial fibrillation, and congestive heart failure. However, the evidence linking GGT with CKD remains controversial and incomplete. Additional areas of research include dementia and pulmonary hypertension.

Various treatment strategies have proven effective in decreasing GGT values in humans. Nevertheless, current knowledge of such strategies is far from complete, and well-designed studies are needed to define whether these interventions will also result in a concomitant reduction in the risk of incident cardiometabolic disorders.

Based on data discussed in this concise review, we conclude that GGT may be utilized in public health campaigns and in research and clinical fields to detect individuals who, being exposed to high cardiometabolic risk, can benefit from proactive preventive and therapeutic approaches.

DECLARATIONS

Authors' contributions

Conceived the design of this article and wrote the first draft. He also participated in the process of revising and editing the manuscript and approved the submitted version of the manuscript: Lonardo A

Involved in data acquisition, analysis, and interpretation, revision of the manuscript for intellectual content, approval the submitted version of the manuscript: Ndrepepa G

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
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Consent for publication
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