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Commentary

Gamma glutamyl transferase: A novel cardiovascular outfit for an old liver test

In Mesopotamian cultures, the liver would be considered the seat of life and the soul and had the same meaning as the heart has in modern western culture[1]. Against this historical background, it comes as no surprise that contemporary medicine has gone back to the past by proposing a functional connection between hepatic and cardiac conditions[2]. Is this connection scientifically justified ?

In this issue Kasapoglu *et al*[3] report on their large series of 982 control individuals without fatty liver compared to 1,818 individuals with various degrees of fatty liver evaluated ultrasonographically. This study has two findings: First, that the risk of cardiovascular disease assessed through the Framingham Risk Score (FRS) increases with the presence and severity of fatty liver disease. Second, gamma-glutamyl transpeptidase/ transferase (GGT) levels and FRS are positively correlated among non-diabetic, non-obese adults. Based on these findings, the authors conclude that elevated (though in the normal range) GGT levels among patients with fatty liver disease should be regarded as an alarm sign of increased cardiovascular risk (CVR).

In order to put these findings into a larger perspective, we should ask ourselves four key questions exploring the GGT-fatty liver liver-vessels triangle.

(i) What is fatty liver and why should it be associated with CVR?

Fatty liver is defined by fatty substrates, mostly triglycerides, exceeding 5 per cent of hepatocytes, predominantly under the form of macro-vesicular steatosis. Given that the only physiological reservoir of fat in the human body is adipose tissue, steatosis is an example of ectopic fat deposition predisposing to organ dysfunction[4]. Metabolic derangements are the most important among several causes associated with the development of steatosis[5]. Hepatic steatosis due to metabolic derangements, usually in the setting of the metabolic syndrome, is most commonly alluded to as primary non-alcoholic fatty liver disease (NAFLD)[6].

NAFLD is a major public health concern on the grounds that it reaches epidemic proportions among the general population worldwide (up to 20-30% of individuals in Eurasia and northern America, respectively), accounts for the large majority of altered liver tests in asymptomatic individuals and poses a substantial health burden in terms of expenditures owing to liver-related, metabolic, cardiovascular and oncologic complications[6,7].

Over the last few years, NAFLD has been increasingly identified as an independent CVR factor[2,8,9]. The biological mechanisms underlying the connection of NAFLD with CVR are not fully understood owing to the close and indissectable relationship linking NAFLD with insulin resistance (IR) and visceral obesity[9]. Overflow of glucolipid substrates, excess synthesis of pro-inflammatory cytokines and a pro-thrombotic milieu are likely to generate a vicious circle of increasing CVR and ongoing liver injury[9-11]. Progress in our understanding of the physio-pathological links of NAFLD with cardiovascular, cardiac and arrhythmic complications has the potential for identifying molecular targets useful in enhancing the efficacy of drug treatment of NAFLD.

(ii) What is GGT and why should it be associated with CVR?

GGT is a membrane-bound enzyme which catalyzes synthesis and trans-membrane transport of proteins, counteracts oxidative stress by making cysteine available for regeneration of intracellular glutathione and contributes to the detoxication of ammonium of

some drugs[12,13]. Various organs with absorption and secretion capacity are rich in GGT, including the liver, the kidney, the pancreas, the bowel and the prostate[14]. Although the kidney is approximately ten-times richer in GGT activity than the liver, serum GGT is deemed to be mainly of hepatobiliary origin and, accordingly, has been used as a "liver test" for decades[12].

The reasons for elevated GGT values in those with hepatobiliary disease include, increased *de novo* synthesis, increased release from cell membranes owing to the detergent effect of bile salts; backflow into the bloodstream, increased permeability and distruction of biliary epithelia[12,15].

Hepatologists are fully aware that GGT is the most sensitive and the least specific among liver enzymes. Not only do GGT serum concentrations increase earlier and last longer than that of other liver enzymes but, of concern, these are associated with an aetiologically diverse spectrum of hepatobiliary disorders and to an ever increasing number of extrahepatic conditions[15]. Among these, over the last decade, GGT enzyme activity has been found to be associated with cardiometabolic conditions such as insulin resistance; the development of hypertension; sub-clinical myocardial injury; atheromatous plaque formation; risk of diabetes, metabolic syndrome and its inherent oxidative stress; increased arterial stiffness, independent of the classical atherosclerotic and cardiovascular disease risk factors and chronic kidney disease in non-hypertensive and non-diabetic individuals[16-20].

In humans, reduced glutathione (GSH) is a critical antioxidant defence, the failure of which will eventually result in impaired endothelial mediated vasodilation owing to unbuffered elevations in free radicals[21]. Oxidative stress, resulting from dysregulated glucolipidic homeostasis and insufficient antioxidant defence, coupled with vascular inflammation, will eventually lead to endothelial dysfunction which, in its turn, is an early manifestation of and a potential contributor to atherogenesis and microvascular disease[22].

Serum GGT activity should be considered a biomarker of increased glutathione demand relevant in the development of endothelial dysfunction and subsequent arteriosclerosis[22]. As a biomarker of GSH status, GGT has several technical advantages such as low cost, easy sample preparation, stability in previously thawed samples and ready availability of clinical laboratory measurement techniques[22]. However, the limitations of GGT as a novel marker of cardiovascular health need to be acknowledged. For example, adding GGT to conventional CVR factors is unlikely to improve the prediction of first-ever cardiovascular events in the general population[23]. Moreover, a large cross-sectional study found no significant association of GGT concentration with carotid intima media thickness or plaques[24].

(iii) What is the evidence for a link between GGT and NAFLD?

A population study conducted in Germany has shown that compared to steatosis-free subjects, individuals with steatosis assessed ultrasonographically have approximatively 10 per cent higher serum alanine transferase (ALT) and GGT levels and approximately 3 per cent higher median serum aspartate transferase (AST) values[25]. Consistently, a multi-centre study from Brazil reported that elevated levels of ALT, AST and GGT are observed in 55.8, 42.2 and 63.1 per cent cases, respectively[26]. Taken collectively, these findings suggest that GGT is more sensitive than transaminases in detecting NAFLD.

However, GGT is less specific than ALT in mirroring the grade of steatosis assessed through the gold standard technique magnetic resonance proton spectroscopy. A cross-sectional study conducted in China in 475 obese adults aged 40-65 yr found that at adjusted logistic regression analysis, intrahepatic triglyceride content was significantly associated with increasing ALT but not with serum AST or GGT values[27].

A study conducted in twins[28] offers a potential clue in understanding why GGT is less specific than other liver tests. Loomba *et al*[28] performed a phenotypic study in 362 twins and concluded that the beta2-adrenergic receptor gene had pleiotropic effects on plasma levels of GGT and triglycerides, indicating linked adrenergic pathways between the genetic susceptibility to develop both NAFLD and the metabolic syndrome. Therefore, genetic and metabolic influences modulate the risk of developing elevated GGT values in NAFLD.

(iv) How should CVR be diagnosed and managed in those with fatty liver?

Given that, in NAFLD patients, cardiovascular (rather than liver-related) events are the leading cause of morbidity and mortality, NAFLD is increasingly recognized as an independent CVR factor[2,8]. Thus, in the future, properly designed and conducted studies

need to ascertain whether adding NAFLD will result - as expected - in the currently used risk scores, *e.g.* the FRS, predicting cardiovascular events more accurately[9].

Recently, based on current evidence and expert opinion, a pragmatic algorythm for the diagnosis and management of CVR in NAFLD patients without a history of coronary artery disease or other clinical complications of atherosclerotic disease has been proposed[9]. However, this algorithm needs prospective validation before it can be applied to clinical practice.

Optimal management of nonalcoholic steatohepatitis (NASH) should ideally include a patient-tailored approach aimed at, on the one hand, controlling cardiometabolic risk factors and, on the other hand, protecting the liver from necro-inflammatory and fibrotic changes. Various innovative agents are/will be available to this end, including mipomersen, obethicolic acid, simtuzumab and RO5093151, the efficacy and safety profile of which needs to be further clarified[9]. Finally, although premature to be proposed for clinical use today, antiplatelet and anticoagulation therapies may, in principle, reduce the risk of developing various hepatic complications and possibly improve liver histology[9]. On these grounds, their use will have to be more extensively evaluated in experimental NAFLD before it can be proposed in future randomized controlled trials in NAFLD patients at high CVR.

In conclusion, it looks as if modern medicine is going back to historically remote cultures by highlighting those functional connections linking the heart with the liver. Full understanding of such mechanistic links offers an opportunity to be exploited for diagnostic, preventive and therapeutic purposes both in the hepatological and in the cardiovascular arena.

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