Quo Vadis: From Oxidative Stress to Gamma-Glutamyltransferase Upregulation to Mortality

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Serum levels of the hepatobiliary enzyme gamma-glutamyltransferase or gamma-glutamyl transpeptidase (GGT) have recently been associated with hepatic involvement of patients with atherosclerotic cardiovascular disease (CVD).^{1–3} In the current issue of JCEH, Loomba et al.⁴ report a study showing that elevated serum GGT (>51 U/L in men and >33 U/L in women) seems to be an independent predictor of CVD, liver mortality and all-cause mortality in older adults (mean age 70 years). These observations were made in a prospective study of 2,364 individuals. The study results indicate that individuals with elevated GGT were more likely to be obese, hypertensive with higher systolic blood pressure, dyslipidemic, and diabetic. These risk factors are associated with the profile of an individual with metabolic syndrome who may have a very high likelihood of having underlying non-alcoholic fatty liver disease (NAFLD).

In the last 5 year, there has been a renewed interest in serum GGT as an indicator of chronic diseases such as NAFLD, metabolic syndrome, CVD as well as other chronic heart diseases such as congestive heart failure.⁵ In the upper reference range, GGT has been found to be an independent biomarker of metabolic syndrome (abnormal body mass index and levels of high-density lipoprotein (HDL) cholesterol, glucose, triglycerides, and systolic and diastolic blood pressure), with a 20% per GGT quartile trend rise.⁶

As noted previously, GGT maybe a marker of an underlying subclinical liver disease, especially, NAFLD. This is supported by the association of a number of risk factors with GGT such as glucose, insulin resistance, cholesterol, HDL, low-density lipoprotein (LDL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).^{7,8} These risk factors are however, not independent and are clustered and associated with each other. The risk factors are also associated with metabolic syndrome and its hepatic manifestation, NAFLD. In this case, adjustment for the presence of the above mentioned risk factors should decrease the strength of association of GGT with mortality. Interestingly, adjustment for the associated risk factors does not fully account for the association seen between GGT and mortality.^{8,9} This is also shown in the study by Loomba et al.⁴ All together, these data suggest that GGT, indeed, might directly relate to certain pathogenetic processes that may involve the liver as well

as other organs, rather than being a simple co-correlate of other clinical variable.

The key to untangling this relationship is in understanding the enzymatic function of GGT. This enzyme catalyzes the transfer of the gamma-glutamyl moiety of its major substrate-glutathione (GSH) to an acceptor that may be an amino acid, a peptide or water (forming glutamate), thus playing an important role in the homeostasis of GSH. It is located on the cell surface and by breaking down of extracellular GSH, it provides the rate limiting substrate-cysteine, for intracellular *de novo* synthesis of GSH.¹⁰ The GGT mediated cleavage of GSH, could initiate a redox-cycling mechanism by providing intracellular GSH, thus explaining the association of GGT with oxidative stress.¹¹ This hypothesis is supported by the observation of increased GGT gene expression during oxidative stress. The importance of this enzyme for the functioning of human body is obvious as evidenced by multiple gene copies of this enzyme in the human genome.¹²

GGT may serve as a reflection of increased oxidative stress due to underlying subclinical disease such as hepatic steatosis, insulin resistance, and inflammation or of increased oxidative stress which accompanies aging. Oxidative stress and the above mentioned risk factors are known to increase with age.^{13,14} Given that GGT is closely associated with these risk factors, an increased association between GGT levels and all cause mortality in older population may be attributed to this phenomenon. Increased accumulation of free radicals as a result of aging mitochondria and decreased antioxidant defenses are believed to underlie increased oxidative stress in elderly subjects.¹⁴ However, studies are conflicted on whether age related increase in oxidative stress is due to increase in generation of free radicals and/or decrease in antioxidant mechanisms.^{15,16} The prevalence of the latter mechanism would be unable to explain the age attributed increase in GGT levels in older patients.

Alternatively, the mechanistic relationship of GGT with CVD associated mortality may be rooted in the proatherogenic properties of GGT.¹⁷ GGT has been shown to occur in atherosclerotic plaques¹⁸ where it may enter along with LDL lipoproteins. Once in the plaques, cysteinyl-glycine moieties released by action of GGT on GSH, reduce Fe³⁺, leading to the formation of superoxide anion radical and hydrogen peroxide, thereby, increasing oxidative stress.¹⁸

Up to now, however, the mechanism of association of serum GGT with liver, CVD and all-cause mortality remains unclear, especially in the older subjects. The question of whether GGT is an independent predictor of

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all-cause mortality in older subjects or an indicator of general decline in function with age needs to be further investigated. Pathways leading to increased expression of GGT may hold the answer in explaining the association between increased GGT and all-cause mortality. Future studies should include and adjust for all the risk factors associated with high GGT such as insulin resistance, iron overload, or oxidative stress, as inclusion of these in the model might change the conclusion about whether GGT is an independent risk factor of mortality or an indicator of underlying subclinical disease.

REFERENCES

1. Sakuta H, Suzuki T, Yasuda H, Ito T. Gamma-glutamyl transferase and metabolic risk factors for cardiovascular disease. *Intern Med*. 2005;44:538–541.
2. Lee D-H, et al. Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28 838 middle-aged men and women. *Eur Heart J*. 2006;27:2170–2176.
3. Lee DS, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27:127–133.
4. Loomba R, et al. Serum γ -glutamyltranspeptidase predicts all-cause, cardiovascular and liver mortality in older adults. *J Clin Exp Hepatol*; 2012; doi: 10.1016/j.jceh.2012.10.004.
5. Kasapoglu B, Turkay C, Bayram Y, Koca C. Role of GGT in diagnosis of metabolic syndrome: a clinic-based cross-sectional survey. *Indian J Med Res*. 2010;132:56–61.
6. Mason JE, Starke RD, Van Kirk JE. Gamma-glutamyl transferase: a novel cardiovascular risk biomarker. *Preventive Cardiology*. 2010;13:36–41.
7. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol*. 1995;142:699–708.
8. Arndt V, et al. Elevated liver enzyme activity in construction workers: prevalence and impact on early retirement and all-cause mortality. *Int Arch Occup Environ Health*. 1998;71:405–412.
9. Brenner H, et al. Distribution, determinants, and prognostic value of gamma-glutamyltransferase for all-cause mortality in a cohort of construction workers from southern Germany. *Prev Med*. 1997;26:305–310.
10. Zhang H, Forman HJ, Choi J. Gamma-glutamyl transpeptidase in glutathione biosynthesis. *Meth Enzymol*. 2005;401:468–483.
11. Lee D-H, Blomhoff R, Jacobs DR. Review is serum gamma glutamyl-transferase a marker of oxidative stress? *Free Radical Research*. 2004;38:535–539.
12. Chikhi N, Holic N, Guellaen G, Laperche Y. Gamma-glutamyl transpeptidase gene organization and expression: a comparative analysis in rat, mouse, pig and human species. *Comp Biochem Physiol B, Biochem Mol Biol*. 1999;122:367–380.
13. Boden G, Chen X, DeSantis RA, Kendrick Z. Effects of age and body fat insulin resistance in healthy men. *Dia Care*. 1993;16:728–733.
14. Junqueira VBC, et al. Aging and oxidative stress. *Mol Aspects Med*. 2004;25:5–16.
15. Kasapoglu M, Özben T. Alterations of antioxidant enzymes and oxidative stress markers in aging. *Experimental Gerontology*. 2001;36:209–220.
16. Andriollo-Sanchez M, et al. Age-related oxidative stress and antioxidant parameters in middle-aged and older European subjects: the ZENITH study. *Eu J Clinical Nutrition*. 2005;59:S58–S62.
17. Emdin M, Pompella A, Paollicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease triggering oxidative stress within the plaque. *Circulation*. 2005;112:2078–2080.
18. Paollicchi A, et al. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. *Circulation*. 2004;109:1440.

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