RESEARCH ARTICLE

Can Gamma Glutamyl Transferase Serve as a Marker to Predict the Risk of Metabolic Syndrome in Patients with Type 2 Diabetes Mellitus?

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Abstract

Background and aim: Metabolic syndrome (MS) is a constellation of atherosclerotic risk factors and identifies patients who are at high risk for diabetes mellitus and cardiovascular disease (CVD). The interrelationship between gamma glutamyl transferase (GGT), obesity, and other metabolic disturbances raises the possibility that elevated GGT levels can help predict the risk of CVD in patients with MS and was proposed as a component of MS.

Materials and methods: Patients with type 2 diabetes mellitus, presenting with central obesity, were enrolled as cases if they satisfied criteria for diagnosis of MS. Serum GGT levels were measured in cases as well as age- and gender-matched controls to assess the significance of difference, if any.

Results: On analysis, we found an important association between serum GGT levels and MS, as shown by a significant difference in the levels of GGT in cases as compared to controls and the range of area under curve (AUC) for GGT was 0.648–0.827.

Conclusion: Gamma glutamyl transferase may play a role in early diagnosis of MS with a high predictive value for both MS and risk for CVD, due to its association with insulin resistance. It is independent of other confounding factors. Due on its wide availability, simplicity, and universal standardization, GGT has the potential to be considered in algorithms for MS.

Clinical significance: Including a raised GGT in the criteria for MS could increase its predictive nature for CVD. Considering the CVD risk, primary prevention may be emphasized in patients of MS with high GGT values.

Keywords: Biochemical parameters, Cardiovascular risk, Gamma glutamyl transferase, Laboratory research, Metabolic syndrome, Risk factors, Type 2 diabetes.

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Introduction

Metabolic syndrome (MS) is a constellation of atherosclerotic risk factors and identifies patients who are at high risk for diabetes mellitus (DM) and cardiovascular disease (CVD).[1] It is known by multiple names such as syndrome X, insulin-resistance syndrome, and the deadly quartet.[2–4] Its prevalence is increasing worldwide and as a result, considerable scientific interest is gaining momentum since the past few decades due to its association with greater risk of developing CVDs and/or cerebrovascular diseases. Currently, the diagnosis of MS, as per ATP III or International Diabetes Federation criteria, involves increased waist circumference, raised triglycerides, low HDL cholesterol, raised fasting glucose, and raised blood pressure (BP).

Gamma glutamyl transferase (GGT), a plasma membrane-bound enzyme, found in various organs including liver,[2,5–7] is considered as a marker of oxidative stress, fatty liver disease, and chronic hepatitis. It is known to facilitate glutathione hydrolysis.[7] The interrelationship between GGT, obesity, and other metabolic disturbances raises the possibility that elevated GGT levels can help predict the risk of CVD in patients with MS and was proposed as a component of MS.[8] Prospective studies from various geographic locations have found that increased levels of GGT is an independent risk factor of MS, diabetes,[9,10] and CVD,[11,12] but consistent data in Indian population are sparse. Therefore, the present study was designed to assess the significance of liver enzyme GGT in predicting the risk of MS in type 2 DM patients in a tertiary care hospital in Karnataka.

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Materials and Methods

A hospital-based study was designed and conducted among patients attending the outpatient and inpatient departments of a tertiary care hospital in Karnataka after obtaining institutional ethical clearance (in accordance with declaration of Helsinki) and informed written consent from all the study participants. Those patients

diagnosed with type 2 DM (according to the ADA criteria) and presenting with central obesity (waist circumference ≥90 cm for men; ≥80 cm for women) were enrolled as cases if they exhibited at least two of the following four factors: (a) raised TG level ≥150 mg/dL or specific treatment for this lipid abnormality, (b) reduced HDL cholesterol <40 mg/dL or specific treatment for this lipid abnormality, (c) raised BP: systolic ≥130; diastolic ≥85 or treatment for previously diagnosed hypertension, and (d) raised FPG ≥100 mg/dL or previously diagnosed type 2 diabetic patient. We carefully excluded patients with hypothyroidism or malignant diseases or severe renal insufficiency or acute or chronic liver diseases, in addition to those who chronically consume alcohol or those on drugs like anti-epileptics, oral contraceptive agents, trimethoprim, sulphamethoxazole, erythromycin, or cimetidine. Equal numbers of age- and gender-matched controls were also recruited for comparison. We estimated serum GGT (by the enzymatic rate method using gamma-glutamyl-*p*-nitroaniline and glycyl-glycine) in cases as well as controls to test the significance of difference between the groups, if any. Statistical analysis was performed using SPSS 20. Data were expressed as mean ± SD. *p* value <0.05 was considered as statistically significant.

Results

The study was conducted on 100 subjects divided into two groups of 50 cases and 50 controls. On analysis, we found an important association between serum GGT levels and MS, as shown by a significant difference in the levels of GGT in cases as compared to controls and the range of area under curve (AUC) for GGT was 0.648–0.827. Numerical data obtained in the study are represented in Table 1.

Discussion

A need for the early diagnosis of MS is to prevent and decrease morbidity and mortality due to CVD. Obesity and increased central adiposity are pivotal to the pathogenesis of MS and CVD. Elevated systolic BP is an important contributing factor for MS, while chronic alcohol consumption and smoking are among its risk factors.[13] On the other hand, GGT, basically an enzyme of liver function assessment, is expressed in several other organs and tissues also, like kidney, epididymis, fibroblasts, lymphocytes, and lungs. GGT is central to cellular glutathione homeostasis, the principal thiol antioxidant in humans, and can serve as a sensitive and reliable marker of oxidative stress. Gamma glutamyl transferase enhances the availability of cysteine to promote intracellular glutathione (GSH) resynthesis, and the activity of ecto-enzymatic GGT may also modulate the redox status of protein thiols at the cell surface, leading to the production of reactive oxygen species and membrane-permeable H_2O_2, thereby counteracting oxidative stress. Gamma glutamyl transferase even localizes to atheromatous plaques containing oxidized LDL and is proinflammatory, further implicating this protein in atherogenesis.[2,5,9,11]

Table 1: Mean and SD values of serum GGT levels in cases and controls

	Groups	*Mean*	*SD*	*p value*
GGT (U/L)	Cases	40.02	27.21	<0.001*
	Control	19.88	8.47	

*Highly significant

Several studies have revealed that elevated serum GGT is a predictor for the development of DM. Serum GGT levels even in higher normal range are associated with some atherosclerotic risk factors and are predictors of future heart disease, hypertension, stroke, and type 2 DM. Although the exact mechanism responsible for this association is unknown, several possible mechanisms have been proposed for the role of serum GGT in increasing cardiovascular risk. The most widely accepted mechanism is oxidative stress, followed by insulin resistance, subclinical inflammation, and the direct influence of disturbed glucose metabolism on GGT. Through these mechanisms, elevated GGT is thought to play a role in the initiation and progression of atherosclerosis. Second, elevated serum GGT might be a marker of non-alcoholic fatty liver disease (NAFLD) (R4), which is thought to cause insulin resistance, and patients with this condition are at high risk for CVDs. Thus, GGT acts as a marker of hepatic steatosis or visceral obesity too. An association between GGT and systemic inflammation has also been demonstrated. The third likely mechanism implicated is subclinical chronic inflammation. Indeed, oxidative processes are components of chronic inflammation acting on different pathways. In presence of Fe^{3+} and Cu^{2+}, GGT is involved in generating oxygen-free radicals. The final mechanism implicated explains about the direct influence of disturbed glucose metabolism on GGT.[6,9–11,14] Nakanishi et al. reported that GGT activity was related to the development of impaired fasting glucose or type 2 DM. These authors also found an association between serum GGT and white blood cell count, thus providing evidence for subclinical inflammation as an underlying mechanism.[14] Gamma glutamyl transferase measures a degree of CVD risk not assessed by standard MS criteria.[5] So far, insulin resistance has been shown to be directly associated with increased GGT in only a few studies, but it provides a potential unifying factor to connect GGT with areas such as obesity and fat distribution, dyslipidemias, hypertension, smoking, exercise, etc. In relation to cardiovascular risk factors (such as obesity, hypertension, and dyslipidemias), the path from these factors or from MS through glutathione depletion to GGT induction is less clear, but there is evidence that these are associated with fatty liver and that fatty liver produces oxidative stress.[6,10] Further, it has been proposed that GGT is actually a risk marker for the development of type 2 diabetes, rather than its consequence. Gamma glutamyl transferase is associated with a higher incidence of MS (independent of alcohol intake), which is a risk marker for insulin resistance and type 2 diabetes.[9,12] In order to estimate insulin resistance, GGT is easier to use in epidemiological studies or in clinical practice.[9]

Additional possible ways of GGT in enhancing the risk of MS and atherosclerotic CVDs and cerebrovascular diseases are the following: GGT adsorbs onto circulating LDL particles and can catalyze their oxidation. It is expressed on the atheromatous core of coronary plaques, where it colocalizes with oxidized LDL and foam cells. Gamma glutamyl transferase may also be pro-inflammatory, because it mediates interconversion of glutathione-containing inflammatory mediator LT-C4 into LT-D4. Therefore, serum GGT would be associated with elevated risk of new-onset MS, incident CVD, and all-cause mortality after accounting for established and novel cardiovascular risk factors. The association of GGT with new-onset MS remained robust in few models adjusted for serum aspartate transaminase (AST) and alanine transaminase (ALT). Adjusting for age, sex, body mass index (BMI), fasting glucose, systolic BP, diastolic BP, log-triglycerides, alcohol consumption, smoking status, and log-CRP, the association of GGT with MS

remained significant.[11] Therefore, serum GGT can be used as an important predictor of MS. High GGT was significantly correlated with a higher prevalence of MS after adjusting for age, BMI, history of alcoholic fatty liver, and medication use as by Hwang et al. Oxidative stress is recognized to be related to obesity.[14] In summary, it may be said that GGT levels seem to be elevated in patients with MS, a condition that poses a high risk for atherosclerotic CVD. Our findings suggest that GGT might act as an intervening factor in the association between obesity, MS, and diabetes.

Data on serum GGT levels and MS are limited. Bo et al. reported that serum levels of GGT in healthy adult subjects with no measurable metabolic abnormalities were associated with fasting glucose levels of normal range, providing evidence for oxidative stress (increased nitrotyrosine levels) and inflammation (elevated CRP levels).[1] Rantala et al. investigated the relationship between GGT and MS and revealed a highly significant relationship between GGT and the components of the MS even after adjustment for age, BMI, and alcohol consumption. In another study of Phepale et al., the serum GGT level was found to be correlated with components of MS.[13] Liu et al. conducted a meta-analysis of prospective cohort studies to comprehensively evaluate the exact association between GGT and risk of MS. Results showed that GGT levels were positively associated with risk of MS independently of alcohol intake. Similar findings were noted by Oda et al. in Japanese men and women. Similar results were seen in a study by Kasapoglu et al. They found that the mean values of ALT, AST, and GGT levels were significantly higher in the MS group.[2] Phepale et al. found that 84% cases had increased GGT levels in patients with MS.[13] Bozbas et al. found that GGT patients with MS have higher serum GGT and CRP levels compared with controls. They concluded that increased GGT might be a marker of increased oxidative stress and premature atherosclerosis.[1] Tao et al. found that increased levels of GGT are positively associated with clustered components of MS in both men and women.[14]

Limitations

Several limitations of our approach merit comment. Establishing that GGT is a "risk factor" for CVD would require additional mechanistic studies that further assess systemic oxidative stress and evaluate hepatic steatosis and insulin resistance. We did not obtain repeated GGT measurements but used baseline values, which is a potential limitation because changes could occur over time. Also, we did not extend this study to other emerging biomarkers of vascular risk. Nonetheless, GGT assays are widely available analytes that are routinely measurable in clinical laboratories.

Conclusion

Elevated liver enzymes play a central role in early diagnosis of fat overflow to the liver. Raised liver enzymes are associated with increased prevalence of CVDs. Due on their wide availability, simplicity, and universal standardization, these tests, especially GGT, have the potential to be considered in algorithms for MS. Moreover, GGT may play a role in early diagnosis of MS with a high predictive value for both MS and risk for CVD, due to its association with insulin resistance. It is independent of other confounding factors. Gamma glutamyl transferase is a sensitive but moderately specific marker for the early diagnosis of MS. To add to that, it is inexpensive, easily determined, and widely measured in clinical practice.

Clinical Significance

We therefore suggest that including a raised GGT in the criteria for MS could increase its predictive nature for CVD. Prospective studies with huge sample size and representative population are needed to confirm this finding. Considering the CVD risk, primary prevention may be emphasized in patients of MS with high GGT values.

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