Role of Enzyme Gamma Glutamyl Transferase in Diagnosis of Metabolic Syndrome in Subjects with Normal Liver Function

Vidushi Singh[1], Sunita Tiwari[2], Shraddha Singh[3], D. Himanshu[4], Wahid Ali[5]

ABSTRACT

Introduction: Recently Liver enzymes have gained popularity among researchers regarding their potential role in the field of diagnosis of metabolic disorders including type 2 diabetes and cardiovascular diseases. Studies done in past have documented the presence of GGT in atheromatous plaques of established cases of coronary artery diseases. Also GGT levels are put to assess the prognosis of patients suffering from cardiovascular events like myocardial infarction, stroke, etc. Scientific community lacks sufficient data on levels of GGT at the stage of primordial and primary prevention. The study was conducted with an aim to establish an association between GGT levels and metabolic syndrome in subjects having normal liver function. Also, the study has evaluated the role of GGT as a diagnostic biomarker of metabolic syndrome.

Material and methods: In the present study, 120 subjects were enrolled out of which 60 were having metabolic syndrome and 60 were normal individuals. We have measured the levels of GGT in subjects of metabolic syndrome and compared them with normal individuals.All the subjects enrolled in the study had normal liver function test.

Results: We found a significant difference in levels of Serum GGT in subjects with and without metabolic syndrome (p-value <0.001).On ROC analysis, Among other liver enzymes, GGT showed the maximum area under the curve, and a sensitivity of 61.1%, a specificity of 69.8% in the diagnosis of metabolic syndrome.

Conclusion: Liver enzymes assay is simple yet sensitive and cheap test to diagnose the cases of Metabolic Syndrome, more than that their role in development and progression of atherosclerosis, make GGT, a potential biomarker for risk stratification of subjects for cardiovascular diseases.

Keywords: Metabolic Syndrome, Cardiovascular Diseases, GGT (Gamma-glutamyl Transferase), Liver enzymes.

INTRODUCTION

Metabolic syndrome (MS) refers to a constellation of pathological conditions including obesity, hyperglycemia, insulin resistance, dyslipidemia, and hypertension. Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban-rural environment, composition (sex, age, race, and ethnicity) of the patient, and the definition used.[1-6] Asian Indians have a high predisposition to metabolic syndrome.Definition of metabolic syndrome has been proposed various scientific committees including The National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP-III 2001, Revised version 2005), World Health Organization (WHO 1999), EGFR and IDF(International Diabetes Federation). The presence of Insulin resistance has been the essential feature in the WHO criteria, while waist circumference (WC) rather than body mass index (BMI) has been the Key aspect of MS definition in the ATP-III panel. NCEP ATP-III criteria is supported by The American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) except for a lowering of the threshold for impaired fasting glucose (IFG) from 110 to 100 mg/dl (Grundy 2005) as recommended by IDF.[7]

Liver enzymes - aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP) are commonly used markers of liver pathology.[8] Recently, these enzymes have emerged as the topic of interest in the domain of risk assessment for Metabolic syndrome and cardiovascular diseases. Liver enzyme, particularly GGT have gained interest of various researchers since last decade, for its role in atherosclerosis and coronary artery diseases.[9], but there is uncertainty regarding the aetiological relationship between Serum GGT level and cardiovascular disease (CVD) as there is lack of sufficient data on GGT at the level of risk factors for cardiovascular diseases.

Studies conducted by Anand et al 2003, Young et al 2004, Ang et al 2005, and Copan 2005 have shown that Components of metabolic syndrome are independent risk factors for cardiovascular diseases.[10] Elevated levels of serum gamma-glutamyl transferase (GGT) have been demonstrated to be associated with poor prognosis in patients with coronary artery diseases.

This is a well-known fact that Atherosclerotic changes begin quite early in life, and the presence of additional risk factors, like genetic predisposition, obesity more precisely

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abdominal obesity, dyslipidemia including low levels of HDL, Hypertension, and smoking may accelerate the disease progress, resulting in acute coronary syndromes.[11]

Serum GGT, within its high reference range, has shown to be an early and sensitive enzyme that is related to oxidative stress and it plays a central role in the pathogenesis of atherosclerosis.[12-14]

Lee et al 2007[15] have shown in their study that elevated levels of GGT are a marker of the metabolic syndrome. Other researchers have also reported that high levels of GGT are associated with fatty liver, insulin resistance, type 2 diabetes, obesity. and other metabolic risk factors. In the Light of the growing evidence, the liver, which is considered as the primary source of circulating GGT, is also a key target organ for the development of the metabolic syndrome. Raised levels of GGT are seen to be closely related to hepatic steatosis[16,17] which, in turn, has a strong association with the metabolic syndrome.[18-20] Probably the mechanism behind raised GGT in Steatosis is excessive fat accumulation in the liver, which could cause hepatocellular damage and in turn, would stimulate the synthesis of GGT. Also, excess fat in the liver could increase oxidative stress, which leads to overconsumption of Glutathione, a major thiol oxidant of body, along with a compensatory increase in GGT production. Finally, an increase in GGT synthesis could be due to a low-grade hepatic inflammation which is induced by hepatic steatosis.

Also, one thing should be kept in mind that high levels of serum GGT are not the only hepatic biomarker of hepatic steatosis. In cases of Fatty liver, irrespective of histological evidence of inflammation, levels of transaminases are also found to be elevated.[21-23]

Association between higher levels of serum transaminases in different populations and metabolic syndrome and CVS have been established by studies done in past.[24-27]

Association between GGT and metabolic syndrome has been supported by various studies in which the relationship between GGT and different parameters of metabolic syndrome has been evaluated.[28-32]

Studies have shown the association between GGT levels and Obesity, particularly those with abdominal obesity.[33-35]

The connection between GGT and the metabolic syndrome extends to an association of higher GGT levels with increasing blood pressure. Thus, It clearly shows that all of the major components of the metabolic syndrome are associated with increased levels of serum GGT.[36-38]

In the present study, we have tried to find an association between GGT and metabolic syndrome, in individuals with normal levels of other liver enzymes. the current study has assessed GGT as a biomarker for the diagnosis of metabolic syndrome.

MATERIAL AND METHODS

The present study was a cross-sectional analytical study, which was conducted in King George medical university, U.P from January 2019 till August 2019. Ethical clearance was obtained from the Ethical Committee of K.G.MU. A total of 120 subjects were enrolled in the study. Subjects were divided into two groups of 60 each, based on the history given by them. Group, I composed of subjects without metabolic syndrome and Group II composed of Subjects with metabolic syndrome, subjects were taken from Clinical OPD of medicine Department KGMU.U.P.

Sample size calculation: A sample size of 120 is calculated by a formula mentioned below, assuming 80% power and 0.05 level of significance (95% confidence interval).

$N=2(Z\alpha/2 + Z\{1-\beta\})^2 * \sigma 2/(\mu 1-\mu)^2$

Metabolic syndrome, traditional components: In the present study, we have taken NCEP ATP III modified criteria for the diagnosis of metabolic syndrome. Compared to other definitions of metabolic syndrome, where one or the other component is a must for diagnosis, NCEP ATP III is one definition, which doesn't make the presence of any component compulsory for diagnosis. Thus it gives each component an equal weightage and therefore no bias for any risk factor. Criteria for diagnosis of metabolic syndrome: NCEP ATP III modified version:

Any 3 criteria out of 5 if present, the individual is considered as a subject of metabolic syndrome and was included in Group II.

A self-administered questionnaire ascertained demographic characteristics, lifestyle habits (including alcohol consumption and smoking status), medical history, and menopausal status (for women). Briefly, inclusion criteria included age 30 -60yrs, three out of five components for metabolic syndrome acc too NCEP ATP II guidelines, normal liver function test.

Normal subjects comprising Group I, where the individuals of age 30-60yrs, without any component of metabolic syndrome, having normal liver function tests.

Any individual with a history of chronic alcoholism or intake of alcohol within 3 months, smokers, any known bone disorder, renal disease, liver disease, and history of a cardiovascular event is not included in the study.

Detailed Drug History was taken for each subject and individuals on Anticonvulsants, Oral contraceptives, methotrexate, etc were not included.

Laboratory analyses

Estimation of Serum GGT

Sample collection: Fasting of 12 hours was must before collection of blood sample.it is seen that GGT levels are usually raised after taking meals, therefore fasting sample was taken with strict precautions. Subjects were asked to be present after 12-hour fasting on a scheduled date.

Fasting Morning samples were taken by venipuncture of antecubital vein, 4ml of the blood sample was collected and divided into two parts. One part was collected in fluoride vial containing sodium fluoride-potassium oxalate as an anticoagulant for the estimation of fasting plasma glucose. The second part was collected in a plain vial for lipid profile and liver function test, and GGT estimation. The sample was allowed to clot for 2 hours at room temperature before centrifugation for 15min at 1000*g

at 2-8 degrees Celcius for collection of serum. Serum for collective estimation of GGT levels was stored at -20 Degree Celcius.

Once the sample collection was complete, GGT levels were estimated through ELISA Method, by using Elisa Kit, provided by Elabscience.: Human γ GT1(Gamma Glutamyl Transferase 1) Elisa kit, Catalog No: E-EL-H1012. The kit uses a sandwich – Elisa principle, with a detection range of 1.56ng/Ml and a sensitivity of 0.94ng/mL.

Estimation of Serum Alanine aminotransferase,Aspartate aminotransferase, and Alkaline phosphatase

Standard assay of all blood tests was simultaneously performed according to the

standard clinical laboratory procedures by automated analyzers. Estimation of Liver enzymes level including Serum Alanine aminotransferase, Aspartate aminotransferase, alkaline phosphatase, and serum bilirubin was done for each individual, and subjects with levels of liver enzymes within the normal range were only included in the study.

Liver function test including Serum Bilirubin is measured by Malloy-Evelyn Modified End Point[39] Enzymes Aspartate aminotransferase (AST) also known as SGOT, Alanine aminotransferase(ALT), also known as SGPT levels is measured by IFCC Method without pyridoxal phosphate(P-5'-P). Kinetic –UV.[40] Serum Alkaline phosphatase measured by DGKC and SCE method (DEA Buffer) Enzymatic – Kinetic.[41,42]

Blood sugar level

Fasting blood glucose level is measured by Enzymatic (GOD-PAP)-colorimetric Trinder –End Point.[43]

Lipid profile

Lipid profile including Total Cholesterol and Triglyceride is measured by Enzymatic colorimetric (CHOD-PAP) Trinder –Endpoint.[44,45] Serum HDL levels measured by Direct Enzymatic (PVS/PEGME) End point method (Two –Point for Fully Automated Analyzers).[46]

Anthropometric measurement

Anthropometric parameter taken in the present study is waist circumference.waist circumference is measured with a flexible and inelastic measuring tape, according to WHO's a recommendation with the subject standing, after a regular expiration, to the nearest centimeter midway between the lowest rib and the iliac crest.

Blood pressure measurement

Blood Pressure is measured indirectly by sphygmomanometry in sitting position, Mean of Two readings taken at Interval of 5 min was taken as data.

STATISTICAL ANALYSIS

Statistical analysis was performed by SPSS 16.0 version for windows and Graph pad. Data are expressed as mean ± standard deviation, categorical data have been expressed as frequency(%). A 2-tailed P value of <0.05 was considered significant. A comparison of liver enzymes level between metabolic syndrome and non-metabolic syndrome subjects is done by independent t-test. ROC analysis has been done for AST, ALT, ALP, and GGT. Sensitivity, specificity, positive and negative predictive value has been calculated for GGT in cases of metabolic syndrome.

RESULTS

GROUP I is composed of subjects without metabolic syndrome and GROUP II comprises of subjects with metabolic syndrome. Demographic and clinical profiles of both the groups include Age, Gender, serum level of AST, ALT, Alkaline phosphatase, bilirubin, and Serum GGT levels. All the subjects in the study group are in the age group between 30yrs -60yrs with Group I mean =44.75, SD= 5.87 and Group II mean= 45.50, SD=4.14, as shown in Table 1a,Fig 1a. A total of 23 (38.33%) male and 37 (61.67%) female in group I, and 29 (48.33%) male and 31 (51.67%) female in group II, as shown in Table 1b,Fig 1b. There was no significant difference in age group of individuals in both

Table 1a:

	Group 1		Group 2		[1]p-Value
	Mean	±SD	Mean	±SD	
Age (yrs)	44.75	5.87	45.50	4.14	0.420

Table 1b:

	Group 1		Group 2		[1]p-Value
	n	%	N	%	
Gender					0.273
Male	23	38.33%	29	48.33%	
Female	37	61.67%	31	51.67%	

Table 1a and b: Age and Gender comparison between Group I (on Metabolic Syndrome) and Group II (Metabolic syndrome)

	Group 1		Group 2		[1]p-Value
	Mean	±SD	Mean	±SD	
AST (IU/L)	23.48	10.02	24.24	9.56	0.672
ALT (IU/L)	27.85	7.10	25.85	7.65	0.140
Alkaline Phosphatase (IU/L)	88.72	14.23	88.05	16.32	0.812
SD=Standard deviation, 1=Independent t-test					

Table-2: Comparison of liver enzyme levels between Group I (Non Metabolic) and Group II (Metabolic)

	Group 1		Group 2		[1]p-Value
	Mean	±SD	Mean	±SD	
GGT(IU/L)	9.44	4.87	14.70	8.97	<0.001*
SD=Standard deviation, 1=Independent t-test					

Table-3:

	Area	Std. error	Significant	95% Confidence Interval	
				Lower Bound	Upper Bound
AST (IU/L)	0.479	0.053	0.694	0.375	0.583
ALT (IU/L)	0.574	0.053	0.160	0.471	0.677
Alkaline Phosphatase (IU/L)	0.529	0.053	0.585	0.425	0.633
GGT (ng/dL)	0.719	0.047	<0.001	0.627	0.810

Table-4: Receiver operating characteristic (ROC) analysis of Liver enzymes in metabolic syndrome

Test	Sensitivity	Specificity	PPV	NPV
GGT	61.1%	69.8%	78.3%	50.0%

Table-5: Sensitivity, specificity positive productive value and negative productive value of diagnosing metabolic syndrome for some GGT values

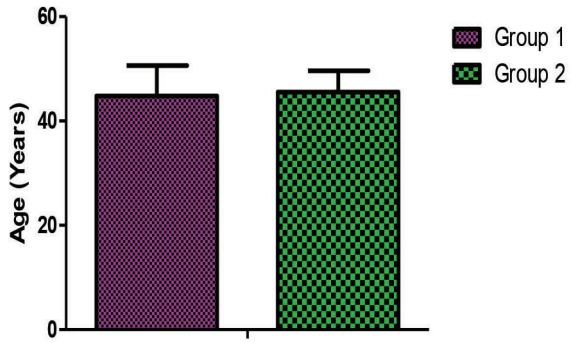

Figure-1a: Distribution of age between group1 (normal/ Non metabolic subjects) and Group 2 (subjects with metabolic syndrome)

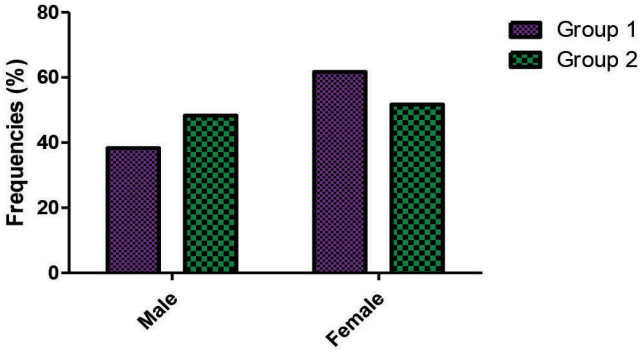

Figure-1b: Distribution of gender in between group 1 (normal/ Non metabolic subjects) and Group 2 (subjects with Metabolic syndrome).

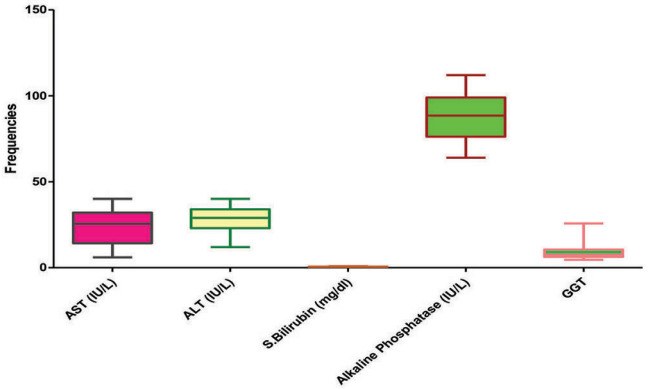

Figure-2a: Box-and-whisker plot shows liver function test {Aspartate aminotransferase AST,Alanine aminotransferaseALT, S. Bilirubin SB, Alkaline Phosphatase AP) and Gamma-glutamyl transferase GGT among group I (Normal/ Non metabolic subjects)}

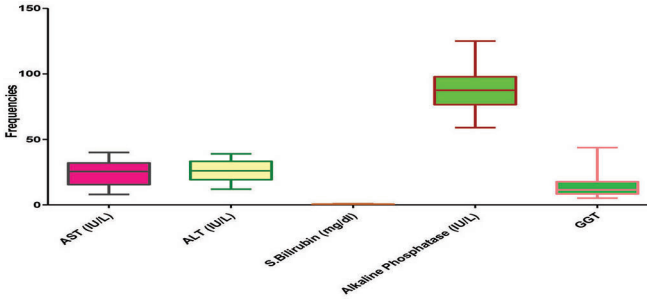

Figure-2b: Box-and-whisker plot shows the liver function test {Aspartate aminotransferase AST,Alanine aminotransferaseALT, S. Bilirubin SB, Alkaline Phosphatase AP) and Gamma-glutamyl transferase GGT among group II (Subjects with metabolic syndrome}.

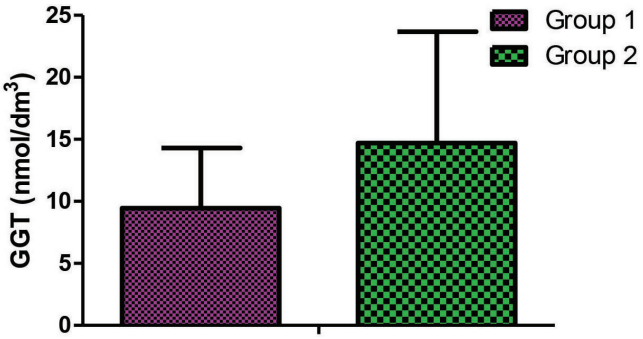

Figure-2c: Distribution of gamma-glutamyl transpeptidase (GGT) between group 1 (Normal /Non metabolic subjects) and Group 2 (subjects with metabolic syndrome).

groups.

Comparison of liver enzymes level between group I and II

Mean Aspartate aminotransferase (AST) of subjects in group I and group II were 23.48±10.02IU/L and 24.24±9.56IU/L respectively. Mean alanine aminotransferase (ALT) of subjects in group I and group II were 27.85±7.10IU/L and 25.85±7.65IU/L respectively. Mean alkaline phosphatase of subjects in group 1 and group 2 were 88.72±14.23 IU/L and 88.05±16.32 IU/L respectively. The difference in Levels of AST,ALT and Allaline phosphatase of subjects in group I and group II is insignificant (p =0.672) (p =0.140), (p =0.812), as shown in Table 2.

The levels of liver enzyme AST,ALT,Alkaline phosphatase are compared in Group I and Group II.No significant difference was found in values of these enzymes between

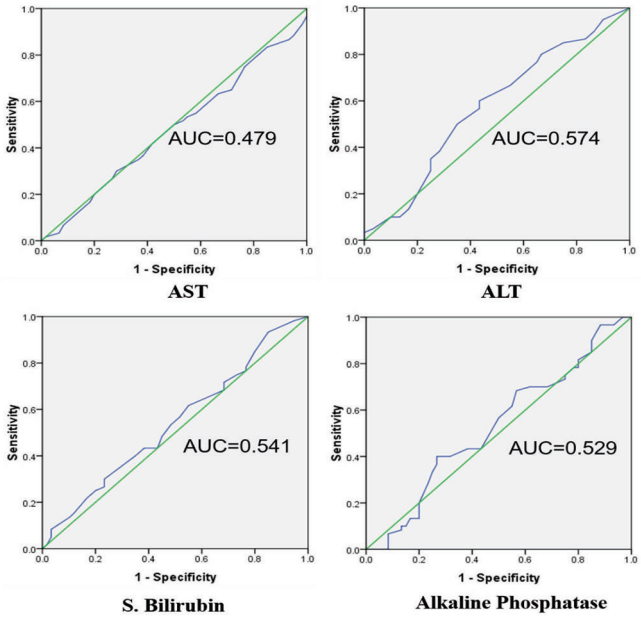

Figure-3: Receiver operating characteristic (ROC) curve analysis of AST(Aspartate amino transferase) (IU/L), ALT (Alanine aminotransferase) (IU/L), S. Bilirubin (mg/dl), Alkaline Phosphatase (IU/L) screening tests for metabolic syndrome. Each receiver characteristic curve is expressed as a solid line. AUC: area under the curve.

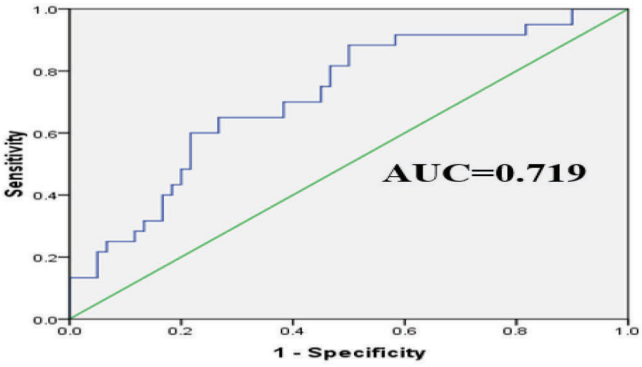

Figure-4: Receiver operating characteristic (ROC) curve analysis of GGT tests for metabolic syndrome. Each receiver characteristic curve is expressed as a solid line. AUC: area under the curve.

Group I and Group II, p value (0.672,0.140,0.812).

On Roc analysis, GGT showed maximum area under curve, compared to other liver enzymes as shown in Table 4. Roc curve for GGT is shown in Fig 4, which can be compared with ROC curve of AST, ALP, AP in Fig 3. The sensitivity, specificity, NPV, and PPV were calculated for GGT in the diagnosis of metabolic syndrome. The cut-off value for GGT was 11.53 (median) to make a diagnosis of metabolic syndrome. With these cut-off values, GGT had a sensitivity of 61.1%, a specificity of 69.8%, PPV of 78.3% and NPV of 50.0% in the diagnosis of metabolic syndrome among all other liver enzymes, it is shown in table 5.

DISCUSSION

The current study shows that individuals with Metabolic syndrome have increased GGT activity, which is a marker of oxidative stress. Our findings have demonstrated that there is a strong association between GGT and some atherosclerotic risk factors like hypertension, visceral obesity, and dyslipidemia that are predictors of non-communicable diseases like atherosclerotic coronary artery diseases, stroke, and type 2 DM.[47,48] exact mechanism of GGT involvement in the pathogenesis of cardiovascular diseases is unknown, several possible mechanisms have been proposed for explaining the role of serum levels of GGT in metabolic syndrome which in turn increases the cardiovascular risk.

Components of metabolic syndrome are all associated with a certain degree of high oxidative stress, chronic inflammation and insulin resistance. Through these proposed mechanisms, elevated GGT is thought to play a role in the initiation and progression of atherosclerosis.GGT at physiological serum levels works as a protein catalyst in the degradation of thiol oxidant in the body that is glutathione. Glutathione is a molecule consisting of amino acids as glutamic acid, cysteine, and glycine. It is synthesized within the cell and is present both in the reduced state and in the state of oxidized dimer by thiol bonding. In the form of an antioxidant, single glutathione molecules are formed and they are metabolically inactive therefore require simultaneous degradation. Glutathione reductase is the enzyme involved in preparation for the recycling of glutathione. It reduces the oxidized form of Glutathione. This antioxidant, glutathione is hydrolyzed by GGT into glutamate and a cysteinyl glycine dipeptide, and these amino acids are transferred back into the cell to be subsequently reused, in production of additionally reduced glutathione.} This whole mechanism is known as g-Glutamyl cycle, which is also an amino acid transport cycle in the body.[49]

The second possible mechanism can be that, elevated serum GGT may be a marker of NAFLD, which in turn is considered to produce a certain degree of hepatic insulin resistance. Although other liver enzymes like serum ALT, AST are also found to be associated with fatty liver, It is only GGT whose activity has been reported to be related to oxidative stress. Various studies have demonstrated an association between GGT.[50,51] Studies have shown that NAFLD with elevated liver enzymes (including GGT), is associated with insulin resistance, and patients with this condition are at high risk for cardiovascular diseases.[52,53]

Another mechanism implicated is subclinical chronic inflammation. oxidative processes are components of chronic inflammation acting on different pathways and stimulating the inflammatory response. Obesity, particularly abdominal obesity which gives information regarding visceral fat deposition is associated with subclinical inflammation. Evidence indicates that an elevated level of GGT in serum might be due to inflammation, which is an important mechanism in almost all stages of atherosclerotic cardiovascular disease.[54] An Important marker of systemic inflammation, that is C-reactive protein which is synthesized by the liver is associated with Metabolic syndrome, DM, and cardiovascular disease.[55] which clearly shows that there is a subclinical inflammation in metabolic syndrome, which usually begins within the target organ that is liver.this is the

reason why C-reactive protein which is an established marker of inflammation and GGT a known marker of oxidative stress, are shown to be elevated in chronic inflammatory conditions and metabolic syndrome.[56]

Serum GGT levels are on the higher range though within reference limits in subjects with metabolic syndrome, whereas other liver enzymes level showed no significant difference between, Metabolic and non-metabolic. this clearly indicates that even at a very early stage of hepatic involvement in metabolic syndrome, serum GGT levels are helpful in the diagnosis of metabolic syndrome, quite early to the changes in other liver enzymes. Also, the values of GGT in individuals with metabolic syndrome may help to scrutinize the individuals at higher risk of atherosclerosis-related cardiovascular diseases.

The present study is unique in its way, from other studies done in the past. As to our best knowledge, levels of GGT have not been assessed prior in subjects of metabolic syndrome who have a normal liver function test in a similar population. Also, this study adds to our present information on the role of GGT in the pathogenesis of metabolic diseases and the risk assessment capability of a liver enzyme for cardiovascular diseases. Elevated levels of Serum GGT in Individuals having a risk factor for cardiovascular diseases, such as obesity, hypertension, dyslipidemia, etc which are all components of metabolic syndrome make it a potential tool for early diagnosis of these conditions, even when the enzyme is within a normal range.

Our study has few limitations too, as we have not performed Ultrasonography to exclude Fatty lever in subjects. Also, we cannot comment on the status of Insulin resistance in individuals as the criteria of NCEP ATP III, includes only hyperglycemia for diagnosis of metabolic syndrome. Lastly, it is a cross-sectional study and a causal relationship cannot be established.

CONCLUSION

Considering the Global Burden of Metabolic syndrome, simple, easy and reliable, the marker will be a boon not only for early diagnosis but also for the pocket of patients in a developing country like India. The results of this study will help in considering GGT in the assessment of High-risk Individuals for Cardiovascular incidents, who are already suffering from Metabolic Syndrome. The present study shows that GGT is not merely a marker of hepatotoxicity, but more than that it carries the high potential to be a diagnostic tool for metabolic conditions.

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