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Original Article

Gamma-Glutamyl Transferase an Oxidative Stress Marker in Metabolic Syndrome

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Abstract

Introduction: Metabolic syndrome refers to the Co-occurrence of a cluster of risk factors, including abdominal obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. MetS, also labeled as "Insulin resistance syndrome," "syndrome X," "hypertriglyceridemic waist," and "the deadly quartet," is increasingly being recognized as an important cardiovascular risk factor. Metabolic syndrome is often characterized by oxidative stress, a condition where there is an imbalance result between the production and inactivation of reactive oxygen species. The present study is done to determine the association of γ-glutamyl transferase (GGT) in metabolic syndrome.

Materials and Methods: A total of 50 individuals were selected based on the criteria for metabolic syndrome as the study group and control group included 50 normal individuals free from any major illness. Both the control and study groups were age- and sex-matched. Blood samples were analyzed for GGT, fasting blood glucose, and lipid profile. GGT was estimated by the carboxy substrate method.

Statistical Analysis: Results were expressed as mean ± S.D. and were statistically analyzed using SPSS software version 16 and Microsoft Excel. A significant increase in serum GGT levels was observed in the study group (85.19 ± 35.32) when compared to the control group (33.31 ± 10.92) and *P* value was statistically significant.

Conclusion: Our study showed elevated levels of GGT in individuals with metabolic syndrome which indicates that there is underlying oxidative stress in these individuals. The evaluation of GGT is simple and cost effective, it not only helps in early identification of high-risk individuals, but also provides an insight to plan lifestyle modification in ameliorating oxidative stress in metabolic syndrome.

Key words: Fatty liver, Gamma-glutamyl transferase, Lipid profile, Metabolic syndrome, Oxidative stress

INTRODUCTION

Metabolic syndrome, also known as syndrome X, is defined by the WHO as a pathological condition characterized by abdominal obesity, insulin resistance, hypertension and dyslipidemia.[1]

According to National Cholesterol Education Program (NCEP) ATP3 2005:
Presence of any three or more of the following is needed for the diagnosis

1. Blood glucose > 5.6 mmol/L (100 mg/dl) or drug treatment for elevated blood glucose
2. High-density lipoprotein (HDL) cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women, or drug treatment for low HDL-C
3. Blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides
4. Waist > 102 cm (men) or > 88 cm (women)
5. Blood pressure > 130/85 mmHg or drug treatment for hypertension.

It is estimated that around 20–25% of the world's adult population have metabolic syndrome. In other words, over a billion people in the world are now affected by metabolic syndrome. With the metabolic syndrome driving the twin global epidemics of type 2 diabetes and cardiovascular diseases, there is always a felt need to diagnose those

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individuals with metabolic syndrome early so that lifestyle modification and treatment may prevent the development of complications.

Recently, epidemiology studies have shown that gamma-glutamyltransferase (GGT) is involved in pathophysiological processes such as oxidative stress and lipid peroxidation which are important to the pathogenesis and development of metabolic syndrome.[2]

GGT, a marker of alcohol consumption and liver disease, has been strongly associated with obesity-related outcomes including metabolic syndrome, diabetes, hypertension, dyslipidemia, cardiovascular diseases and cancer.[3]

GGT is the enzyme found in the liver, kidney, lungs, pancreas and prostate. GGT catalyzes the transfer of γ-glutamyl group from glutathione (GSH) to another peptide or amino acids in γ glutamyl cycle. GGT is concerned with the metabolism of GSH which is a potent intracellular antioxidant. GGT also has a critical role in cysteine metabolism and is linked to insulin resistance as well.

In view of the above facts, the present study is done to determine the association of GGT as a oxidative stress marker in individuals with metabolic syndrome.

MATERIALS AND METHODS

The study was conducted at the Department of Biochemistry, Thanjavur medical college hospital, after getting approval from the ethical committee. Written informed consent was obtained from the participants.

A total of 50 individuals diagnosed as metabolic syndrome based on the NCEP criteria were chosen as study group and control group included 50 normal individuals free from any major illness. Both the control and study groups were age- and sex-matched. Both the groups were analyzed for GGT, fasting blood glucose and lipid profile which included total cholesterol, triglycerides, low-density lipoprotein (LDL), HDL and Very low density lipoprotein (VLDL).

Exclusion Criteria

Patients with diabetes mellitus, hypertension, renal diseases, hepatitis and alcoholism were excluded from the study.

Sample Collection

Under strict aseptic precautions, 5 ml of fasting venous blood were collected from each subjects. The vacutainers containing the blood samples were kept at room temperature for ½ h, allowed to clot, and then centrifuged at 2000 g for 15 min for a clear separation of the serum.

Standing body height and body weight were measured. The waist circumference was measured in a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest. Body mass index (BMI) (kg/m^2) was calculated by dividing weight (in kilograms) by the square of height (in meters).

Estimation of GGT

Methodology

Carboxy substrate method.

Principle

GGT catalyzes the transfer of amino group between L-γ-Glutamyl-3-carboxy-4 nitro anilide and glycylglycine to form L- γ-glutamylglycylglycine and 5-amino-2-nitrobenzoate. The rate of formation of 5-amino-2-nitrobenzoate is measured as an increase in absorbance which is proportional to the GGT activity in the sample.

Normal reference ranges of GGT 11–50 U/L for men and 7–32 U/L for women.

Estimation of Blood Glucose

Fasting blood glucose was estimated by glucose oxidase-peroxidase enzymatic endpoint method.

Estimation of Lipid Profile

In fasting blood samples, serum total cholesterol and triglycerides are estimated by standard enzymatic procedures and HDL cholesterol by direct assay method.

- LDL is calculated by Friedewald 's formula
- LDL - c = Total cholesterol – (HDL c + VLDL)
- VLDL= Triglycerides/5.

Statistical Analysis

Results were expressed as mean ± S.D. and were statistically analyzed using SPSS software version 16 and Microsoft Excel. Student's *t*-test was used to analyze the difference between the study and the control groups. The relationship between the variables was evaluated using Karl Pearson's correlation coefficient. $P < 0.05$ is considered to be statistically significant.

RESULTS

Baseline characters, namely, the anthropometric measurements, BMI, the biochemical data and results of GGT, fasting blood glucose, and lipid profile, are shown in Table 1

Table 2 and Figure 1 show Student 's *t*-test analysis of GGT levels between the control and study group.

Table 2 shows that the mean serum GGT levels in the study group are 85.19 ± 35.52, which is higher than the

Table 1: Descriptive statistics

Parameters	Control (*n*=50)				Study (*n*=50)			
	Min.	Max.	Mean	S.D	Min.	Max.	Mean	S.D
Age	25	50	35.58	6.899	27	50	39.44	6.828
HT	1.45	1.68	1.5520	.05421	1.46	1.65	1.5528	.05280
WT	38	68	55.00	6.587	65	89	77.44	6.600
BMI	18.02	28.30	22.83	2.55	29.9	38.46	32.15	1.70
WC	85.2	97.6	90.6	6.7	102.4	107.2	105.6	9.8
GGT	11.93	56.78	33.31	10.92	31.19	189.40	85.19	35.52
FBG	64	117	88.14	13.339	69	120	91.10	13.715
T.CHO	127	200	167.60	17.607	142	298	220.78	37.335
TGL	65	170	124.64	22.89	156	447	266.96	74.056
HDL	24	66	44.66	9.962	26	44	37.0	4.876
LDL	46.00	135.00	96.16	23.59	66.60	242.00	131.24	42.35
VLDL	13.00	47.00	25.40	5.536	31.20	89.40	53.39	14.81

WC: Waist circumference, BMI: Body mass index, GGT: Gamma-glutamyltransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, FBG: Fasting blood glucose, TGL: Triglycerides

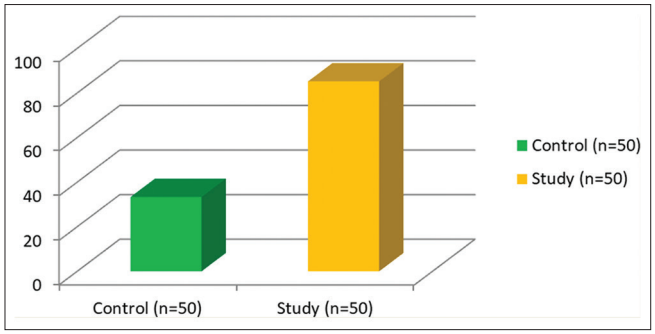

Figure 1: Mean gamma-glutamyltransferase levels between the study and the control group

control group mean 33.31 ± 10.92 which is statistically significant.

Table 3 shows Student *t*-test analysis of lipid profile parameters between control and study group.

Table 4 shows student 's *t*-test analysis of BMI levels between control and study group.

Table 4 shows that the mean serum BMI levels in the study group are 32.15 ± 1.70 which is higher than the control group mean 22.83 ± 2.55 which is statistically significant.

Table 5 shows Pearsons correlation between GGT and other study parameters. A positive correlation is observed between GGT and BMI which are statistically significant.

Table 2: Student *t*-test analysis of GGT between control and study group

S. NO	GGT	Mean±S.D	Statistical inference
1	Control (*n*=50)	33.31±10.92	T=−9.869
2	Study (*n*=50)	85.19±35.52	0.0001<0.05
			Significant

GGT: Gamma-glutamyltransferase

Table 3: Student *t*-test analysis of lipid profile parameters between control and study group

Sample	Mean	S.D	Statistical inference
T.CHOL			
Control (*n*=50)	167.60	17.60	T=−9.110
Study (*n*=50)	220.78	37.33	0.0001 <0.05
			Significant
TGL			
Control (*n*=50)	124.64	22.89	T=−12.983
Study (*n*=50)	266.96	74.05	0.0001 <0.05
			Significant
HDL			
Control (*n*=50)	44.66	9.96	T=4.871
Study (*n*=50)	37.02	4.87	0.0001<0.05
			Significant
LDL			
Control (*n*=50)	96.16	23.59	T=−5.117
Study (*n*=50)	131.24	42.35	0.0001<0.05
			Significant
VLDL			
Control (*n*=50)	25.40	5.53	T=−12.518
Study (*n*=50)	53.39	14.81	0.0001 <0.05
			Significant

HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, TGL: Triglycerides

DISCUSSION

Obesity is a disorder of body weight regulatory mechanisms characterized by the accumulation of excess body fat. Visceral adipose tissue releases bioactive substances such as non-esterified fatty acids, cytokines and proinflammatory substances which are responsible for inflammation, dyslipidemia, and atherogenesis. The prevalence of obesity and metabolic syndrome is rapidly increasing in India and other South Asian countries.

Obesity often predisposes to insulin resistance, where there is the decreased response of the peripheral tissues to the normal circulating concentration of insulin. The

condition that exists between insulin resistance and the development of overt type 2 diabetes mellitus is called metabolic syndrome. The intracellular redox imbalance, along with persistant chronic inflammatory conditions, results in metabolic syndrome[4] [Figure 2].

Oxidative stress arises as a result of an imbalance in the oxidative and antioxidative status. Oxidant molecules are produced endogenously and they are also taken exogenously from the outer environment. Major sources of reactive oxygen species are from electron transport chain and from a range of oxidase enzymes, including xanthine oxidase, glycolate oxidase and monoamine oxidases.[5]

In our present study, we measured serum GGT in individuals with metabolic syndrome and compared the same with healthy controls. The mean GGT in the study group was significantly high (85.19 ± 35.32) when compared to the control group (33.31 ± 10.92) and *P* value was statistically significant. The elevated levels of GGT in the study group suggest that these individuals may be in the early stages of metabolic syndrome where there is oxidative stress, but the defense mechanism is active so that oxidative damage is not detected. This study also correlates with the previous studies done by Kasapoglu *et al.*

A positive correlation is observed between GGT and BMI which are statistically significant, which correlates with the studies done by Blaj *et al.*[6] Similarly, Rantala *et al.* investigated the relationship between GGT and MS and revealed a highly significant relationship between GGT and the components of the metabolic syndrome.[7]

GGT is an extracellular membrane bound glycoprotein that contributes to extracellular catabolism of GSH. GGT is a heterodimeric glycoprotein that is typically anchored to the cell membrane by an amino terminal hydrophobic region. The enzyme may be considered as a type II transmembrane protein because it has a large carboxyl-terminal ectodomain, which exhibits the catalytic activity, and a single transmembrane domain consisting of about 20 amino acid residues that include an apparent signal peptide.[8]

Although the enzyme is produced in various tissues such as liver, kidney, lungs, pancreas and prostate, most of the GGT in serum is derived from the liver. GGT has a central role in the maintenance of intracellular antioxidant defenses through extracellular catabolism of GSH the principal thiol antioxidant in humans. By this action, it enhances the availability of cysteine to promote intracellular GSH resynthesis, thereby counteracting oxidant stress.[9]

Increased expression of GGT can be a response to oxidative stress, facilitating increased transport of GSH precursors into cells. Excess GGT leaked into the serum may be a result of normal cell turnover, due to oxidative stress, proteolysis, increased GGT synthesis, and endothelial cell damage.[10] Thus, increased serum concentrations of GGT could identify people with a low but persistent increase of oxidative and other cellular stresses.[11]

Non-alcoholic fatty liver disease, a condition seen in metabolic syndrome, is one of the common cause for chronic liver diseases worldwide. Excess deposition of fat in the liver causes hepatocellular damage which stimulates increased synthesis of GGT.[12] Secondary to low-grade inflammation triggered by hepatic steatosis GGT level increases, thereby impairing insulin signaling both in the liver and systemically.[13-16] In the view of above facts, GGT

Table 4: Student *t*-test analysis of BMI between control and study group

S. No.	BMI	Mean±S.D	Statistical inference
1	Control (*n*=50)	22.83±2.55	T=−21.421
2	Study (*n*=50)	32.15±1.70	0.0001<0.05
			Significant

BMI: Body mass index

Table 5: Pearsons correlation between GGT and other study parameters

GGT	Correlation value	Statistical inference
Age	0.015	*P* >0.05 Not Significant
Height	−0.034	*P* >0.05 not significant
Weight	0.120	*P* >0.05 not significant
BMI	−0.162(*)	*P* <0.05 significant
FBG	0.033	*P* >0.05 not significant
T.CHOL	−0.107	*P* >0.05 not significant
TGL	−0.161	*P* >0.05 not significant
HDL	−0.220	*P* > 0.05 not significant
LDL	−0.032	*P* > 0.05 not significant

BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, TGL: Triglycerides, FBG: Fasting blood glucose, GGT: Gamma-glutamyltransferase

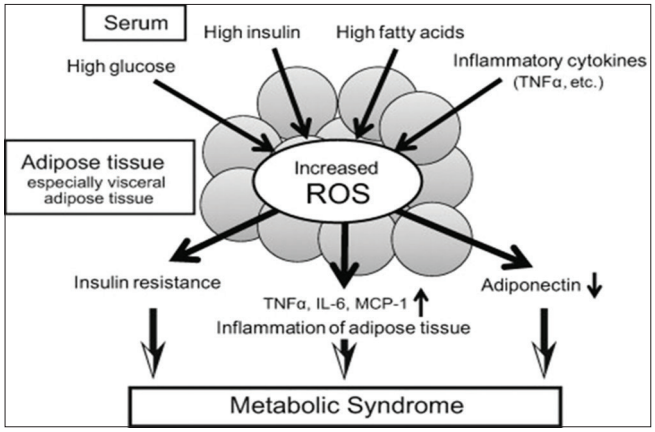

Figure 2: Oxidative stress in metabolic syndrome

has a potential role as a marker of oxidative stress and subclinical inflammation in metabolic syndrome.

CONCLUSION

Our study confirms that GGT is a sensitive oxidative stress marker and a mediator of low-grade systemic inflammation associated with metabolic syndrome. The test for GGT is readily available, easy to perform and cost effective and can be frequently used in clinical practice. Early diagnosis promotes lifestyle modification and treatment interventions, hence, can alleviate the development of complications in metabolic syndrome.

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