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GAMMA GLUTAMYL TRANSFERASE AS A MARKER IN METABOLIC SYNDROME

Dr. Vaishnavi Alam*[1], Dr. V. Lakshmaiah[2], Dr. Prabhakar K.[3], Dr. Harish Kumar[4], Dr. Reddy Prasad[5], Dr. Sumathi[6]

[1]MD. Postgraduate Student, Department of Medicine, Kolar.
[2]MD (Med). DCH. Professor, Department of Medicine. SDUMC, Kolar.
[3]MD. Professor and HOD, Department of Medicine, SDUMC, Kolar.
[4]MD. Associate Professor, Department of Medicine, SDUMC, Kolar.
[5]MD. Assistant Professor, Department of Medicine, SDUMC, Kolar.
[6]MD. Associate Professor, Department of Boichemistry , SDUMC, Kolar.

***Author for Correspondence: Dr. Vaishnavi Alam**
MD. Postgraduate Student, Department of medicine. Kolar.

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OBJECTIVES
To study the association of Gamma Glutamyl Transferase levels with metabolic syndrome and To compare and correlate biochemical parameters between controls and cases. **Materials and Methods:** This is a case control of study of 110 subjects in R.L. Jalappa hospital both inpatients and outpatient of which included are 55 subjects who satisfy IDF criteria for metabolic syndrome and 55 age and sex matched controls. Blood pressure, waist circumference , Liver function tests including GGT, AST, ALT and ALP, Lipid profile, Fasting plasma glucose, Thyroid profile, Renal function tests and USG abdomen were performed in subjects. **Results:** The mean values of GGT, alanine amino transferase(ALT), aspartate aminotransferase (AST) levels were statistically significantly higher in MS group. The mean values of liver enzymes, in MS group, GGT, AST and ALT respectively, were; 51.89±6.31, 31.80±17.37 and 37.71±13.52. In the study sample, increase in GGT was positively correlated with increased MS prevalence. In ROC analysis, GGT is as strongly associated with the IDF diagnostic components as is each individual IDF component, except elevated systolic blood pressure. In covariance analysis, there was significant relationship between elevated GGT levels and MS presence after adjustment for age, sex and MS diagnostic criteria. In multivariance analysis, in MS group, a high GGT was positively associated with CVD prevalance compared to low GGT group independent of age, sex and smoking habits. **Conclusion:** Elevated liver enzymes, although in normal ranges, especially at upper quartiles, play a central role in early diagnosis of fat overflow to the liver. Regarding the availability and simplicity of these tests in routine clinical practice, they, especially GGT, have potential to be considered in algorithms for metabolic syndrome.

KEYWORDS: GGT - liver function Tests - Metabolic Syndrome.

INTRODUCTION

The Metabolic Syndrome (MetS) also known as **'plurimetabolic syndrome', 'syndrome X' 'deadly quartet', 'insulin resistance syndrome', 'hypertriglyceridemic waist' and 'dysmetabolic syndrome'** is an aggregation of metabolic abnormalities that presage increased risk for the development of atherosclerotic cardiovascular disease (ASCVD).[1] The constellation of metabolic abnormalities includes glucose intolerance (type 2 diabetes, impaired glucose tolerance, or impaired fasting glycaemia), insulin resistance, central obesity, dyslipidaemia, and hypertension.[2]

Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. This increase is associated with the global epidemic of obesity and diabetes.[3] With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome, there is urgent need for strategies to prevent the emerging global epidemic.[3]

The prevalence of metabolic syndrome in India is 25. 8%. It is estimated that around 20-25 % of the world's adult population have the MetS and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.[2,4]

Various bodies have defined metabolic syndrome based on biochemical parameters and clinical examination. The new IDF definition for metabolic syndrome establishes a comprehensive 'platinum standard' list of additional criteria to be included in epidemiological studies and research and addresses both clinical and research

needs, providing an accessible, diagnostic tool suitable for worldwide use.[5]

IDF CRITERIA

The presence of CENTRAL ADIPOSITY defined as waist circumference of ≥90 cm in males and ≥80 cm in females in the Indian population . Along with central adiposity two of the following four factors should be present to define metabolic syndrome[5]

1. Fasting triglycerides ≥150 mg/dl or specific medication.
2. HDL cholesterol < 40 mg/dl and < 50 mg/dl for men and women, respectively or specific medication.
3. Blood pressure ≥ 130 mm systolic or ≥85 mm diastolic or previous diagnosis or specific medication .
4. Fasting plasma glucose ≥ 100 mg/dl or previously diagnosed Type 2 diabetes.

Gamma -glutamyl transferase (GGT) is shown to be an independent risk factor for the mortality and morbidity of cardiovascular diseases in recent epidemiological and clinical studies.[6] Several prospective studies reported that baseline serum GGT concentration was an independent risk factor for the development of coronary artery disease (CAD), diabetes mellitus, stroke and hypertension.[7,8] Raised liver enzymes, as relatively sensitive and easily obtained markers of NAFLD, reflect chronic ectopic fat deposition in the liver that may be useful in MS diagnosis.

With respect to our clinical observations, we hypothesize that high liver function tests, especially GGT levels, are associated with prevalent metabolic syndrome and in this aspect they may have a predictive value in diagnosis of metabolic syndrome.

MATERIALS AND METHODS

The study samples were collected from the Medicine OPD and in-patient department of R.L. Jalappa hospital, kolar The study subjects included both male and female MS patients and age and sex matched non MS individuals in the age group of 18-60 years . The study period spanned over one year from March 2014-March 2015. Total 110 patients were enrolled into the study. Of them, 55 had Metabolic syndrome and 55 were age and sex controlled individuals. The applied selection criteria were as follows

INCLUSION CRITERIA

Patients of either sex aged 18 to 60 years and diagnosed with metabolic syndrome on the basis of IDF Criteria who attended the OPDs during the study period and gave their voluntary written informed consent for the study

EXCLUSION CRITERIA

1. Hypothyroidism.
2. Malignant diseases.
3. Severe renal insufficiency.
4. Acute and chronic liver disease.
5. Chronic alcohol consumption
6. Drugs- antiepileptics, oral contraceptives, erythromycin, cimetidine.
7. Pregnant women.

STUDY PROTOCOL

SAMPLE COLLECTION, ANALYSIS

Before collection of data or blood sample, each patient was explained the details of the study including rationale, expected benefits, risk profile, confidentiality safeguards and study protocol. For some patients, help of appropriate interpreter(s) was taken. Only those patients who were willing to follow the study protocol and gave their written consent were included in the study. There was neither any financial cost nor any financial incentive for the patient for being part of the study.

1. Appropriate blood samples were collected from MS patients and age and sex matched non MS individuals. For estimation of serum GGT, cholesterol, triglyceride, HDL and plasma glucose fasting blood sample were drawn into serum (without anticoagulant) gel containing yellow colour capped BD Vacutainer tubes. All samples were immediately centrifuged and stored at 2-8^{0}C until analysis for the relevant biochemical parameters. All analyses were performed within 3 hours of sample collection.

2. Serum Cholesterol was measured by XL600 autoanalyzer using CHOD-PAP principle.[9]

3. Serum Triglyceride was measured by XL600 autoanalyzer using Glycerol Kinase principle.[10]

4. Serum HDL was measured by ERBA Chem 5 V2 semi-autoanalyzer using PEG Precipitation principle.[11]

5. Serum GGT level was measured by XL600 autoanalyzer using Gamma Glutamyl p-Nitroanilidine (GPNA) principle.[12]

6. Plasma glucose was measured by XL600 autoanalyzer using GOD-POD principle.

7. Serum Albumin was measured by XL600 autoanalyzer using BCG principle.

8. Serum total protein was measured by XL600 autoanalyzer using Biuret principle.

9. Patients' recent-most blood/plasma/serum values of the afore-mentioned biochemical parameters were noted, if already available, provided they were done on the same day.

Patients' relevant anthropometric like height , weight, Body mass index, waist- hip ratio were collected and Blood pressure is recorded in both arms after 5 mins

of rest in both arms both supine and sitting position. The serum levels of GGT, Cholesterol, Triglyceride, HDL and fasting plasma glucose levels of the two groups were compared for presence or absence of statistically significant differences

STATISTICAL METHODS

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and SD. Independent t test was used as test of significance to identify the mean difference between two groups. p value <0.05 was considered as statistically significant. ROC curve was plotted to find the area under curve and sensitivity and specificity of GGT in Metabolic syndrome.

RESULTS

The present study confirms the finding of earlier studies that serum GGT level in MS patients is higher than their non MS counterparts. In the study there was no significant difference in age and gender between two groups. Serum levels of cholesterol, triglyceride, HDL and fasting plasma glucose levels were significantly different in two groups.

TABLE 1: The Biochemical Parametres Of Ms And Non Ms Group

	MS GROUP	CONTROL GROUP
NUMBER OF PATIENTS	55	55
MALE/FEMALE	36/19	19/36
AGE (YRS)	39.49±11.11	43.96±10.17
SBP(mmHg)	133.58±15.76	120.26±7.55
DBP(mmHg)	84.91±8.78	74.44±5.54
BMI (Kg/m^2	29.30±2.57	24.16±0.90
FBS(mg/dl)	142.30±59.98	88.31±10.32
PPBS(mg/dl)	181.87±65.02	131.26±13.49
HBA1C(%)	8.37%	6.20%
WAIST CIRCUMFERENCE	97.62±5.31	78.35±3.02
AST	31.80±17.37	25.59±5.23
ALT	37.71±13.52	28.50±5.03
GGT	51.89±6.31	38.09±8.10
HDL	35.63±8.74	49.74±6.29
LDL	108.84±39.07	68.63±14.94
TRIGLYCERIDES	208.76±92.85	101.93±20.07

Seventeen per cent of overall patients were diagnosed with hypertension and 21 per cent were with dyslipidemia, 4 per cent with diabetes mellitus and 9 with impaired glucose tolerance. Although plasma total cholesterol and LDL-cholesterol levels did not differ between the 2 groups; HDL-C levels were lower and triglyceride levels were higher in MS patients when compared with control group. The mean body mass index value (BMI) was higher in MS group than controls, but the difference was not statistically significant. The mean values of LFT (ALT, AST, and GGT) were statistically significantly higher in MS group (TABLE 1).

The levels of AST, ALT and GGT in subjects with diabetes mellitus, impaired glucose tolerance and abdominal obesity were significantly higher than those in subjects without these components of MS. The highest mean values of liver enzymes has been found in abdominal obesity group (ALT=30.6 U/l; AST= 24.0 U/l; GGT= 43.8 U/l). Only GGT levels were significantly higher in subjects with dyslipidemia than subjects without.

When the sample is divided into quartiles of the GGT levels, increase in GGT is positively correlated with increased metabolic syndrome prevalence. Moreover increased GGT levels were also positively correlated with increased CVD presence.

Table 2 shows the ROC analysis when GGT is compared with other MS diagnostic criteria. The range of area under curve (AUC) for GGT was: 0.855-0.959. Transaminases displayed a weaker association than GGT for MS: ALT 0.64-0.83, and AST 0.45-0.69. This indicates that GGT is as strongly associated with the IDF diagnostic components as is each individual IDF component, except elevated systolic blood pressure.

Table 2: Receiver operating characteristic (ROC) analysis of metabolic syndrome components and liver function tests (LFTs)

Test Result Variable(s)	Area Under the Curve	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
GGT	0.907	<0.0001*	0.855	0.959
AST	0.573	0.188	0.456	0.690
ALT	0.742	<0.0001*	0.642	0.842
SBP	0.736	<0.0001*	0.641	0.831
DBP	0.830	<0.0001*	0.751	0.909
FBS(mg/dl)	0.852	<0.0001*	0.781	0.923
PPBS(mg/dl)	0.752	<0.0001*	0.651	0.853
HbA1c (%)	0.740	<0.0001*	0.641	0.839
Total Cholesterol	0.581	0.142	0.467	0.696
Triglyceride	0.880	<0.0001*	0.806	0.954
HDL Cholesterol	0.088	<0.0001*	0.028	0.148
LDL Cholesterol	0.813	<0.0001*	0.722	0.905

Table 3: Sensitivity and specificity of diagnosing MS for some GGT values

GGT Value	Sensitivity	Specificity
23	1.000	0.000
36.5	1.000	0.481
41.5	0.909	0.593
45.5	0.818	0.778
48.5	0.727	0.889
54.5	0.436	1.000
57.5	0.182	1.000
62	0.000	1.000

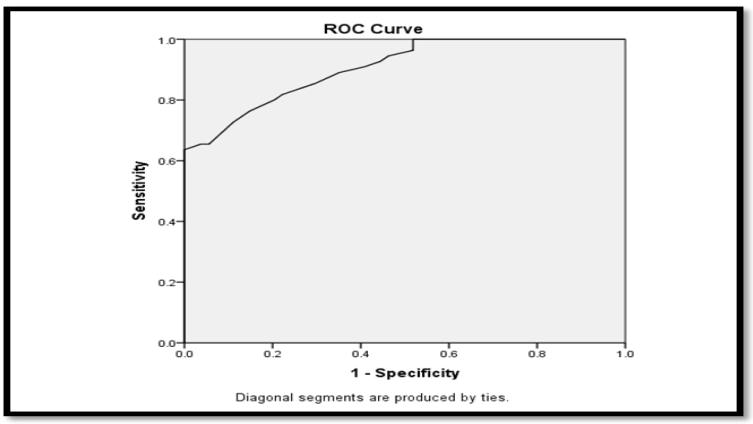

Figure 1: ROC curve of GGT in Metabolic Syndrome Cases

In covariance analysis, there were significant relationships between elevated GGT levels and MS presence after adjustment for age, sex and MS diagnostic criteria; but not AST and ALT levels. In multivariance analysis, in MS group, a high GGT was positively associated with CVD prevalance (odds ratio: 2.011, 95% CI 1.10-4.57) compared to low GGT group, independent of age, sex and smoking habits. Similarly, high GGT was positively associated with prevalant CVD in control group (odds ratio: 1.76, 95% CI 1.02-3.91).

DISCUSSION

We compared the hepatic enzyme levels in subjects with metabolic syndrome with those age and sex match controls . The predictive ability of increased GGT levels to diagnose MS was higher than hypertriglyceridemia, increased waist circumference and impaired glucose tolerance for both genders. Among the various components of MS, increased systolic blood pressure showed highest predictive ability to diagnose MS in men and increased waist circumference in women.

In our study, transaminases are in normal ranges in 91.2 per cent and GGT are in normal ranges in 83.4 per cent of MS patients. Especially ALT and GGT values are significantly higher than control group but still remain in normal ranges. As our results show, normal liver enzymes values could coexist with metabolic syndrome. In a study of Balogun *et al.*[13] on 90 patients with type 2 diabetes and 90 nondiabetic controls the ALT and GGT

values were significantly higher (52.9 IU/l and 24.3 U/l respectively) in the diabetic group compared to the controls (34.4 IU/l and 9.2 IU/l respectively). Moreover, the most predominant LFT abnormality in diabetic group was found to be isolated elevation of GGT.

In our study, liver function tests are higher in subjects with MS than the controls. In some other studies, it has been demonstrated that circulating GGT and transaminases activities are elevated in patients with metabolic syndrome.[14, 15]

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases commonly seen with MS and elevated liver enzymes is a manifestation of fatty liver. NAFLD represents the ectopic fat accumulation in the liver and is now considered to be the most common cause of chronic liver disease worldwide.[16]

Nannipieri *et al* revealed an association with mild elevations in liver function tests and metabolic syndrome.[17] Moreover, Wannamethee *et al*[18] revealed that; elevated levels of ALT and GGT within the normal ranges are found to be the independent predictors of type 2 diabetes mellitus.

In covariance analysis we found a significant relationship between elevated GGT levels and MS presence after adjustment for age, sex and body mass index. 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 even after adjustment for age, body mass index and alcohol consumption.[19] In another study of Sakugawa *et al*[20], the serum GGT level found to be correlated with components of MS. Although this relationship between GGT and metabolic syndrome is not clearly understood, some mechanisms including presence of oxidative stress and/or NAFLD can explain the relationship.

Using ROC analysis, we found significant variability in the prediction of MS by IDF diagnostic components, with diabetes mellitus being the strongest and diastolic BP the weakest. The GGT cut-off points were determined from their association with other MS criteria. Interestingly the cut-off point for 'high' GGT is still within the normal laboratory range. In this aspect, we speculate that, clinicians should be aware of the risk of oxidative stress although liver enzymes are in normal ranges especially at upper quartiles.

When we consider GGT above these cut-offs, there was an association with previous CVD in addition to the effect of MS (odds ratio: 2.011, 95% CI 1.10-4.57). This suggests that GGT measures a degree of CVD risk not assessed by standard MS criteria. Recently, Ruttmann *et al.*[21] showed that GGT activity was independently associated with cardiovascular mortality; in a large unselected cohort. Some epidemiological studies[22] also suggest that higher serum GGT levels is associated with development of CVD risk factors, including diabetes, hypertension, and the metabolic syndrome.

CONCLUSION

In conclusion, elevated liver enzymes, although in normal ranges, especially at upper quartiles, play a central role in early diagnosis of fat overflow to the liver. Moreover, GGT may play a role in early diagnosis of metabolic syndrome with a high predictive value for both metabolic syndrome and cardiovascular disease presence. Regarding the availability and simplicity of these tests in routine clinical practice and their universal standardization, these findings indicate the potential of liver enzymes, especially GGT, to be considered in algorithms for metabolic syndrome.

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