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A study of GGT as a diagnostic marker of metabolic syndrome

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Abstract
Introduction: Metabolic syndrome is a clustering of at least three of the five following medical conditions: central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL). There has been a consistent effort to evaluate biochemical markers to predict an early onset of metabolic syndrome and subsequently intervene appropriately by means of lifestyle changes and drug therapy and thereby reduce cardiovascular morbidity and mortality. Gamma Glutamyl Transferase (GGT) is one such marker which is cost effective, easily available and performed as part of liver function tests.
Aims and Objectives: (1) To assess the role of GGT as a marker in the diagnosis of metabolic syndrome. (2) To assess the sensitivity and specificity of GGT in the diagnosis of metabolic syndrome.
Materials and Methods: This was hospital based cross sectional study was conducted on 200 subjects who attended the Medicine Outpatient and Inpatient services (OPD and IPD) at MBGH, Udaipur.
Results: In our study, total 200 subjects were recruited comprising 100 cases of metabolic syndrome and 100 age and sex matched control. A total 75 out of 100 cases satisfied the IDF criteria of FPG>100mg/dl. The mean HbA1c was 8.25±2.18 and elevated in 71 out of 100 cases. A total 55 out of 100 patients satisfied the IDF criteria of SBP>130mmHg. The values of TG, HDL and LDL cholesterol were highly significant among cases. Among cases, 80 out of 100 had GGT values above normal while only 2% of control had high GGT values. GGT values were compared with respective parameters of metabolic syndrome. Out of 55 patients with SBP > 130mmHg, 49 had GGT level above the reference range. Out of 80 patients with hypertriglyceridemia, 66 had GGT level above the reference range. Among 75 patients with FPG>100mg/dl, 60 had higher GGT. With respect to burden of cardiovascular disease, 25 out of 100 patients were suffering from CVD. In all these patients, higher levels of GGT were noted.
Conclusion: This study has critically evaluated the utility of GGT as a diagnostic marker of metabolic syndrome. Elevated levels were found to be associated with metabolic syndrome and is strong predictor of cardiovascular risk. Hence GGT has position in algorithms for evaluation of metabolic syndrome and CVD risk assessment. The primary prevention may be emphasized in patients of metabolic syndrome with high GGT values.

Keywords: Metabolic syndrome, gamma glutamyl transferase (GGT), cardiovascular disease (CVD)

Introduction
Metabolic syndrome, sometimes known by other names such as Syndrome X, insulin resistant syndrome, is a clustering of at least three of the five following medical conditions: central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL) [1].
It is associated with the risk of developing cardiovascular disease and type 2 diabetes. In the US about a quarter of the adult population has metabolic syndrome, and the prevalence increases with age, with racial and ethnic minorities being particularly affected. Insulin resistance, metabolic syndrome, and prediabetes are closely related to one another and have overlapping aspects.
The syndrome is thought to be caused by an underlying disorder of energy utilization and storage. The cause of the syndrome is an area of ongoing medical research.
The criteria for metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations.

The rise in the prevalence of obesity in India is threatening to increase the burden of atherosclerotic cardiovascular disease (ASCVD). The prevalence of metabolic syndrome worldwide is 20-25% (IDF) [2, 3]. Among the complications, cardiovascular events produce the greatest morbidity and mortality. Others include dyslipidaemia, hypertension, systemic inflammation, and a thrombotic tendency.

Recently there has been a trend in the cardiovascular field to group all these factors together under the heading of metabolic syndrome. This syndrome does not include, but is strongly associated with other complications of obesity, for example, fatty liver, cholesterol gallstones, obstructive sleep apnoea and polycystic ovarian syndrome [4].

There has been a consistent effort to evaluate biochemical markers to predict an early onset of metabolic syndrome and subsequently intervene appropriately by means of lifestyle changes and drug therapy and thereby reduce cardiovascular morbidity and mortality. Studies are lacking among the adult Indian population.

Markers like adiponectin have been studied as a measure of increased adipose tissue but have not proven to be cost effective and easily available. Clearly a prompt, cost effective and easily available biochemical marker is required to predict an early onset of this syndrome. Gamma Glutamyl Transferase (GGT) is one such marker which is cost effective, easily available and performed as part of liver function tests [5].

High levels of GGT have been associated in populations with increased risk of atherosclerotic cardiovascular disease (ASCVD) [2, 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].

The purpose of this study is to evaluate the utility of GGT as an early diagnostic marker of metabolic syndrome.

AIMS and Objectives

1. To assess the role of GGT as a marker in the diagnosis of metabolic syndrome.
2. To assess the sensitivity and specificity of GGT in the diagnosis of metabolic syndrome.

Materials and Methods

This was hospital based cross sectional study was conducted on subjects who attended the Medicine Outpatient and Inpatient services (OPD and IPD) at MBGH, Udaipur. In our study, total 200 subjects were recruited comprising 100 cases of metabolic syndrome and 100 age and sex matched control (who were not fulfilling criteria of metabolic syndrome). The detailed clinical history, demographic profile, socioeconomic status, contact number and consent were taken and recorded. General physical examination as well as relevant systemic examination was done. Relevant investigations (LFT including GGT, RFT, fasting lipid profile, fasting and post prandial plasma glucose, thyroid profile, USG abdomen) were done. All the collected informations were filled in predesigned proforma for final analysis.

Inclusion Criteria

1. Patients aged above 18 years.
2. Central obesity is defined as waist circumference ≥90cm for men and ≥80 cm for Women (Indian population)
   Plus any two of the following four factors -

- Raised TG level ≥150 mg/dl or specific treatment for this lipid abnormality
- Reduced HDL cholesterol ≤40 mg/dl or specific treatment for this lipid
  abnormality
- Raised BP systolic ≥130 and diastolic ≥85 or treatment for previously diagnosed hypertension.
- Raised FPG ≥100 mg/dl or previously diagnosed type 2 DM

Exclusion Criteria

1. Hypothyroidism
2. Malignant diseases
3. Renal insufficiency
4. Acute and chronic liver disease
5. Chronic alcohol consumption
6. Drugs (antiepileptics, oral contraceptive pills, erythromycin, cimetidine etc.)

Statistical Analysis

Data entered in M S excel and analysed using SSPS Version
Descriptive statistics

- All quantitative data like age, vital signs and investigations will be presented as mean and standard deviation with 95% confidence intervals.
- All qualitative data like sex, symptoms, baseline medical characteristics, clinical examination findings will be presented as frequency and percentage

Analytical statistics

- Correlation and regression statistics will be applied to assess the association of GGT level in metabolic syndrome and comparison with control groups.
- Validity measures such as sensitivity and specificity shall be computed for GGT in diagnosis of metabolic syndrome.

The result for each parameter (number and percentage) for discreate data and average (mean ± SD) for continuous data are presented in tables and figures.

1. Proportions were compared using Chi-square test of significance

Degree of freedom (DF) = (r-1) (c-1)
r = rows, c = column

2. Student ‘t’ test was used to determine whether there was a statistical difference between study groups in parameter measured

In all the above test, p value 0f less than 0.05 was accepted as indicating statistical significance. Data analysis was carried out using Statistical Package for Social Science (SPSS) package.

Observations

Table 1: Duration of co-morbidities (diabetes, hypertension and dyslipidaemia)

		Cases	Control	
Duration of diabetes (years)	< 5	42	87	Chi=47.95 *P*<0.001
	5-9	38	13	
	>10	20	0	
Duration of hypertension(years)	<5	58	90	Chi=29.18 *P*<0.001
	5-9	29	10	
	>10	13	0	
Duration of dyslipidaemia (years)	<5	49	92	Chi=46.85 *P*<0.001
	5-9	43	8	
	>10	9	0	

The mean duration of diabetes was 5.25±4.27 years in cases and 1.04±2.19 years in control group.
The mean duration of hypertension was 4.58±4.73 years in cases and 1.03±2.1 years in control group.
The mean duration of dyslipidaemia was 5.19±3.76 years in cases and 0.68±1.74 years in control group.

Table 2: Comparison of systolic and diastolic blood pressure among subjects

		Cases	Controls	Chi- Square value	P value
SBP	≤130	45	91	48.62	<0.001 (HS)
	>130	55	9		
DBP	≤80	17	85	92.51	<0.001 (HS)
	>80	83	15		

Among cases 55% had SBP above 130 mmHg and 83% had DBP above 80 mmHg. The value of both SBP and DBP among cases were highly significant.

Table 3: HbA1c, Triglyceride, HDL, LDL and FBS levels in cases and controls

		Cases		Controls		Chi- Square value	P VALUE
		No.	%	No.	%		
HbA1c	≤6.5	29	29	77	77	46.24	<0.001 (HS)
	>6.5	71	71	23	23		
Triglyceride	≤150	20	20	90	90	98.99	<0.001 (HS)
	>150	80	80	10	10		
HDL cholesterol	<40/50	76	76	42	42	23.89	<0.001 (HS)
	≥40/50	24	24	58	58		
LDL cholesterol	<100	47	47	95	95	55.94	<0.001 (HS)
	≥100	53	53	5	5		
Fasting blood glucose	<100	25	25	82	82	65.30	<0.001 (HS)
	≥100	75	75	18	18		

The values of HbA1c, TG, LDL and fasting blood glucose were highly significant among cases.

Table 4: Serum GGT levels in study population (above normal)

GGT (IU/L)	Cases		Controls		Chi- Square value	P Value
	No.	%	No.	%		
<55/38	20	20	98	98	125.75	<0.001 (HS)
≥55/38	80	80	2	2		

Table 5: Serum GGT levels in study population (including patients with upper limit of normal)

GGT (IU/L)	Cases		Controls		Chi- Square value	P Value
	No.	%	No.	%		
<50/35	5	5	88	88	138.45	<0.001 (HS)
≥50/35	95	95	12	12		

Reference range for normal GGT values at MBGH, Udaipur:
Male < 55 IU/L
Female <38 IU/L
Among cases, 80% had GGT values above normal while only 2% of control had high GGT values. These values are highly significant.

Table 6: Comparison and correlation of GGT with SBP and DBP

		GGT (IU/L)				Chi- Square value	P Value
		<55/38 (n=20)		≥55/38 (n=80)			
		No.	%	No.	%		
SBP	≤ 130	14	70	31	38.75	6.31	0.01 (S)
	>130	6	30	49	61.25		
DBP	≤ 80	12	60	30	37.50	3.32	0.06 (NS)
	>80	8	40	50	62.50		

Table 7: Comparison and correlation of GGT with HDL cholesterol, serum triglyceride and fasting blood glucose

		GGT (IU/L)				Chi- Square value	P Value
		<55/38 (n=20)		≥55/38 (n=80)			
		No.	%	No.	%		
HDL Cholesterol (mg/dl)	<40/50	9	45	51	63.75	2.34	0.12 (NS)
	≥40/50	11	55	29	36.25		
Triglyceride mg/dl	≤150	6	30	14	17.50	1.56	0.21 (NS)
	>150	14	70	66	82.50		
Blood Glucose Level	<100	5	25	20	25	0.00	1 (NS)
	≥100	15	75	60	75		

Table 8: Correlation of GGT with cardio-vascular disease

		GGT (IU/L)				Chi- Square value	P VALUE
		<55/38 (n=20)		≥55/38 (n=80)			
		No.	%	No.	%		
Cardiovascular disease	No	20	100	55	68.75	8.33	0.04 (S)
	Yes	0	0	25	31.25		

Incidence of cardiovascular disease in cases with high serum GGT levels was statistically significant.

Table 9: Sensitivity and specificity of GGT in diagnosis of metabolic syndrome

GGT level	Patients with metabolic syndrome	Patients without metabolic syndrome	Total
Positive	80	2	82
Negative	20	98	118
Total	100	100	200

Sensitivity	=	80%
Specificity	=	98%
Positive predictive value	=	97.56%
Negative predictive value	=	83.05%
False negatives	=	20%
False positives	=	2%
Accuracy	=	89%

Discussion

The clustering of CVD risk factors that typifies metabolic syndrome is now considered to be the driving force behind a CVD epidemic. A need for early diagnosis of metabolic syndrome is essential to prevent and decrease mortality and morbidity due to cardiovascular disease. Studies are lacking in adult Indian population. The role of GGT as a diagnostic marker of metabolic syndrome has been critically evaluated in this study.

In our study, total 200 subjects were recruited comprising 100 cases of metabolic syndrome and 100 age and sex matched control. The mean age in study group was 58.2±10.35 and 58.17±10.34 in control group. Patient in this study group were found to be clustered in sixth decade of life with 37% belonging to this category. There were 49% males and 51% females in study group whereas 52% males and 48% females in control group.

Similar study done by B Kasapgolu *et al.* [5], the mean age was 51.3±3.2 and gender distribution showed 62% females and 38% male in study group. This difference may suggest an equal incidence of metabolic syndrome in both sexes in Indian sub-continent.

The mean duration of diabetes was 5.25±4.27 in cases and 1.04±2.19 in control group. A total 75 out of 100 cases (75%) satisfied the IDF criteria of FPG>100mg/dl inferring impaired fasting glucose or type2 diabetes. The mean HbA1c was 8.25±2.18 and elevated in 71 out of 100 cases (71%). These observations suggest a high prevalence of type 2 diabetes in patients with metabolic syndrome.

The mean duration of hypertension was 4.58±4.73 in cases and 1.03±2.1 in control group. The mean systolic blood pressure in cases was 134.8±14.2 and 121.7±8.5 in control group. The mean diastolic blood pressure was 86.8±6.5 and 74.9±6.17 in cases and controls respectively. A total 55 out of 100 patients (55%) satisfied the IDF criteria of SBP>130mmHg. The observations suggest that elevated systolic and diastolic blood pressure is an important contributing factor in metabolic syndrome.

In the reference study done by B Kasapgolu *et al*. [5], similar results were found; mean SBP and DBP being 138.2±11.7 and 86.7±7.2 respectively.

The mean duration of dyslipidaemia was 5.19±3.76 in cases and 0.68±1.74 in control group. The mean total cholesterol was 181±45.9, TG was 196.6±76.5, HDL was 37.56±8.62 and LDL was 106.2±36. A total 80 out of 100 cases had TG>150 mg/dl including 39 males and 41 females. A total 76 out of 100 cases had HDL<40 for males and <50 for females. A total 53 out of 100 cases had LDL>100 mg/dl. The values of TG, HDL and LDL cholesterol were highly significant among cases. Hypertriglyceridemia was found in maximum number of cases in study group and predominant dyslipedemic abnormality.

The values in our study group with respect to lipid profile were lower than the reference study done by B Kasapgolu *et al.* [5], where in mean TG was 273.8±25.2, LDL was

131.4±8.9 and HDL was 42.1±9.7. This difference may suggest variation in diet and familial metabolic parameters in particular geographic distributions.

In the evaluation of liver function tests, GGT is a biomarker being evaluated in this study. The mean GGT in study group was 52.44±6.17 and in control group was 35.62±8.42. Among cases, 80 out of 100 (80%) had GGT values above normal including 35 males and 45 females ($P<0.001$) while only 2% of control had high GGT values. These values are highly significant.

Similar study done by B Kasapgalu *et al*. [5]. the mean GGT in study group was 40.9±10.2 and 21±7.1 in control group.

GGT values were compared with respective parameters of metabolic syndrome. Out of 55 patients with SBP > 130mmHg, 49 had GGT level above the reference range comprising 49% of study population. Out of 80 patients with hypertriglyceridemia, 66 had GGT level above the reference range comprising 66% of study population. Among 75 patients with FPG>100mg/dl, 60 had higher GGT. The above observations suggest that GGT had the highest correlation with hypertriglyceridemia.

With respect to burden of cardiovascular disease, 25 out of 100 patients were suffering from CVD, including 10 males and 15 females. In all these patients, higher levels of GGT were noted. These values were higher when compared with to study subjects without cardiovascular disease. This may suggest a direct correlation of GGT levels with cardiovascular disease with higher values conferring increased CVD risks.

Similar study done by B Kasapgalu *et al*., [5], high GGT was positively associated with CVD prevalence (odds ratio; 2.011, 95% CI 1.10-4.57) compared to low GGT group, independent of age sex and smoking habits.

Ruttmann *et al*. [6] showed that GGT activity was independently associated with cardiovascular mortality.

Devers *et al*. [8] also suggested that higher serum GGT levels is associated with CVD risk factor, including diabetes, hypertension and metabolic syndrome.

In another observation, 14 patients were suffering from cerebrovascular disease, out of which 5 had higher GGT values suggesting that GGT levels may not directly correlate with cerebrovascular disease.

Validity measures were computed taking the reference values of GGT≥55 in males and ≥38 in females. 80 (80%) out of 100 patients had GGT levels above normal while only 2% in controls had high GGT levels. Sensitivity and specificity of GGT to diagnose the patients with metabolic syndrome was 80% and 98%.

An interesting observation noted in study group with respect to GGT that most of the subject with level less than 55/38 IU/L were clustered in the upper limit of normal (males>50IU/L and females >35IU/L). A total 95 out of 100 patients (95%) had GGT values above normal with 15% falling in range of upper limit of normal. This therefore suggests that GGT values even in upper limit of normal may have a predictive value in diagnosis patients with metabolic syndrome.

Bruckert E *et al*. [9] and Onat A. *et al*. [10] demonstrated that circulating GGT and transaminases activities are elevated in patients with metabolic syndrome.

Rantalaet *et al*. [11] showed the highly significant relationship between GGT and components of metabolic syndrome.

Sakugawa *et al*. [12], the serum GGT level was found to be correlated with components of metabolic syndrome.

Conclusion

This study has critically evaluated the utility of GGT as a diagnostic marker of metabolic syndrome. Elevated levels were found to be associated with metabolic syndrome and is strong predictor of cardiovascular risk. GGT levels correlated well with all parameters of metabolic syndrome especially with hypertriglyceridemia with which it was the highest. It was also noted that there was a clustering of patients in the range of upper limit of normal values for GGT indicating the possible need for considering even such values in context of metabolic syndrome and CVD risk. The sensitivity of the test to diagnose metabolic syndrome was better in females but specificity had no gender bias. Considering the CVD risk, primary prevention may be emphasized in patients of metabolic syndrome with high GGT values. Hence GGT has position in algorithms for evaluation of metabolic syndrome and CVD risk assessment.

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