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Original article:

Gamma glutamyl transferase as a diagnostic marker of metabolic syndrome

KISHOR PHEPALE, ARCHANA GOKHROO , RAJESH JAIN, RAMESH CHAND SHARMA, SUNIL KUMAR AREN

Department of Medicine , JLN Medical College Campus, Ajmer (RAJ.)
Name of the Institute/college: JLN Medical College Campus, Ajmer (RAJ.)
Corresponding author: Kishor Phepale

Abstract

Introduction: In an era of a cardiovascular epidemic an imminent search for more sensitive and specific markers of sub-clinical inflammation, atherogenesis, and increased adiposity has been sought. This study attempted to assess how serum Gamma GlutamylTransferase performed as an ideal endogenous substance for the diagnosis of metabolic syndrome and hence estimate cardiovascular risk.

Aim: To assess the role of GGT as a marker in the diagnosis of metabolic syndrome, and to determine the sensitivity and specificity of the same

Methods: 250 subjects were chosen comprising cases of metabolic syndrome and equal number of controls. Patients were recruited into the study group after satisfying the IDF criteria for Metabolic Syndrome. GGT values were obtained for both groups apart from other parameters. The patients in the study were also evaluated for the presence of cardiovascular disease.

Results: 84% cases had higher GGT levels in patients with metabolic syndrome. The sensitivity and specificity of GGT to diagnose patients with metabolic syndrome was found to be 84% and 91% ($p<0.01$).

Conclusion: Serum GGT appears to be a cost effective, easily available and fairly good marker for diagnosing patients with metabolic syndrome and is independent of other parameters. It is also a strong predictor of cardiovascular disease. Hence GGT probably has a position in algorithms for the evaluation of patients with metabolic syndrome.

Introduction

The **metabolic syndrome** (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and cerebrovascular disease[1]. The criteria for the 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 major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia, and hypertension.[1]

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. A significant portion of the latter occurs in persons in whom obesity precedes type II diabetes. But diabetes is only one of several conditions that associate strongly with obesity. Others include dyslipidemia, hypertension, systemic inflammation, and a thrombotic tendency. Recently there has been a trend in the cardiovascular field to group all of these factors together under the heading of **metabolic**

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syndrome[1]. In this sense, metabolic syndrome can be taken to represent a multiplex cardiovascular risk factor. 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]. The current definition generally regards hyperglycaemia in the range of type II diabetes to be one of the components of metabolic syndrome. The clustering of CVD risk factors that typifies metabolic syndrome is considered to be the driving force behind a CVD epidemic.

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 in 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 GlutamylTransferase (**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 atheroscleroticcardiovascular disease ASCVD.Several prospective studies reported that baseline serumGGT 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 Gamma-glutamyltransferaseas a marker in thediagnosis of metabolic syndrome
2. To assess the sensitivity and specificity of Gamma-glutamyltransferasein the diagnosis of metabolic syndrome

Materials and methods

Source of data

Patients attending the medicine outpatient & inpatient services at JLN Medical College and Hospital, Ajmer (Raj.)

Inclusion criteria

1. Patients aged above 18 years
2. Central obesity – 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>=150mg/dl or specific treatment for this lipid abnormality
- Reduced HDL cholesterol<40mg/dl or specific treatment for this lipid abnormality
- Raised B.P systolic>=130 diastolic>=85 or treatment for previously diagnosed hypertension.
- Raised FPG>=100mg/dl or previously diagnosed type 2 diabetic

Exclusion criteria

- Hypothyroidism
- Malignant diseases
- Severe renal insufficiency
- Acute and chronic liver disease
- Chronic alcohol consumption
- Drugs - antiepileptics, Oral contraceptive agents, trimethoprim, sulphamethoxazole, erythromycin, cimetidine

Study period

A period of one year from December 2014 – December 2015

Study design

A hospital based cross sectional study

Sample size

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- Sample size was estimated to be approximately a minimum of 250
- An equal number of age group and sex matched normal controls were recruited to compare the GGT levels.
- Hence the study was done on a minimum total of 500 patients inclusive of both groups.

Method of data collection

Written informed consent was taken from the patients.Data was be collected by pretested semi structured questionnaire, clinical examination and investigations.An estimation of gamma glutamyltransferase (GGT) was done for all the study subjects including cases and controls.

GGT analysis

Statistical analysis

The following methods of statistical analysis have been used in this study.

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

2) The student 't' test was used to determine whether there was a statistical difference between study groups in the parameters measured.

In all the above test the p value of less than 0.01 was accepted as indicating statistical significance.

Results

Table 1: HbA1C, TG, HDL and LDL levels in cases and controls

		Control (N=250)		Case (N=250)		□2 value	'p' value
		n	%	n	%		
HBA1C (%)	<=6.5	190	76%	66	26.4%	123.07	<0.01
	>6.5	60	24%	184	73.6%		
Triglyceride	<=150	250	100.0%	63	25.2%	298.72	<0.01
	>150	0	0.0%	187	74.8%		
HDL Cholesterol	<40	26	10.4%	156	62.4%	146.00	<0.01
	>=40	224	89.6%	94	37.6%		
LDL Cholesterol	<100	250	100.0%	112	44.8%	190.60	<0.01
	>=100	0	0.0%	138	55.2%		

Table 2: Serum GGT levels in cases and controls (above normal values)

		Control (N=250)		Case (N=250)		□2 value	'p' value
	(M/F)	n	%	n	%		
GGT(IU/L)	<50/32	228	91.2%	40	16%	370.09	<0.01
	≥50/32	22	8.8%	210	84%		

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Table 3: Sensitivity and specificity of GGT in diagnosis of metabolic syndrome

GGT result	Patients withMetabolicsyndrome (IDFcriteria)	Patients withoutmetabolic syndrome	Total
Positive(≥50/32 IU/L)	210	22	232
Negative(<50/32 IU/L)	40	228	268
Total	250	250	500

Sensitivity= 84%

Specificity=91.2%

Positive predictive value=90.5%

Negative predictive value=85.1%

False negatives=16%

False positives=8.8%

Discussion

A need for the early diagnosis of metabolic syndrome is essential to prevent and decrease morbidity and mortality due to cardiovascular disease. The role of GGT as a diagnostic marker of metabolic syndrome has been critically evaluated in this study. In our study, 500 subjects were recruited comprising 250 cases of metabolic syndrome and 250 age and sex matched controls. Patients in the study group were found to be clustered in the sixth decade of life with 55% cases belonging to this category. There were 60% males and 40% females in the study group. In a similar study done by B Kasapgoluet al[5], gender distribution showed 62% females and 38% males in the study group. This difference may suggest a higher incidence of metabolic syndrome in males in the Indian sub continent.

In our study 195(78%) patients were from the urban population while 55(22%) belonged to the rural setting. This finding may be due to selection of patients from a tertiary care center, but is consistent with other similar studies referring it to as the disease of urban society.BMI observation indicates that obesity and increased central adiposity are pivotal to the pathogenesis of metabolic syndrome. The SBP observations suggest that elevated systolic blood pressure is an important contributing factor for metabolic syndrome. An interesting observation was that 214 patients comprising 86% of the study group had DBP>85mmHg. However, elevated diastolic blood pressures as a contributing factor to this syndrome may be a subject for further studies. In The reference study done by B kasapgoluet al[5]. Similar results were found. In another study done by A O Rantalaet al[8]. higher values were observed with SBP and DBP which was significantly different from our study.Alcohol consumption and smoking are important risk factors for metabolic syndrome and hence cardiovascular disease.

A total 190 out of 250 cases (76%) satisfied the IDF criteria of FPG>100 mg/dl inferring impaired fasting glucose ortype 2 diabetes.The distribution of cases indicating impaired fasting glucose (FPG 100-125mg/dl) and diabetes (FPG≥126mg/dl) was 24% and 52% respectively. In PPBS, 47% cases suggested IGT (PPBS 140-199mg/dl) and 36% inferred type 2 diabetes (PPBS>200mg/dl). In HbA1C, with 26% in the IGT group (HbA1C 5.7-

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6.4) and 74% in the diabetes group (HbA1C>6.5). These observations suggest a high prevalence of type 2 diabetes in patients with metabolic syndrome.

A total of 187 out of 250 cases had TG>150 including 176 males and 74 females. A total of 156 out of 250 cases had HDL <40mg/dl for males and <50mg/dl for females. The values in our study with respect to lipid profile were lower than the reference study. This difference may suggest variations in diet and familial metabolic parameters in particular geographic distributions. Hypertriglyceridemia was found in maximum number of cases in the study group and also the predominant dyslipedemic abnormality. A similar finding was noted in the reference study[5] as well.

In the evaluation of liver function tests, GGT which is the biomarker being evaluated in this study had the following results. The mean GGT in the study group was 52.49±6.04 and that in the control group was 34.58±8.20. A total of 210 out of 250 cases had values of GGT (≥50 (males)/≥32 (females) IU/L) including 111 males and 99 females, comprising 84% of the study group (P<0.01).In a similar study done by B.Kasapgolu et al. the mean GGT in the study group was 40.9±10.2 and it was 21.0±7.1 in the controls.

GGT values when compared with the respective parameters of metabolic syndrome showed the following results. Out of 144 patients with SBP>130mmHg 109 had GGT levels above the reference range comprising 56% of the study population. Among 190 patients with FPG>100, 152(61%) had higher GGT levels. Among 193 cases with HDL<40 for males and <50 for females, 145(58%) had GGT values above the reference range and in 187 patients with hypertriglyceridemia, 150 had higher GGT levels comprising 60% of the study population. The above observations suggest that GGT had the highest correlation with hypertriglyceridemia.

With respect to the burden of cardiovascular disease, 50 out of 250 patients were suffering from CVD comprising 20% of the study population, including 29 males and 21 females. In all these patients higher levels of GGT values were noted. These values were higher when compared to study subjects without cardiovascular disease. This may suggest a direct correlation of GGT levels with cardiovascular disease with higher values conferring increased CVD risk. In the reference study[5], in MS group, a high GGT was positively associatedwith CVD prevalence (odds ratio: 2.011, 95% CI 1.10-4.57) compared to low GGT group, independent of age, sex and smoking habits. Ruttmannet al[9] showed that GGT activity was independently associated with cardiovascular mortality. Devers et al[10] also suggested that higher serum GGT levels is associated with development of CVD risk factors, including diabetes, hypertension, and the metabolic syndrome.

Validity measures were computed taking the reference values of GGT as ≥50 for males and≥32 for females, in general the sensitivity and specificity of GGT to diagnose patients with metabolic syndrome was found to be 78% and 100%. In males and females the sensitivity and specificity was 68% and 100% and 94% and 100% respectively.

Rantalaet al[8] 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. In another study of Sakugawaet al[11], the serum GGT level was found to be correlated with components of MS.

Several important associations were also observed in this study. 74 out 250 cases comprising 30% of the study group had features of NAFLD on

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ultrasound imaging whereas 61 had the same in the control group. This indicates a higher prevalence of NAFLD in MS patients, contributing to itspathogenesis. In this study it was found that GGT levels were higher in patients with metabolic syndrome when compared to controls. GGT had the highest correlation with hypertriglyceridemia. GGT levels were higher in all patients suffering from cardiovascular disease compared to subjects without CVD. The sensitivity and specificity of GGT to diagnose MS was found to be 84% and 91% respectively.

Conclusion

This study has critically evaluated the utility of GGT as a diagnostic marker of metabolic syndrome, with good results. An elevated level of GGT was found to be associated with metabolic syndrome and is a strong predictor of cardiovascular risk. GGT correlated well with all the parameters of metabolic syndrome especially with hypertriglyceridemia with which it was the highest. The sensitivity and specificity was found to be 84% and 91% respectively. GGT was found to be significantly higher in patients with cardiovascular disease. 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 the context of metabolic syndrome and CVD risk. Considering the CVD risk primary prevention may be emphasized in patients of metabolic syndrome with high GGT values. Hence GGT probably has a position in algorithms for the evaluation of metabolic syndrome and CVD risk assessment.

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