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RESEARCH ARTICLE

ASSOCIATION BETWEEN GAMMA GLUTAMYL TRANSFERASE AND METABOLIC SYNDROME IN YOUNG ADULTS IN EASTERN INDIA: AN OBSERVATIONAL STUDY

Dan Subhasish[1], Aditya Papia[2], *Banerjee Prithwijit[3], Rahaman Musfikur[4],Roy Himansu[5], Adak Shiuli Roy[6], Jana Tamoghna[7].

1. MD. Demonstrator, Department of Biochemistry, Medical College Kolkata.
2. M Sc, Assistant Teacher, Tejganj High School, Burdwan.
3. MD. Demonstrator, Department of Pharmacology, Medical College Kolkata.
4. MD. Assistant Professor, Department of Pharmacology, Medical College Kolkata
5. MD. Associate Professor, Department of General Surgery, Medical College, Kolkata.
6. MD. Associate Professor, Department of Biochemistry, North Bengal Medical College, Darjeeling.
7. MBBS, DLO, Post graduate trainee, Department of ENT, Medical College Kolkata.

**Corresponding Author's e-mail: drprithwijit@gmail.com, Contact no: +91-9830500513*

ABSTRACT

Introduction: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma glutamyl transferase (GGT) are the principal hepatic enzymes in clinical laboratory setup. ALT and AST are elevated in various types of hepatitis, cirrhosis and hepatic neoplasia. GGT is usually elevated in alcoholism. Recently, in some studies, the elevation of GGT has been observed in metabolic syndrome. **Objective:** To study the relationship of gamma glutamyl transferase (GGT) with Metabolic Syndrome (MS) in a population. **Materials and Methods:** 91 MS patients and 94 age and sex matched control individuals were recruited into the study, after obtaining their voluntary informed consent. Serum GGT levels along with other biochemical parameters of all the participants were compared statistically **Results:** Serum GGT level was significantly higher in MS group than in non MS group (p = 0.007).**Conclusion:** MS contributed towards higher GGT level in our study population.

Key words: Metabolic Syndrome (MS), Gamma glutamyltransferase (GGT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST).

INTRODUCTION:

HTN, obesity, dyslipidemia are often various symptoms of a metabolic disorder called Metabolic Syndrome (MS).Various bodies have defined metabolic syndrome based on biochemical parameters and clinical examination. According to *National Cholesterol Education Programme – Adult Treatment Plan III* (NCEP ATP III)[1], presence of any three of the followings make the diagnosis of metabolic syndrome.

Abdominal obesity (Waist circumference)

Men >102 cm (>40 inch)

Women >88 cm (>35 inch)

Triglycerides >150 mg/dL

HDL cholesterol

Men < 40 mg/dL

Women < 50 mg/dL

Blood pressure >130/>85 mmHg

Fasting glucose >110 mg/dL

International Diabetes Federation (IDF) has defined metabolic syndrome by presence of:

Central obesity (defined as waist circumference ≥ 90cm for South Asian men and ≥ 80cm for South Asian women, with ethnicity specific values for other groups)

Plus any two of the following four factors:

• **Raised TG level:** ≥ 150 mg/dL (1.7 mmol/L), or **specific treatment for this lipid abnormality**

•**Reduced HDL cholesterol**: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, **or specific treatment for this lipid abnormality**

• **Raised blood pressure:** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, **or treatment of previously diagnosed hypertension**

• **Raised fasting plasma glucose** (FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes**

As per the IDF Consensus Worldwide Definition of the Metabolic Syndrome, both IR and central obesity are considered the principal factors responsible for clustering of the pentad of CVD risk factors in MS. As per NCEP-ATP III, overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI).

An estimated 47 million U.S. residents have the metabolic syndrome[2]. Epidemiological studies have recorded a high prevalence of metabolic syndrome[3, 4, 5] and cardiovascular mortality[6, 7, 8] among Indians, including those settled outside of India.

Gamma Glutamyl Transferase (GGT) is an enzyme which is used as a marker of alcohol intake and

subsequent hepatic injury. Cellular GGT is widely distributed in human body and is usually localized to the plasma membrane with its active site directed into the extracellular space[9]. The highest activity of GGT is found in kidney, on the luminal surface of proximal tubular cells. Interestingly, although serum GGT is known as one of the liver enzymes, cellular GGT activity in homogenates of liver is approximately one-fifth that in kidney. Principal role of GGT is to breakdown extracellular reduced GSH, allowing the precursor amino acids to be assimilated into cell and reutilized for intracellular GSH synthesis.

Essential hypertension is often associated with insulin resistance (IR). 25-50 % of non-obese, non-diabetic patients with EHTN have IR[1].

In some studies, a significant association was found between serum GGT level and prehypertension[10] (SBP 130-139 and/or DBP 80-89) and hypertension[11]. Furthermore, GGT level has been found to be good predictor of susceptibility to type II diabetes mellitus[12,13] and hypertension[8]. Considering these atypical features of GGT and keeping in mind that the above-mentioned studies have been carried out in people of different ethnicity, there is a perceived need to verify if the association between GGT and MS holds for eastern Indian population too.

MATERIALS AND METHODS

The study samples were collected from the OPD of Clinical Biochemistry Laboratory at the Department of Biochemistry, Medical College, Kolkata. The study subjects included both male and female MS patients and age and sex matched non MS individuals in the age group of 18-35 years.

The study period spanned from December 2011 to March 2012.

Total 185 patients were enrolled into the study. Of them, 91 had MS and 94 were controlled individuals. The applied selection criteria were as follows:

Inclusion Criteria

Patients of either sex aged 18 to 35 years and diagnosed with metabolic syndrome on the basis of NCEP ATP III criteria with age and sex matched controls, who attended the OPDs during the study period and gave their voluntary written informed consent for the study.

Exclusion Criteria

- Pregnant and lactating mothers.
- If the patient is suffering from any of the following conditions:

1. Renal Disease
2. Liver Disease
3. Cardiac Disease
4. Active Infection
5. Any malignancy
6. Known alcoholic patients.

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^{o}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.
3. Serum Triglyceride was measured by XL600 autoanalyzer using Glycerol Kinase principle.
4. Serum HDL was measured by ERBA Chem 5 V2 semi-autoanalyzer using PEG Precipitation principle.
5. Serum GGT level was measured by XL600 autoanalyzer using Gamma Glutamyl p-Nitroanilidine (GPNA) principle.
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 data were collected. 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 Analysis

The statistical software R version 2.11.1 was used to analyze the data. All values were expressed as mean $\pm$ standard deviation unless otherwise indicated, and differences in mean values between two groups were analysed using Student's t-test (Table 1). Descriptive information regarding categorical variable were presented as frequency. Fischer's exact probability test was used for comparison of categorical data. All tests were two tailed and considered statistically significant if p-value < level of significance, 0.05.

RESULTS

The present study confirms the finding of earlier studies that serum GGT level in MS patients is higher than their non MS counterparts (p=0.007). There were no significant differences in age, serum albumin, serum total protein between the two groups. Serum levels of cholesterol, triglyceride, HDL and fasting plasma glucose levels were significantly different in two groups. Systolic blood pressure was also found to be higher among the MS group, which stood statistically significant.

Table 1: The biochemical parameters of MS and non MS groups

	Control Group	MS Group	p-value
Number of patients	94	91	
Male/Female	56/38	50/41	0.62
Age (years)	27.02 ± 6.78	26.81 ± 7.81	0.177
SBP (mmHg)	126±12	130 ± 16	0.006*
DBP (mmHg)	79 ± 9	81 ± 8	0.262
Waist Circumference (cm)	79 ± 8	89 ± 10	0.033*
Total Protein (g/dL)	7.1 ± 0.5	6.9 ± 0.6	0.082
Albumin (g/dL)	5.1 ± 0.6	4.9 ± 0.5	0.083
Cholesterol (mg/dL)	177 ± 56	211 ± 62	0.331
Triglyceride (mg/dL)	129 ± 39	169 ± 48	0.048*
Fasting Plasma Glucose (mg/dL)	86 ± 12	92 ± 15	0.033*
HDL (mg/dL)	46 ± 8	39 ± 6	0.006*
Gamma glutamyltransferase (U/L)	43.7 ± 51.7	61.8 ± 68.2	0.007*

** p<0.05 is considered to be statistically significant*

DISCUSSION

Our study confirms the empirical validity of the observation made in earlier studies that serum GGT level is higher in metabolic syndrome patients compared to age and sex matched normal individuals.

GGT has hitherto been used as a marker of alcohol consumption[14]. In earlier studies, it had been shown that correlation between GGT and hypertension is independent of alcohol intake[15]. A similar significant association had been found among non-drinkers[16] too. However, another study, taking the contribution of insulin level in determining GGT level, had established a non-significant correlation between GGT level and hypertension but a significant correlation between GGT level and plasma insulin level[17]. Further credence has been lent to the hypothesis that plasma insulin level is the principal determinant of GGT in metabolic syndrome patients and hypertensives[18].

A mechanism has been put forward to account for the pathological role of insulin in elevation of GGT. Elevated insulin level may lead to hepatic steatosis[19,20,21], and subsequently, Non Alcoholic Fatty Liver Disease (NAFLD). Steatosis appears when insulin secretion is sufficient to block free fatty acid oxidation but not sufficient to block free fatty acid mobilization from adipose tissue[22]. Free fatty acids are markedly cytotoxic and may cause alteration in hepatic cell membrane function and leakage of GGT[23].

GGT is also known to act as an antioxidant by virtue of its central role in GSH cycle. Hypertension being a state of high oxidative stress, elevated GGT level can be explained as a compensatory mechanism[24].

Furthermore, recent studies have revealed a pro-oxidant generating[25,26,27,28] role of GGT. GGT generates ROS in presence of free iron or other transition metal. These authors suggested that the GGT mediated generation of the more reactive thiol cysteinyl- glycine could cause the reduction of ferric iron Fe(III) to ferrous Fe(II), thus starting a redox- cycling process liable to result in the production of reactive oxygen species (ROS). Considering that insulin stimulates ferritin synthesis[29,30,31] and hypertension is a hyperinsulinemic state, it is more likely than not that hypertensive individuals have higher ferritin level. In vitro experimental studies have reported that free iron can be released from iron storage proteins such as ferritin by superoxide radicals or nitric oxide[32,33,34]. It is well known that substantial oxidative stress exists in diabetes[35,36] and hypertension[37,38]. Therefore, patients with diabetes or hypertension might have a potential to have free iron released from iron storage protein, and in this case, cellular GGT might act as a pro-oxidant.

CONCLUSION

The results of this population-based cross-sectional study suggest that GGT may serve as a marker for metabolic syndrome. It should be borne in mind in the clinical practice that elevated levels of GGT may not always indicate increased alcohol consumption, but may simply suggest the existence of metabolic syndrome with its subsequent deleterious consequences viz. type II diabetes mellitus, hypertension and carotid atherosclerosis.

Conflict of interest: There was nothing to best of our knowledge.

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