ASSOCIATION OF GAMMA-GLUTAMYL TRANSFERASE WITH METABOLIC SYNDROME

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ABSTRACT

BACKGROUND
Metabolic Syndrome (MeS) is associated with an increased risk of cardiovascular morbidity and mortality. Elevation of liver enzymes particularly alterations in Gamma-Glutamyl transferase (GGT) levels are observed in metabolic syndrome in response to oxidative stress.

MATERIALS AND METHODS
In this case-sectional study, 100 cases of metabolic syndrome and 100 apparently normal healthy subjects in the age group between 25-65 years were included. Anthropometric measurements such as height, weight, waist/hip ratio and BMI were measured for both the study groups and serum levels of blood glucose, total cholesterol, triglycerides, HDL, LDL, ALT, AST and Gamma-Glutamyl transferase (GGT) were measured using enzymatic methods. Patients with hypothyroidism, malignant disease, severe renal insufficiency, cirrhosis, active liver disease and alcohol consumption were excluded.

RESULTS
Among the various biochemical parameters, fasting blood glucose, serum triglycerides, total cholesterol and HDL showed statistically significant elevation among the MeS subjects when compared to healthy controls with p value <0.05. The mean values of GGT and Alanine Aminotransferase (ALT) levels were statistically significantly higher in MeS group. The mean values of liver enzymes in MeS group, GGT, AST and ALT respectively were 74.77±15.36, 27.3±10.25 and 37.6±6.5.

CONCLUSION
Patients with MeS have more significantly elevated levels of GGT showing a significant association of GGT with metabolic syndrome. Moreover, GGT may play a role in early diagnosis of metabolic syndrome and risk for cardiovascular disease.

KEYWORDS
Metabolic Syndrome, GGT, Insulin Resistance, Inflammation, Oxidative Stress.


BACKGROUND
The Metabolic Syndrome (MeS) is a cluster of metabolic abnormalities that promotes the risk for development of atherosclerotic cardiovascular disease. Its main components are obesity, dyslipidemia, hypertension, insulin resistance and abnormal glucose tolerance. The overall prevalence of MeS in Indian population is 31.4% where females (48.2%) are more affected than their male counterparts (16.3%).¹ The age wise MeS prevalence had increased from 2.9% in those aged 18-30 years to 31.0% in those aged 60-69 years in Asians.² There has been a marked increase in the number of people with the metabolic syndrome worldwide over the past few decades. This increase in MeS is concomitant with the global epidemic of obesity and diabetes. Hence, there is imperative need for strategies to prevent the incidence of MeS as it poses a risk for the development of type 2 Diabetes mellitus and cardiovascular disease.

Insulin resistance is generally considered to be the central component that is involved in the common pathogenesis of the metabolic syndrome. Gamma-Glutamyl transferase (GGT), a sensitive marker of oxidative stress and lipid peroxidation plays a key role in the pathogenesis and development of insulin resistance and the metabolic syndrome.³ GGT is an enzyme involved in the extracellular catabolism of glutathione. Serum GGT is a marker for various clinical conditions like alcohol consumption, body fat content, plasma lipids, glucose levels and medications.⁴,⁵ A number of studies have shown that the serum level of GGT directly correlates with increased risk of obesity, hypertension, diabetes, insulin resistance, dyslipidemia and metabolic syndrome even after adjustment for alcohol consumption and established risk factors.⁶-¹⁰ It is hypothesised that elevated liver enzymes particularly GGT levels are associated with metabolic syndrome and found to have a predictive value in diagnosis of metabolic syndrome. Thus, this study aims in finding the association of serum GGT levels with the risk of development of metabolic syndrome in south Indian population.
MATERIALS AND METHODS
This case control study was carried out between May 2014 and January 2015 in Government Villupuram Medical College, Villupuram, Tamil Nadu. The study was conducted in the patients who attended the Department of Internal Medicine Outpatient Clinics. Using National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, 100 subjects of MeS were included as cases for the study. Hundred sex and age matched healthy subjects were selected as controls.

Patients with hypothyroidism, malignant disease, severe renal insufficiency, cirrhosis, active liver disease attributable to viral infection (positive serology for virus hepatitis B and C) and alcohol consumption were excluded. Institutional ethical committee clearance was obtained and informed consent was taken from all the study participants.

The height (in mts.) and weight (in kgs.) of all study subjects were recorded. The Waist Circumference (WC) 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/m²) was calculated by dividing weight (in kilograms) by the square of height (in meters). Blood pressure was also recorded after at least 5 mins. of rest in a chair with feet on the floor and arm supported at heart level using a mercury sphygmomanometer.

Blood samples of 5 mL was drawn after 8-12 hrs. Overnight fasting for the measurement of lipid profile (total cholesterol, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) and Triglycerides (TGL)), liver function tests, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Gamma-Glutamyl transferase (GGT) and fasting plasma glucose levels. Plasma glucose was measured using the glucose oxidase peroxidase method, serum total cholesterol and triglycerides by standard enzymatic procedures and HDL cholesterol by direct assay method. LDL cholesterol was calculated using Friedewald’s formula. Liver enzymes like AST, ALT and GGT were measured using enzymatic kits by IFCC method. All the parameters were measured in Beckman Coulter AU480 clinical chemistry analyser.

Statistical methods
Statistical analysis was done using SPSS software version 16. Results are presented as mean and Standard Deviation (SD). Tests for significance were calculated using Student’s t-test. A p value of <0.05 was considered as statistically significant.

RESULTS
The present study analyses the association of liver enzymes particularly GGT in metabolic syndrome patients with that of apparently healthy age matched controls. The study subjects included 100 metabolic syndrome patients and 100 non-metabolic syndrome patients.

The age group of the study population was between 35 years to 65 years. The mean age in metabolic syndrome patients was 54.7±8.9 years and in controls was 52.6±7.9 years. Table 1 shows gender distribution in the study groups. Patients with metabolic syndrome consisted of 42 males and 58 females. In the control group, there were 47 males and 53 females. It is observed that the prevalence of MeS is more among females (58%) than men (42%). This is also shown graphically as pie charts in Figure 1.

The mean and SD of anthropometric measurements and lipid parameters among MeS and controls are compared in Table 2. It is evident from the table that BMI, waist circumference, fasting blood glucose, serum triglycerides, total cholesterol and HDL showed statistically significant elevation among the MeS subjects when compared to healthy controls. The statistical significant difference in the mean values of the above parameters between study groups was <0.05. This is also shown graphically in terms of mean as bar diagrams in Figure 2.

Table 3 shows the comparison of mean and SD of liver enzymes among the MeS and controls. Of them, GGT and ALT were significantly high among the cases compared to controls. The statistical significant difference in the mean values of the above parameters between study groups was <0.05. This is also shown graphically in terms of mean as bar diagrams in Figure 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases Mean±SD</th>
<th>Controls Mean±SD</th>
<th>Significance P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Waist Circumference (WC) (cms)</td>
<td>105.7±6.1</td>
<td>88.72±5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>2. BMI</td>
<td>30.98±3.5</td>
<td>26.49±4.8</td>
<td>0.001</td>
</tr>
<tr>
<td>3. Fasting plasma glucose (mg/dL)</td>
<td>152.77±5.7</td>
<td>96.38±10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>4. Serum triglycerides (mg/dL)</td>
<td>163.08±33.8</td>
<td>151.44±20.37</td>
<td>0.04</td>
</tr>
<tr>
<td>5. Total cholesterol (mg/dL)</td>
<td>219.76±29.2</td>
<td>172.5±22.5</td>
<td>0.001</td>
</tr>
<tr>
<td>6. HDL cholesterol (mg/dL)</td>
<td>33.06±7.6</td>
<td>48.36±9.37</td>
<td>0.001</td>
</tr>
<tr>
<td>7. LDL cholesterol (mg/dL)</td>
<td>87.46±31.46</td>
<td>77.94±24.5</td>
<td>0.130</td>
</tr>
</tbody>
</table>

Figure 1. Gender distribution between the study groups

Table 1. Gender distribution among MeS and controls

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases (n=100)</th>
<th>Controls (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>42%</td>
<td>47%</td>
</tr>
<tr>
<td>Females</td>
<td>58%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Table 2. Comparison of anthropometric measurements and biochemical parameters between MeS cases and control subjects
DISCUSSION

In our study, the prevalence of metabolic syndrome was more among women and the percentage was 58% and 42% between women and men, respectively. The gender difference could probably be due to different cut offs set as criteria for WC and HDL levels.11 Also, there is increase in obesity with 2 million more women than men being affected in the United States as well as in the under developing countries including South East Asian countries.12

The mean of the waist circumference for among cases is 105.7±8.1, which is statistically significant compared to the controls (88.72±5.4). Abdominal obesity is the most frequently observed component of MeS. The measurement of waist circumference provides information about the distribution of body fat and is a measure of risk for conditions such as Coronary Heart Disease (CHD). Studies report that WC is a better predictor of metabolic abnormalities than percent fat measured by bioimpedance method in elderly whites.13 It is seen that increased WC is responsible for the development of insulin resistance, which decreases the level of HDL cholesterol fraction increases the level of triglycerides and leads to the development of arterial hypertension.14

In our study, BMI among the cases was 30.98±3.5 and 26.49±4.8 among the controls, which is statistically significant. It has been recently reported that both overweight and obese middle-aged individuals were at an increased risk for the cardiovascular events and total mortality.15 Current studies suggest that combined evaluation of both these anthropometric indices are optimal for identifying those at risk for CHD.16

The mean of fasting blood glucose of cases is 152.77±5.7 and controls are 96.38±10.8, which is statistically significant. This is because of insulin resistance, which is characteristic feature associated with metabolic syndrome, which further proceeds to type II diabetes.

On comparing the lipid parameters, the mean of total cholesterol, HDL, TGL were (219.76±29.82, 33.06±7.6, 163.08±33.8, respectively) for the cases, which is significantly elevated when compared with the controls (172.5±22.57, 48.36±9.37, 151.44±20.37). The pathophysiology behind the development of dyslipidaemia in MeS is insulin resistance, which causes increased lipolysis.17 The increased flux of free fatty acids from the peripheral tissues to the liver in the insulin resistant state stimulates increased hepatic TG synthesis, which in turn enhances the assembly and secretion of VLDL as well as the ApoB production in the liver.18

Low HDL cholesterol observed in MeS is considered as secondary to raised TGL. In the presence of increased plasma TGL levels, the cholesteryl ester transfer protein mediates exchange of TGL and cholesteryl ester between LDL and VLDL as well as between VLDL and HDL particles forming TG rich HDL that are more prone to be catabolized. Furthermore, the changed lipid flux in the liver attributable to insulin resistance may reduce the hepatic production of ApoA1 thereby reducing HDL levels. Thus, dyslipidaemia in MeS patients is caused due to a combination of increased production of very low-density lipoprotein (VLDL), ApoB-100, reduced catabolism of ApoB containing particles and increased catabolism of HDL-ApoA-1 particles.19

Several epidemiologic studies20,21,22 have reported associations between elevated serum levels of liver enzymes and increased cardiovascular risk. This is in concordance with this study where the ALT were significantly elevated among MeS (37.6±6.5) compared to cases.

The mean for the GGT levels for the cases was 74.77±15.36 as compared to controls 40.91±8.3, which is statistically significant. Similarly, Rantala et al23 and Sakugawa et al24 revealed a significant association between GGT and the components of the metabolic syndrome even after adjustment for age, body mass index and alcohol consumption. The probable explanation for the elevation of hepatic enzymes could be an expression of excess fat deposition in the liver as illustrated by Nonalcoholic Fatty Liver Disease (NAFLD), which is considered as a feature of the metabolic syndrome. There is clear evidence that cellular GGT level acts either as an antioxidant or a pro-oxidant and closely related to oxidative stress.25 Evidences suggest that GGT has a key role in oxidative stress, lipid peroxidation and mitochondrial dysfunction. GGT is the prime enzyme that
causes the extracellular hydrolysis of Glutathione (GSH). The cleavage of GSH catalysed by GGT produces reactive products that cause the reduction of ferric iron to ferrous iron. Elevated levels of GGT thus result in increased production of Reactive Oxygen Species (ROS) aggravating oxidative stress. The generation of highly reactive free radicals causes peroxidation of lipids. Recent evidences also suggest that GGT activity was independently related with cardiovascular mortality and some epidemiological studies also showed that increased serum GGT levels were associated with development of risk factors for CVD including diabetes mellitus, hypertension and the metabolic syndrome.

CONCLUSION
From this study, we can conclude that serum GGT levels can be used as predictive marker for the development of metabolic syndrome and thereby early recognition of cardiovascular disease. The assay of GGT is simple to perform, standardised, cost effective and its easy accessibility in routine clinical practice indicates the prospective role of GGT to be considered in algorithms of metabolic syndrome.

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25. Hsueh WA, Quinones MJ. Role of endothelial dysfunction in insulin resistance. Am J Cardiol 2003;92:10J-17J.


