A Study to Determine the Association of Gammaglutamyl Transferase Levels in Metabolic Syndrome

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ABSTRACT

Metabolic syndrome has already emerged as the major health problem in both developed and developing countries that causes huge economic burden to the world. Insulin resistance and inflammation are the two main underlying factors which leads to Metabolic syndrome. Oxidative stress plays an important role in the etiology and progression of the metabolic syndrome. Increased production of reactive oxygen species (ROS) species may leads to the production of pro inflammatory adipokines TNF-α and IL-6 which leads to insulin resistance. Glutathione(GSH), the most important non protein antioxidant in the cell requires Gammadglutamyl transferase enzyme for its metabolism. Gammadglutamyl transferase also known to have a pro-oxidant role may indicate the incidence of cellular oxidative stress. The aim of the study is to determine the levels of Gamma glutamyl transferase in metabolic syndrome patients and in normal healthy controls. 82 individuals were included in the study, 41 are selected as controls and 41 are selected as metabolic syndrome patients. BMI, Lipid profile, GGT and uric acid were estimated and Statistical analysis was done using SPSS (version 21). GGT and body mass index values are higher in cases than controls. High Density Lipoprotein and Total Cholesterol values are lower in cases than controls. The study may be concluded that Gamma glutamyl transferase a marker of oxidative stress is important in the diagnostic and prognostic aspect of metabolic syndrome.

Keywords: Metabolic syndrome, GGT, oxidative stress.

INTRODUCTION

Metabolic syndrome also known as metabolic syndrome X, cardiometabolic syndrome, Reaven’s syndrome, insulin resistance syndrome is defined as a constellation of metabolic abnormalities, including hypertension, dyslipidemia and hyperglycemia associated with insulin resistance1. The probable causes of metabolic syndrome and its complications are inflammation and oxidative stress. Oxidative stress is shown to be involved in the lifestyle related diseases such as Diabetes mellitus, Hypertension, Coronary artery disease and metabolic syndrome. Oxidative stress is defined as a “state in which oxidation exceeds the antioxidant systems in the body secondary to a loss of the balance between them”. It is involved in the physiological adaptation, regulation of intracellular signal transduction. But it can also cause increased production of reactive oxygen species, lipid peroxidation and DNA damage.

Atoms consists of central nucleus with paired number of electrons in nature. If an atom has unpaired electron in the outermost shell, it is called free radical. These free radicals are highly reactive towards the biological membrane and damages the DNA, proteins and lipids in it. This happens only when the formation of free radicals and its removal by the antioxidants is impaired. These leads to induction of diseases2.

When a cell is exposed to oxidative stress, it will decrease the glutathione pool transiently however it is well documented that cells can respond to low levels of oxidants and GSH depleting agents by increasing GSH levels. GSH synthesis is up regulated and increased expression of GGT during oxidative stress facilitates GSH turnover, denovo GSH synthesis and detoxification of GSH conjugates increases cell resistance to subsequent stress. Therefore regulation of GGT gene expression is an important adaptive response and helps in the protection of cells and tissues from oxidative injury3.

According to the modified NCEP-ATP III, the presence of any three of the following five factors is required for a diagnosis of Metabolic Syndrome: abdominal obesity, hypertriglyceridemia (triglycerides ≥1.7 mmol/L or >150 mg/dl ); low HDL cholesterol (HDL cholesterol ≤1.03 mmol/L or <40 mg/dl for men and ≤1.29 mmol/L or <50mg/dl for women); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or current use of antihypertensive drugs); impaired fasting glucose (fasting plasma glucose ≥6.1mmol/L or >126 mg/dl)4.

Both the NCEP-ATP III and IDF (International diabetes federation) guidelines for diagnosis of Metabolic Syndrome places emphasis on abdominal obesity as a required factor plus any two of the other four criteria. Both IDF and NCEP-ATPIII criteria uses ethnic-specific for waist circumference cut-off points as a requirement for diagnosis of metabolic syndrome5.

The metabolic syndrome prevalence rate is estimated to be around 20-25% of the world’s adult population6. In South India the prevalence of Metabolic syndrome is around 18.3-41%, according to NCEP ATP III guidelines7.
According to WHO criteria a higher prevalence of 46.4% was reported from South India.

Previous studies have shown that Gammaglutamyl transferase enzyme, an oxidative stress marker have an association with metabolic syndrome.

The aim of the present study is to find out the association between Gammaglutamyl transferase and metabolic syndrome and the clinical value of Gammaglutamyl transferase levels in the risk analysis of metabolic syndrome.

MATERIALS AND METHODS

Fasting blood samples were collected from the subjects. 5ml of Blood sample and personal case history were obtained from 82 subjects. Out of 82 subjects, 41 subjects with Metabolic syndrome were taken as patients and 41 subjects without Metabolic syndrome were taken as controls.

Subjects who have Acute liver failure, chronic liver disease, Acute Hepatitis (of any origin) Alcoholic hepatitis, acute inflammatory conditions and Binge drinking were excluded from the study. The diagnosis of metabolic syndrome was done using the diagnostic criteria given by WHO. The blood samples are processed on the same day by Autoanalyser. (SIEMENS-DADEBEHRING). Total cholesterol was estimated by cholesterol oxidase-peroxidase method. Triglycerides was estimated by GPO-POD method. High density lipoprotein was estimated by end point method. Gammaglutamyl transferase was estimated by enzymatic method uses the substrate L-Gamma-glutamyl -3-carboxy -4-nitranilide as a substrate.

Statistical Analysis

Data analysis of this study was done by SPSS statistical software version 21. Mean values of all these variables are obtained and on analysis with independent t-test gives highly significant p-values for Total Cholesterol (0.002), High Density Lipoprotein (0.000), Body mass index (0.000) and GGT (0.005).

RESULTS

Figure 1: Showing the Mean Values of GGT among Cases and Controls

Figure 2: Comparison of TGL, HDL and BMI between cases and controls

<table>
<thead>
<tr>
<th>Z Variables</th>
<th>Groups</th>
<th>Independent Samples t-test</th>
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<tbody>
<tr>
<td></td>
<td>Mean (n=41)</td>
<td>SD Mean (n=41)</td>
</tr>
<tr>
<td>Age</td>
<td>53.12</td>
<td>9.02</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>42.89</td>
<td>18.38</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>160.20</td>
<td>42.62</td>
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<tr>
<td>TGL (mg/dl)</td>
<td>176.22</td>
<td>97.53</td>
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<tr>
<td>HDL (mg/dl)</td>
<td>30.56</td>
<td>6.27</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.34</td>
<td>1.35</td>
</tr>
<tr>
<td>HT (cm)</td>
<td>158.37</td>
<td>10.67</td>
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<tr>
<td>WT (kg)</td>
<td>66.41</td>
<td>12.87</td>
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<tr>
<td>BMI</td>
<td>26.51</td>
<td>4.47</td>
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</table>
DISCUSSION
Mitochondrial oxidative stress has been suggested to contribute to the metabolic syndrome.
In metabolic syndrome, due to overnutrition and physical inactivity, there will be less ATP demands, high proton motive force and low respiration rate leads to superoxide production.
The elevated mitochondrial ROS production is associated with metabolic syndrome. The accumulation of non specific oxidative damages to the mitochondria plays a major role in the pathogenesis of metabolic syndrome.
Electron transport chain in mitochondria is the major source for reactive oxygen species inside the cell. Superoxide is the main ROS produced inside the mitochondria, which rapidly undergoing dismutation to hydrogen peroxide.
Hydrogen peroxide (H$_2$O$_2$) is the initiator of oxidative damage, it will attack the lipsids, proteins, DNA etc.
The superoxide production is enhanced by electron carrier pools from the mitochondrial electron transport chain, high proton motive force, low respiratory rate.
The last one leads to the increased oxygen concentration inside the mitochondria$^9$.
Data derived from two groups were analyzed with independent t-test to find out the association between the two groups (Table1).
GGT values were higher in metabolic syndrome cases compared to controls which has statistically highly significant p value.
HDL and Total cholesterol values are lower in metabolic syndrome cases compared to controls which has statistically highly significant p value.
Triglycerides and uric acid levels are slightly higher in metabolic syndrome cases compared to controls but it has no statistical significance. Body mass indices (BMI) are higher in metabolic syndrome cases compared to controls which has statistically highly significant p value. The GGT values of cases and controls are shown in Figure1. The mean values of Total cholesterol, HDL and BMI are clearly shown in the Figure 2.
The analysis of this study gives the significant ‘P’ value for the main parameter Gamma glutamyl transferase. This is in accordance with many research studies$^{10,11}$. GGT is also independently associated with metabolic syndrome and its individual components mainly includes insulin resistance$^{12}$.
Experimental studies revealed that both Diabetes and hypertension are significantly associated with Gammaglutamyl transferase enzyme in metabolic syndrome patients$^{13}$.

Hence from these findings it is clear that GGT is having a diagnostic role in the development of metabolic syndrome through oxidative stress which leads to inflammation and insulin resistance.

CONCLUSION
In metabolic syndrome, production of reactive oxygen species by mitochondrial oxidative stress plays a vital role in the pathogenesis of the disease.
Under oxidative stress GGT levels are significantly elevated which increases the cell resistance to oxidative stress. GGT, a marker of oxidative stress may be helpful in predicting the progression and complication of metabolic syndrome.

REFERENCES