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ORIGINAL RESEARCH OPEN ACCESS

Serum gamma glutamyl transferase levels in metabolic syndrome in obese south Indian population

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Abstract

Background: Increased waist circumference in metabolic syndrome (MS), which reflects central obesity is associated with an increased risk of type 2 diabetes, dyslipidemia, hypertension and coronary vascular disease. Generation of free radicals in central obesity depletes intracellular glutathione, thereby induces release of gamma glutamyl transferase (GGT) into circulation. Elevated GGT levels could be a marker of high oxidative stress which is known to be associated with central obesity and metabolic syndrome. Hence the aim of this study was to determine the association of GGT levels with components of metabolic syndrome in obese South Indian population.

Materials and methods: In this case control study conducted at Master Health Check (MHC) Department, Sri Ramachandra Medical College, study population included 60 obese subjects with metabolic syndrome (cases) and 60 non obese subjects (controls) of South Indian population who were non-smokers and non-alcoholics, between the ages of 30-50 years. Components of metabolic syndrome such as waist circumference, blood pressure, fasting plasma glucose, lipid profiles and GGT measured in both the groups. Data between cases and controls compared with unpaired student t-test. Pearson's correlation was performed to find the association of GGT levels with other variables in Metabolic syndrome.

Results: Serum GGT levels were significantly higher in metabolic syndrome patients (cases) than controls with $p < 0.0001$. High levels of serum GGT were also associated with increase in BP and atherogenic lipid levels and ratios.

Conclusion: Elevated serum GGT levels were significantly associated with components of metabolic syndrome in obese South Indian population.

Keywords: metabolic syndrome; syndrome X; obesity; gamma glutamyl transferase; oxidative stress

Introduction

Metabolic syndrome (MS), known as syndrome X is associated with increased risk for cardiovascular disease (CVD) has gained much importance world-wide due to the increase in its prevalence rate [1, 2]. Currently the definition of MS, according to National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (NCEP-ATP III) criteria, includes components such as increased waist circumference, raised triglycerides, low High Density Lipoprotein (HDL), raised fasting glucose and raised blood pressure (BP) [3, 4].

Obesity has reached epidemic proportions in India with morbid obesity affecting 5% of Indian population. Obesity when left unchecked does lead to series of lifestyle diseases [5], like type 2 diabetes, dyslipidemia, hypertension and coronary vascular disease and stroke [6, 7].

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Increased waist circumference (WC), which denotes WC more than 40 inches in males and more than 35 inches in females, reflecting central obesity is an independent and better predictor of risk compared to body mass index and waist hip ratio. High waist circumference, which is one of the important criteria to diagnose metabolic syndrome is not only an indicator of obesity but also associated with an increased risk of type 2 diabetes mellitus, dyslipidemia, hypertension and coronary artery disease. Ethnic and age related differences in body fat distribution modify the predictive validity of WC as surrogate marker of abdominal fat [8, 9].

Gamma glutamyl transferase (GGT, E.C 2.3.2.2) is a cell surface protein enzyme contributing to the extracellular catabolism of glutathione (GSH). Though it is produced in most tissues, most of them in serum is derived from liver. GGT has an important role in the maintenance of intracellular antioxidant defense through mediation of extracellular GSH transport into most types of cells [10]. Oxidative stress plays a major role in various pathological conditions like inflammation, aging, atherosclerosis, reperfusion injury [11]. Most studies focus on the role of oxidative stress in the development of cardiovascular complications in diabetic patients [12].

Generation of free radicals in central obesity depletes intracellular glutathione, thereby induces production and release of GGT into circulation [13, 14]. Elevated GGT levels could be a marker of high oxidative stress which is known to be associated with central obesity and metabolic syndrome [15]. GGT shown to be an independent risk marker for the development of coronary artery disease, diabetes mellitus, hypertension, stroke [7]. Raised liver enzymes especially GGT levels - relatively sensitive & easily obtained marker of Non-alcoholic fatty liver disease (NAFLD) which reflects chronic ectopic fat deposition in liver may be useful in diagnosis of Metabolic syndrome [16].

Thus the aim of this study was to explore the association of GGT levels with the components of metabolic syndrome such as fasting plasma glucose, waist circumference, blood pressure, lipid profile and lipid ratios in the obese south Indian population and to compare the above mentioned parameters with non-obese age and gender matched healthy control group.

Materials and methods

Patients' selection

The present duty was performed after obtaining institutional ethical clearance, 60 non obese (controls) and 60 obese (cases) individuals, from both sexes of age 30- 50 years attending Master Health Check (MHC) Department at Sri Ramachandra Medical College and Research Institute Hospital from February 2019 to February 2020 were selected for this prospective case control study. The study group comprising of 120 subjects from South Indian population were divided into two groups:

(i) Controls were 60 non-obese healthy individuals,

(ii) Cases were 60 obese individuals diagnosed with metabolic syndrome as per NCEP-ATP III guidelines. Both sexes between 30- 50 years who were non -alcoholics and non - smokers were included in the study. Alcoholics, smokers, patients with alcoholic liver disease, hepatitis, cholelithiasis, on anti-epileptics and ages < 30 years and >50 years, were excluded from the study. Data regarding full medical history that included age, sex, occupation, duration of other co-morbid illness, drug history were collected from the study subjects. A written informed consent was obtained from each participant before commencement of the study.

Laboratory measurements

Blood samples were drawn after 8-12 hours of overnight fasting from both controls and cases attending Master Health Check Department. Lipid profile were analyzed with Siemens Advia 1800 in which serum total cholesterol estimated using cholesterol esterase/ oxidase method**,** triglycerides estimated with lipase - glycerol kinase method and HDL cholesterol estimated using polyanion precipitation method while low density lipoprotein (LDL) cholesterol was calculated using Friedwald's equation**,** very low-density lipoprotein (VLDL) calculated using formula TGL/5 and total cholesterol: HDL ratio calculated using total cholesterol/ HDL**.** Fasting plasma glucose was measured using Seimens Advia 1800 by glucose oxidase-peroxidase method**.** GGT levels were measured using Siemens Advia 1800 by Carboxy substrate method.

Standing body height was measured using a commercial stadiometer**.** Weight was measured using a digital weighing scale with an accuracy of ±100 grams. Body mass index (BMI) ($kg/m^{2)}$ was calculated by dividing weight (in kgs) by the square of height (in meters)**.** Waist circumference was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest using standard measuring tape**.** Systolic and diastolic blood pressures were recorded after 5 mins of rest in supine posture by standard sphygmomanometer. An appropriate sized cuff (cuff bladder encircling almost 80% of the arm) was used to ensure accuracy.

Statistical analysis

Statistical analyses were performed using SPSS software version 16.0**.** Parametric continuous variables were given as mean ± standard deviation. Independent sample t- test was used to compare parametric continuous variables to check the statistical significance between the groups. Two - tailed p- values of less than 0.05 were considered to indicate statistical significance. Pearson's correlation was done to find the association between serum GGT levels and variables of MS in cases.

Results

The study population consisted of 120 subjects, which included age and gender matched 60 healthy non-obese controls and 60 obese cases diagnosed with metabolic syndrome as per NCEP - ATP III criteria for both sexes, belonging to the age group of 30 - 60 years.

The age and gender distribution of the study population was depicted in Table 1. There was significant difference in mean age and gender of participants between the two groups.

Table 1: Age and gender distribution of the study population.

Variables		*Cases (n=60)*	*Controls (n=60)*
Gender	Male	40 (66.67%)	30 (50%)
	Female	20 (33.33%)	30 (50%)
Age group (years)	30-40	13 (21.67%)	33 (55%)
	41-50	21 (35%)	16 (26.67%)
	51-60	26 (43.33%)	11(18.33%)

As shown in Table 2, there was a significant difference in the mean age of participants between the two groups. All the physiological and biochemical parameters were expressed as mean± SD and the results of the study were compared using un-paired student t-test.

Systolic and diastolic blood pressures, WC and BMI were high in cases than controls with statistically significant (p value <0.001).

Total cholesterol, triglycerides and LDL cholesterol levels, total cholesterol/ HDL were significantly high in cases when compared to controls while HDL cholesterol levels were low in cases compared to the controls with statistical significance of $p < 0.001$. Alteration in the fasting lipid profiles in cases indicates pro- atherogenic dyslipidemia in metabolic syndrome subjects.

Fasting plasma glucose and serum GGT levels were significantly high in cases than controls with statistical significance of $p < 0.001$.

Table 2: Comparison of parameters between controls and cases.

Parameters	*Controls (n =60)*	*Cases (n=60)*	*p value*
Age	41.5 ± 9.04	48 ± 8.1	0.001**
Systolic blood pressure (SBP) (mmHg)	110 ± 12.2	138.1 ± 17.05	0.000**
Diastolic blood pressure (DBP)	71 ± 8.38	88.67 ± 8.73	0.001**
Waist circumference (WC)	91.5 ± 7.52	101.9 ± 6.69	0.000**
Body mass index (BMI)	22.4 ± 1.85	28.54 ± 2.74	0.000**
Total cholesterol (TC)	159.9 ± 26.1	202.8 ± 40.73	0.000**
Triglycerides	91.37 ± 28.66	238 ± 139	0.000**
Low density lipoproteins (LDL)	102.7 ± 22.9	129.8 ± 31.64	0.000**
High density lipoproteins (HDL)	43.7 ± 7.28	38 ± 7.09	0.000**
Total cholesterol/HDL (TC/HDL) ratio	3.72 ± 0.62	5.47 ± 1.29	0.001**
Fasting plasma glucose	91.8 ± 4.88	142.8 ± 58.7	0.000**
Gamma glutamyl transferase (GGT)	15.4 ± 3.43	42.72 ± 13.77	0.000**

Note: SBP & DBP in mmHg, WC in centimetres, BMI in kg/m^2, TC, triglycerides, LDL, HDL in mg/dl, fasting plasma glucose in mg/dL, GGT in IU/L; $p < 0.05$ = statistical significance (**p value<0.001)

Tables 3 and 4 showed Pearson's correlation analysis between serum GGT levels and other variables and with lipid levels in cases. Statistically significant positive correlation was seen when we correlated serum GGT levels with all the variables of metabolic syndrome. A significant negative correlation was observed with serum HDL levels.

Table 3: Correlation of serum GGT levels with other variables in cases.

Variables		*WC*	*SBP*	*DBP*	*FPG*
Serum GGT	r	0.107	0.064	0.033	0.066
	p	0.036*	0.048*	0.041*	0.032*

Abbreviations: WC = waist circumference (cms), SBP = systolic blood pressure (mmHg), DBP= diastolic blood pressure (mmHg), FPG= fasting plasma glucose (mg/dl), GGT= gamma glutamyl transferase (IU/L), *p value <0.05.

Table 4: Correlation of serum GGT levels with serum lipids in cases.

Variables		*TC*	*TGL*	*LDL*	*HDL*	*TC:HDL*
Serum GGT	r	0.261	0.222	0.079	- 0.008	0.216
	p	0.044*	0.039*	0.054*	0.045*	0.048*

Abbreviations: TC = total cholesterol (mg/dl),TGL = triglycerides (mg/dl), LDL= low density lipoprotein (mg/dl), HDL= high density lipoprotein (mg/dl), TC:HDL = total cholesterol/ HDL, GGT = gamma glutamyl transferase (IU/L), *p <0.05.

Discussion

In this study, serum GGT levels were measured in metabolic syndrome subjects (cases) and compared with that of healthy control population and both cases and control population were non-smokers and non-alcoholics.

A study by Pukka et al., showed that GGT levels rise with age in both sexes [17]. In this study, the mean age of the cases was significantly higher than that of controls. Alcoholics, smokers and subjects with age > 50 years in both sexes were excluded from the study. The major difference between the two study groups was the higher waist circumference in cases than controls. It is a well-known fact that GGT being a powerful anti-oxidant has a protective effect in maintaining appropriate intracellular glutathione levels. Therefore, it is probably that the generation of free radicals, which occurs in central obesity depletes intracellular glutathione and thereby induce the activity of GGT into the circulation. Oxidation stress with the low-grade inflammation has been implicated in a number of pathological conditions like aging, atherosclerosis and diabetes mellitus [18].

This study also shows low HDL, high LDL, high total cholesterol/ HDL ratio in cases compared to the controls, which clearly proves that dyslipidemia, high systolic and diastolic blood pressure in metabolic syndrome patients (cases) were associated with elevated levels of GGT, a significant marker of subclinical atherosclerosis. It is evident that GGT catalyzes the oxidation of LDL and converts it to oxidized LDL, a stage involved in the pathogenesis of atherosclerosis similar to the study by Paolicchi et al., [19].

Elevated serum GGT could reflect excess deposition of fat in the liver termed as non-alcoholic fatty liver disease. Fatty liver causes hepatic insulin resistance and hyperinsulinemia, thus GGT proving to be a marker of insulin resistance syndrome. A study by Gohel and Chako et al., proved a strong relationship between GGT and fasting, 2 hours post prandial plasma glucose, HbA1c levels [20]. Our study also shows significant relationship between fasting plasma glucose and metabolic syndrome/ insulin resistance syndrome.

Elevated GGT levels prove to be a marker of oxidative stress and subclinical inflammation. Rantala et al., in his study investigated the relationship between GGT and MS and revealed a highly significant relationship between GGT and the components of metabolic syndrome even after adjustment of age, body mass index and alcohol consumption [21].

In a study by Sakugawa et al., serum GGT levels were found to be correlated with the components of MS [22]. In our study also there is a significant correlation between GGT levels and all the components of Metabolic syndrome.

Hence estimation of simple, reliable and sensitive diagnostic biomarker GGT can help to assess the risk of impending complications like hypertension, atherosclerosis, Type 2 diabetes mellitus (DM) and coronary artery disease in metabolic syndrome patients. Elevated serum GGT levels is a risk factor for myocardial infarction and stroke [23, 24], thereby can aid in the initiation of non-pharmacological interventions in these subjects which includes lifestyle and dietary modifications.

In this study we have documented that high serum GGT levels in individuals need not be attributed only to alcoholism but could also be an indicator of oxidative stress, chronic inflammatory state and fatty liver in obese and metabolic syndrome patients. Supplementation of anti- oxidants will definitely reduce the risk of various complications related to atherosclerosis and type 2 DM. GGT estimation can be a useful and cost - effective diagnostic screening tool in rural population to assess the risk of developing various complications related to atherosclerosis.

GGT could serve as an early predictor and reliable biomarker of subclinical atherosclerosis and its complications. In routine clinical practice, we currently deploy sophisticated techniques such as echocardiography, color doppler and other radiological imaging modalities to detect vascular abnormalities resulting from atherosclerosis. However, these highly sophisticated imaging modalities are still unavailable in many of the primary and secondary health care centres, owing to the cost factor. Morbidity related to vascular changes in atherosclerosis still remains undetected, in view of low socio-economic status and large population size. Hence estimation of GGT levels in serum can serve as a simple, reliable and cost effective screening tool

besides being a novel approach to overcome these socio-economic barriers. However further studies on a larger size of population would give us a better perspective.

Implications and future scope

With an increasing incidence of morbid obesity related complications such as DM, atherosclerosis and coronary artery disease, very few published data on South Indian population are available related to this field. Hence this study with increased GGT levels in serum could pave a way in advocating pharmacological and non - pharmacological interventions to prevent further complications related with central obesity. Supplementation of anti-oxidants along with lifestyle and dietary modifications can reduce the incidence of various complications related to atherosclerosis, type 2 DM and coronary artery disease.

Limitations: The present study was conducted on a limited number of patients attending the Master Health check-up department. Further studies on relationship of GGT levels with the components of metabolic syndrome are required on a larger South Indian population. The effects of lifestyle and dietary modifications on serum GGT levels can also be explored.

Conclusion

This study concludes that significant association is seen between elevated serum GGT levels and components of metabolic syndrome, namely high waist circumference, increased systolic and diastolic blood pressure, impaired fasting glucose, atherogenic dyslipidemia which clearly indicated oxidative stress and chronic inflammation. Serum GGT levels can be used as a useful, cost - effective screening test especially in primary and secondary health centres to assess the risk associated with various complications related to metabolic syndrome and refer them for tertiary and comprehensive health care. Larger number and multicentric studies are required to confirm these results.

Conflicts of interest

Authors declare no conflicts of interest.

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