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Research Article

Correlation of Serum Gamma Glutamyl Transferase with Atherogenic Dyslipidemia in Obese Individuals

P. Josephine Latha*, S. Ganesan
Associate Professor of Biochemistry, Thanjavur Medical College, Thanjavur -613004, The Tamilnadu Dr. M. G. R. Medical University, Tamilnadu, India

***Corresponding author**
P. Josephine Latha
Email: lathapasel@gmail.com

Abstract: Obesity is one of the major public health concerns and is a growing epidemic in the present scenario. Recent studies have shown increased association of the medical complications of obesity with gamma glutamyl transferase(GGT) levels. Some studies have also found that obese individuals with high normal serum γ-glutamyltransferase (GGT) activity are associated with the risk of type 2 diabetes. Moreover GGT activity in atherosclerotic plaques has also been proved recently. In the present study we propose to establish the correlation of serum GGT levels with atherogenic dyslipidemia in obese individuals. The study included 100 obese subjects and 100 non-obese healthy controls. BMI, waist circumference and blood pressure (BP) were measured as per the standard guidelines. Lipid profile, Fasting blood sugar and GGT levels were assayed in a fasting venous sample using standard kits in an autoanalyzer. Statistical analysis was done using SPSS software. In this study atherogenic dyslipidemia in obese individuals was evident from their TGL, HDL levels and lipid ratios. The fasting blood sugar, total cholesterol, triglycerides, LDL-C VLDL-C, GGT were significantly increased and HDL-C was decreased in cases compared to controls ($p< 0.001$). Serum GGT was significantly positively correlated with TC (r: 0.72, $p<0.001$), TGL (r: 0.662, $p<0.001$), atherogenic lipid ratios TC/HDL (r: 0.817, $p<0.001$) and TGL/HDL (r: 0.814, $p<0.001$)) and negatively correlated with HDL (r: -0.773, $p<0.001$) in obese individuals ($p<0.001$). Hence GGT can be considered as an early, reliable and cost-effective marker of atherosclerosis and visceral fat. Further large population prospective cohort studies are needed to consider GGT in screening people at risk for developing atherosclerosis.
Keywords: Atherogenic dyslipidemia, Gamma glutamyl transferase (GGT), Lipid profile, Obesity, Type 2 diabetes.

INTRODUCTION

Obesity has now become an epidemic in India which leads to host of metabolic diseases [1]. The disordered metabolism with hyperinsulinemia and dyslipidemia has been found to play an important role in the cause of diseases like Diabetes mellitus, hypertension, coronary artery disease and stroke [2-4]. According to the WHO definition, a body mass index (BMI) of 25–29.99 and ≥30 kg/m2 were taken as cutoff values for overweight and obesity, respectively. Based on the ATP III definitions, central obesity was defined as Waist Circumference (WC)>102 cm for males and >88cm for females [5]. A high WC is associated with an increased risk of atherogenic dyslipidemia which is an important independent risk factor for Cardio vascular diseases. This was confirmed by principal component analysis of lipoprotein sub fractions in a large prospective cohort study [6]. The prevalence and incidence of obesity are increasing rapidly in both developed and developing countries. This leads to an increase in obesity-related morbidity which has become a challenge for health care systems and lowered the quality of life.

Serum gamma-glutamyl transferase (GGT) is a known biomarker of hepatobiliary disease and alcohol consumption. But cellular GGT is an ectoplasmic enzyme, responsible for the extracellular catabolism of glutathione and is widely distributed in various cells with high secretory or absorptive activities [7]. Serum GGT levels are raised in obese individuals and are particularly strongly associated with central obesity. It has been figured out that elevated GGT level is a marker for visceral fat, and specifically for hepatic steatosis (fatty liver). GGT is expressed in the liver, kidney, cerebrovascular endothelium and pericytes and is an enzyme which acts as a pro-oxidant in the extracellular space. Elevated serum GGT levels may be reflecting high degree of oxidative stress and is known to be associated with risk factors of metabolic syndrome in obese people [8].

It is evident from many recent studies that there is a strong association of serum GGT activities within the reference interval with many cardiovascular disease risk factors or components of metabolic

syndrome [9-13].These studies also have shown the predictive nature of baseline serum GGT activity to future diabetes, hypertension, stroke, and myocardial infarction and most strongly predicted diabetes. There is increasing evidence that human atherosclerotic plaques have GGT enzyme activity [12, 14-16] which implies that GGT may directly contribute to atherosclerosis progression. With the increasing association of GGT with obesity, metabolic syndrome and atherosclerosis, we proposed to evaluate Lipid profile and GGT levels in obese individuals and compared that with non-obese healthy controls and also to correlate GGT with lipid profile in obese individuals.

MATERIALS AND METHODS

This was a cross-sectional study done in Thanjavur Medical College Hospital, Thanjavur, Tamilnadu. In this study we included 100 obese and 100 healthy non-obese adults who were non-smokers and non-alcoholics, between the ages 19 to 40 years.

Subjects with liver diseases like alcoholic liver disease, obstructive jaundice, hepatitis were excluded from the study. People who were on anti-epileptics and other drugs that are hepatotoxic were also excluded from the study. A proper informed consent was obtained from all the subjects.

Waist Circumference (WC) was measured at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin. Blood pressure was measured using standard sphygmomanometer (Manual) in supine posture; while the plasma glucose, lipid profile and GGT were estimated using standard kits in the auto analyzer with 5 ml of fasting blood sample from the subjects. Biochemical parameters were estimated as follows:

GGT - Carboxy substrate method, Fasting plasma glucose - glucose oxidase and peroxidase method, Total cholesterol - cholesterol oxidase method, Triacylglycerol- Lipase-glycerol kinase method, LDL cholesterol was calculated by Friedewald's equation, HDL cholesterol - phosphotungstate method and VLDL was calculated by the formula VLDL= TAGs/5.Statistical analysis was done using SPSS version 21 software. Datas were expressed as mean+/- SD. A p value < 0.01 was considered significant. The association between serum GGT levels and other variables was found using Pearson's correlation.

RESULTS

The percentage of male and female subjects was 57 and 43 in obese category respectively. In control group the gender distribution was 55 males and 45 females. There was no significant difference in the mean ages of the participants between the two groups. Waist circumference, fasting blood sugar, systolic and diastolic blood pressures were significantly higher in obese subjects compared to the control group (p < 0.001) (Table 1).

Table 1: Comparison of fasting and post-prandial blood sugar, blood pressure and waist circumference between obese and non-obese individuals

Variables	Obese subjects (n=75) (Mean ± SD)	Non-obese subjects (n=75) (Mean ± SD)	p value
FBS(mg/dl)	165.10± 58.29	87.00± 11.80	< 0.001
SBP (mm/Hg)	169.96± 22.91	113.78± 9.32	< 0.001
DBP (mm/Hg)	95.48 ± 8.47	76.08 ± 5.55	< 0.001
WC (cm)	114.07 ± 12.24	82.23 ± 14.43	< 0.001

(FBS = Fasting Blood Sugar, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, WC = Waist Circumference, SD = Standard Deviation).

In the study group all the lipid parameters were significantly elevated in obese individuals compared to non-obese subjects. The difference between the groups was statistically significant (p<0.001). The atherogenic nature of obese individuals is shown by marked increase in triglycerides, Total Cholesterol and marked decrease in High Density Lipoproteins. Lipid profile of obese group versus non-obese group is shown in the following table (Table 2) as mean ± SD.

Table 2: Comparison of Lipid profile between obese and non-obese individuals

Tests	Obese subjects (n=75) (Mean ± SD)	Non-obese subjects (n=75) (Mean ± SD)	p value
TC (mg/dl)	250.84 ± 48.66	163.88 ± 25.37	< 0.001
TGL (mg/dl)	266.04 ± 69.35	142.36 ± 20.10	< 0.001
LDL (mg/dl)	166.05 ± 44.46	87.91 ± 26.50	< 0.001
VLDL (mg/dl)	53.21 ± 13.87	28.47 ± 4.02	< 0.001
HDL (mg/dl)	31.59 ± 5.07	47.50 ± 7.90	< 0.001

(TC= Total Cholesterol, TGL= Triglycerides, LDL=Low Density Lipoprotein, VLDL=Very Low Density Lipoprotein, HDL= High Density Lipoprotein)

The atherogenic nature was also evident from their lipid ratios that are shown in table-3.

The GGT levels were highly elevated in obese group (46.40±9.46 mg/dl) when compared to non-obese group (18.52±2.19 mg/dl) and the elevation was statistically significant as evident from the p value ($p<0.001$) (Fig. 1).

Table 3: Comparison of the lipid ratios between obese and non-obese individuals

Tests	Obese subjects (n=75) (Mean ± SD)	Non-obese subjects (n=75) (Mean ± SD)	p value
TC/HDL	8.29 ± 2.77	3.56 ± 0.87	< 0.001
TGL/HDL	8.83 ± 3.30	3.09 ± 0.71	< 0.001
LDL/HDL	5.53 ± 2.26	1.94 ± 0.78	< 0.001

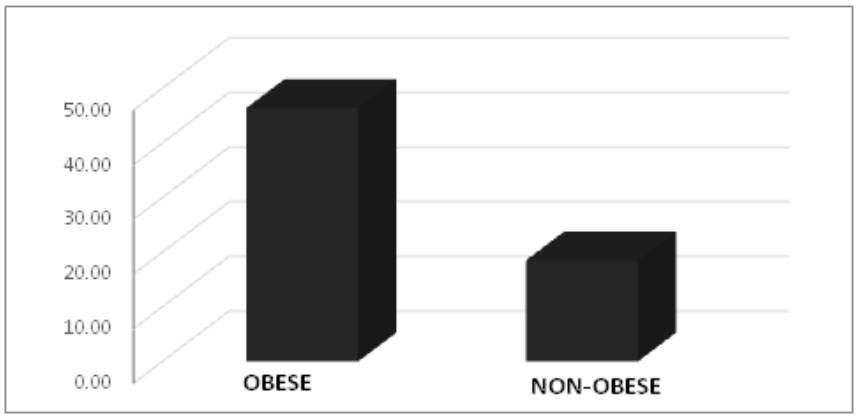

Fig. 1: Comparison of GGT level between the groups

Pearson's correlation analysis was used to analyze the correlation of Gamma glutamyl transferase with other biochemical parameters in obese individuals. From Pearson's correlation it was seen that there was significant positive correlation between GGT and FBS, blood pressure and waist circumference (Table 4). The correlation between PPBS and GGT was not significant in our study (r: 0.142, p = 0.158).

The correlation between GGT and TC, TGL, LDL, VLDL was highly significant positively. It was also seen that there was significant positive correlation between GGT and the risk ratios: TC/HDL, TGL/HDL, LDL/HDL. HDL was negatively correlated with GGT and found to be highly significant (Table 5).

Table 4: Pearson's coefficient of determination (r) of serum GGT with WC, blood pressure, FBS in obese individuals

Variables		SBP	DBP	FBS	WC
GGT	r	0.795	0.627	0.599	0.662
	p	<0.001	< 0.001	<0.001	<0.001

Table 5: Pearson's coefficient of determination (r) of serum GGT with lipid parameters and lipid ratios in obese individuals

Variables		TC	TGL	LDL	VLDL	HDL	TC/ HDL	TGL/ HDL	LDL/ HDL
GGT	r	0.72	0.662	0.669	0.662	- 0.773	0.817	0.814	0.765
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001

DISCUSSION

GGT has been thought of as a diagnostic marker for hepatobiliary disorders and alcohol abuse. But there is accumulating evidence that γ-Glutamyl transferase (GGT), an enzyme catalyzing the extracellular catabolism of antioxidant glutathione, may directly take part in atherogenesis. More recent studies have shown that serum GGT levels can be a promising biomarker for cardiovascular risk, and thus have an application in primary and secondary prevention of cardiovascular disease. All epidemiological studies to date on serum GGT have focused on the main associations of serum GGT with various disease outcomes, including diabetes [17]. It is known that GGT has a protective effect in maintaining appropriate intracellular glutathione levels, which is a powerful

antioxidant. The generation of free radicals, which can occur in central obesity, may deplete intracellular glutathione and thus induce the activity of GGT into the circulation. Oxidative stress plays a crucial role in a variety of clinical settings of atherogenesis, and mediates many pathways linked to atherosclerosis and inflammation [18].

In our study we found that GGT was significantly associated with waist circumference. Serum GGT was positively correlated with blood pressure and atherogenic dyslipidemia in obese subjects. This finding was supported by many previous studies [8, 17, 18]. The role of GGT is to maintain adequate levels of intracellular glutathione and serum GGT has been proposed as a marker of oxidative stress [13]. Serum GGT may be strongly associated with obesity or fat accumulation of liver and contributing to the development of insulin resistance [17]. Some studies also showed that high GGT was an independent and early predictor for chronic disorders as well as cardiovascular disease [10].

Ruttmann *et al*. [19] carried out a study against 163,944 Australians and reported that GGT is a risk factor for cardiovascular disease and it was confirmed to be a key dependent variable for the death caused by cardiovascular failure due to chronic heart disease. Kazemi-Shirazi *et al*. [20] also preformed a study against 283,438 participants for 12 years, and reported that even within the normal group, the highest GGT quartile increases the cause of death by 100% and therefore, is a strong factor for long-term survival. A longitudinal increase in the GGT level, even within the GGT reference interval, may be an independent predictor for metabolic syndrome, regardless of the baseline GGT [21].

Similar to all the above studies we found that elevated GGT levels were associated with increased waist circumference, elevated blood pressure and atherogenic dyslipidemia in our present study.

Atherogenic dyslipidemia is characteristic of obesity, the metabolic syndrome, insulin resistance, and type 2 diabetes mellitus [22, 23] and has emerged as an important marker for the increased CVD risk seen in such spectrum of conditions. We also found increased triglycerides and decreased HDL-C (atherogenic dyslipidemia) in our study population of obese individuals. It is clear that either reduction of dietary carbohydrate content or weight loss will improve an atherogenic dyslipidemic profile [6].

CONCLUSION

A significant relationship between GGT levels, waist circumference and other components of metabolic syndrome (blood pressure, dyslipidaemia) was established in our study. Hence GGT can be considered as an early, reliable and cost-effective marker of atherosclerosis and visceral fat, so that life style modifications in the form of diet and exercise can help in preventing the future cardiovascular risks in this group of people. Further large population prospective cohort studies in various ethnic groups are needed to consider GGT in screening people at risk for developing atherosclerosis.

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