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Research Article

GAMMA-GLUTAMYL TRANSFERASE AS AN INDICATOR OF OBESITY: A CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: Obesity, characterized by an increase in excessive fat accumulation, represents a social problem worldwide and has been recognized as a major underlying factor in the pathogenesis of several diseases. Gamma-glutamyl transferase (GGT) is a cell-surface protein contributing to the extracellular catabolism of glutathione. Elevated GGT is strongly associated with obesity and excess deposition of fat in the liver, termed non-alcoholic fatty liver disease, which is thought to cause hepatic insulin resistance and contribute to the development of systemic insulin resistance and hyperinsulinemia. Therefore, we have investigated the serum GGT levels in obese individuals and the correlation of serum GGT with body mass index (BMI) and waist circumference.

Methods: The study was carried out in 100 obese patients and 100 non-obese individuals.

Results: Patients with obesity showed a significant increase in GGT levels when compared to the control group. The mean levels of BMI, WC, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-c), very LDL-cholesterol, total protein and aspartate aminotransferase were found to be significantly elevated in the obese individuals compared to controls. The mean levels of high-density lipoprotein-cholesterol showed a significant decrease in the obese participants.

Conclusion: Elevated liver enzymes, although in normal ranges, especially at upper quartiles as observed in our study, may play a central role in early diagnosis of fat overflow to the liver. The findings of our study suggest that serum GGT levels may be a simple and reliable marker of visceral fat accumulation.

Keywords: Diabetes mellitus, Gamma-glutamyl transferase, Insulin resistance, Metabolic syndrome, Obesity.

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INTRODUCTION

Obesity, characterized by an increase in excessive fat accumulation, represents a social problem worldwide and has been recognized as a major underlying factor in the pathogenesis of several diseases [1]. In a developing country like India, obesity and malnutrition are two ends of a spectrum: Obesity being an emerging issue which needs close monitoring [2].

Obesity also involves a growing number of children in developed countries. Studies have assessed that children who became obese in an early age were more likely to be obese as adults [3].

Recently, it has also been found that obesity is associated with low-grade chronic systemic inflammation in adipose tissue. This condition is influenced by the activation of the innate immune system in adipose tissue that promotes the pro-inflammatory status and oxidative stress (OS), triggering a systemic acute-phase response. Several chronic diseases such as metabolic syndrome, diabetes mellitus, liver and cardiovascular diseases and cancer are also the result of obesity and associated with OS. It has been hypothesized that inflammation of adipose tissue in obese patient plays a critical role in the pathogenesis of obesity-related complications [4].

Gamma-glutamyl transferase (GGT) is a cell-surface protein contributing to the extracellular catabolism of glutathione (GSH). The enzyme is produced in many tissues, but most GGT in serum is derived from the liver [5]. Measurement of GGT in serum appears to be a sensitive index with low specificity in the diagnosis of alcoholics with hepatitis when correlated clinically [6]. GGT has a pivotal role in the maintenance of intracellular antioxidant defenses through its mediation of extracellular GSH transport into most types of cells [7].

Elevated GGT is strongly associated with obesity and excess deposition of fat in the liver, termed non-alcoholic fatty liver disease, which is thought to cause hepatic insulin resistance and contribute to the development of systemic insulin resistance and hyperinsulinemia [8].

Several mechanisms for GGT leakage are possible and include an increase in oxidative stress, proteolysis, glycosylation, GGT synthesis and endothelial damage [9]. The interrelations between serum GGT, obesity, other metabolic disturbances and plasma insulin raise the possibility that elevated GGT levels can help predict the development of metabolic syndrome and Type 2 diabetes [10]. Therefore, we have investigated the serum GGT levels in obese individuals and the correlation of serum GGT with body mass index (BMI) and waist circumference (WC) in obesity.

METHODS

The study protocol was performed in accordance with the approval of the Institutional Ethics Committee (ECN: 731/IEC/2015) and informed written consent was taken from all subjects.

Patient selection

Inclusion criteria

A total of 100 obese patients (BMI ≥25 kg/m^2); all the patients were in the age group of 18-45 years and the study included both males and females.

Exclusion criteria

Patients with diabetes mellitus, pregnancy, high alcohol consumption, known liver or kidney diseases and patients on medications which are enzyme inducers. 100 apparently healthy non-obese individuals (BMI

18-22.9 kg/m^2), without diabetes, hypertension, renal disease and any other systemic illness were selected for the study and they formed the control group.

Sample collection

Venous blood was collected from all the participants after an overnight 12 hrs fast. 2 ml of the blood sample was collected in an oxalate fluoride Vacutainer for estimation of fasting plasma glucose. 3 ml of blood collected in a plain Vacutainer was allowed to clot and serum was separated by centrifugation at 3000 RPM for 10 minutes.

Plasma glucose (FBS), total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), total protein, aspartate aminotransferase (AST), alanine transaminase (ALT) and GGT were measured by using standard kits in Beckmann Coulter auto analyzer on the same day of sample collection.

RESULTS

Comparison was made between the two groups using student's *t*-test.

Patients with obesity showed a significant increase in GGT levels (25.42±9.5 vs. 17.52±7.05; p<0.001) when compared to the control group.

The mean levels of BMI, WC, total cholesterol, triglycerides, LDL-c, Very LDL (VLDL-c), total protein and AST were found to be significantly elevated in the obese individuals compared to controls. The mean levels of HDL-c showed a significant decrease in the obese participants (Table 1).

GGT levels in obese individuals were found to correlate positively with serum triglycerides (r=0.4236, p<0.001) (Table 2).

GGT levels in obese individuals were found to correlate positively with BMI (r=0.1036, p=0.4288) (Table 3).

GGT levels in obese individuals patients were found to correlate positively with WC (r=0.0445, p=0.7670) (Table 4).

DISCUSSION

GGT is central in GSH hemostasis which is an important antioxidant defense for the cell. Therefore, GGT plays an important role in antioxidant defense systems. Elevated GGT levels could be a marker of oxidative stress and subclinical inflammation.

Elevated GGT is strongly associated with obesity and excess deposition of fat in the liver, termed non-alcoholic fatty liver disease, which is thought to cause hepatic insulin resistance and to contribute to the development of systemic insulin resistance and hyperinsulinemia [11]. Increased serum concentration of GGT could identify people with low but persistent increase of oxidative and other cellular stresses [12].

In our study, obese individuals have shown a significant increase in serum GGT levels when compared to the non-obese control group. At the same time, we have observed that the serum GGT levels in the obese group are in the high normal range only.

Recent population-based epidemiological studies have shown a strong association of serum GGT activities within the reference interval with many cardiovascular disease risk factors or components of metabolic syndrome. In addition, in prospective studies, baseline serum GGT activity predicted future diabetes, hypertension, stroke and myocardial infarction. Among these diseases, serum GGT within the reference interval most strongly predicted incident Type 2 diabetes [13].

Three prospective cohort studies found an interaction, not statistically significant, in which obesity was weakly associated with incident diabetes in people with low-normal serum GGT but strongly associated in those with high normal serum GGT [14].

Table 1: Comparison of mean±SD of the measured biochemical parameters between the control and obese groups and the statistical significance of the differences

Parameters	Control (n=100)	Obese individuals (n=100)	p
BMI (Kg/m^2)	19.84±1.26	29.07±1.98	<0.001
WC (cm)	77.36±4.25	102.48±6.38	<0.001
GGT (U/L)	17.52±7.05	25.42±9.5	<0.001
T. protein (g/dl)	7.10±0.53	7.30±0.50	0.0063
AST (U/L)	23.64±7.80	27.22±10.40	0.0064
ALT (U/L)	24.71±15.50	25.28±14.80	0.7906
Total cholesterol (mg/dl)	140.33±17.77	194.27±24.83	<0.001
Triglycerides (mg/dl)	108.35±45.94	155.23±80.06	<0.001
HDL-c (mg/dl)	42.99±7.47	32.66±7.24	<0.001
LDL-c (mg/dl)	92.28±22.42	134.79±27.49	<0.001
VLDL-c (mg/dl)	22.66±9.62	32.42±16.43	<0.001
FPG (mg/dl)	93.81±7.66	94.19±5.44	0.6863

Values are expressed in mean±standard deviation. The values are statistically significant if the p<0.05, GGT: Gamma-glutamyl transferase, SD: Standard deviation, BMI: Body mass index, WC: Waist circumference, AST: Aspartate aminotransferase, ALT: Alanine transaminase, HDL-c: High-density lipoprotein-cholesterol, LDL-c: Low-density lipoprotein-cholesterol, VDL-c: very density level-cholesterol

Table 2: The Pearson's correlation analysis between GGT levels and triglycerides in obese individuals

Parameters	Mean±SD	r (p)
GGT (U/L)	25.42±9.5	r=0.423 (<0.001)
Triglycerides (mg/dl)	155.23±80.06	

GGT: Gamma-glutamyl transferase, SD: Standard deviation

Table 3: The Pearson's correlation analysis between GGT levels and BMI in obese individuals

Parameters	Mean±SD	r (p)
GGT (U/L)	25.42±9.5	r=0.1036 (0.4288)
BMI (Kg/m^2)	29.07±1.98	

GGT: Gamma-glutamyl transferase, BMI: Body mass index, SD: Standard deviation

Table 4: The Pearson's correlation analysis between GGT levels and WC in obese individuals

Parameters	Mean±SD	r (p)
GGT (U/L)	25.42±9.5	r=0.0445 (0.7670)
WC (cm)	102.48±6.38	

GGT: Gamma-glutamyl transferase, WC: Waist circumference, SD: Standard deviation

Moreover, Wannamethee *et al*. revealed that elevated levels of ALT and GGT within the normal ranges are found to be the independent predictors of Type 2 diabetes mellitus. Hence, elevated liver enzymes, although in normal ranges, especially at upper quartiles as observed in our study, may play a central role in early diagnosis of fat overflow to the liver [15].

BMI, WC and serum triglycerides are components of metabolic syndrome. We observed that the GGT levels in obese individuals of our study were found to correlate positively with BMI. Our results are consistent with the findings of Puukka *et al*., who observed a positive correlation between GGT and BMI measured in 2490 participants [16].

WC is used as a measure of abdominal adiposity because a correlation between WC and the amount of intra-abdominal fat has been observed with computed tomography [17]. In our study, the GGT levels in obese individuals correlated positively with WC. The GGT levels in obese individuals were also found to correlate positively with serum triglycerides and this association was found to be statistically significant.

Rantala *et al*. and Sakugawa *et al*. investigated the relationship between GGT and metabolic syndrome and found that the serum GGT levels correlated with components of metabolic syndrome. Hence, estimation of GGT levels can be considered in the algorithm for metabolic syndrome [18]. Pangaluri *et al*. found metabolic syndrome to be associated with subclinical hypothyroidism and compounded cardiovascular risk factors [19].

A prospective cohort study involving 7458 non-diabetic men has concluded that a raised serum GGT is an independent risk factor for diabetes mellitus. In a study including 6217 Japanese men, Nakanishi *et al*. indicated that serum GGT may be an important predictor for developing metabolic syndrome and Type 2 diabetes [10].

A number of recent studies have suggested that abnormal hepatocellular function is associated with obesity, insulin resistance and Type 2 diabetes [20]. Elevation of serum GGT could be an expression of excess fat deposited in the liver, which is regarded as a feature of the insulin resistance syndrome.

We found the mean levels of total cholesterol, triglycerides, LDL-c and very LDL-cholesterol (VLDL-c) to be significantly elevated in the obese individuals compared to controls. The mean levels of HDL-c showed a significant decrease in the obese participants.

Various studies suggested that elevated serum GGT could be the expression of subclinical inflammation which also contributes to the development of Type 2 DM. Gohel and Chacko have found a statistically significant positive linear relationship between serum GGT and hsCRP in patients with Type 2 DM [12]. Elevated liver enzymes may reflect inflammation, which impairs insulin signaling both in the liver and systemically [21]. Vinodhini *et al*. have reported the presence of elevated hsCRP concentrations in obese females with polycystic ovary syndrome [22]. As serum GGT is highly associated with WBC count and some features of low-graded inflammation, an elevated GGT could be the expression of subclinical inflammation or an insulin-resistant state [23].

CONCLUSION

We have observed a comparative increase in serum GGT levels in obesity which was found to correlate positively with serum triglycerides, BMI and WC. The findings of our study suggest that serum GGT levels may be a simple and reliable marker of visceral fat accumulation.

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