Original Article

Comparison of gamma glutamyltransferase in normal and in type 2 diabetics

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Abstract

Objective: Comparison of gamma glutamyltransferase in normal and type 2 diabetics.

Methods: In a cross-sectional study, 100 apparently normal healthy subjects and, 47 type 2 diabetic subjects were selected from either sex with ages between 18-65 years.Subjects were measured for waist/hip ratio, BMI and serum levels of ALT, AST,Alk Phosphatase and Glutamyl Transferase (GGT). The study excluded by screening for AntiHCV, HBsAg and patients with aspartate amino transferase (SGOT), alanine amino transferase (SGPT), GGT levels more than three times the normal and subject with a total leukocyte count more than 10,000/μl.

Results: The levels of GGT levels were found to be most significant among all the liver enzymes (P = 0.001). The levels of GGT compared with type 2 diabetics was found to be significantly increased when compared with BMI, waist/circumference, cholesterol, triglycerides (TG), High Density Lipoprotein (HDL), Low density Lipoprotein (LDL), fasting blood sugar level and blood pressure (P = 0.001). The pearson regression analysis showed a positive relation with systolic, diastolic blood pressure and fasting blood sugar.

Conclusion: These results indicate that levels of GGT were raised with increased waist girth, BMI, blood pressure TG and low HDL, all of these are the features of metabolic syndrome according to ATP III criteria. Hence, serum GGT may be an important investigation for diabetes and metabolic syndrome (JPMA 60:945; 2010).

Introduction

The liver is a large, complex organ that is well designed for its central role in carbohydrate, protein and fat metabolism. It is responsible for synthesizing and secreting bile and synthesizing lipoproteins and plasma proteins, including clotting factors.[1] Gamma glutamyltransferase (GGT) is the enzyme responsible for the extracellular catabolism of glutathione (GSH, glutamyl-cisteinyl-glycine), the main thiol intracellular antioxidant agent in mammalian cells.[2] It is present, linked through a small lipophilic sequence of its larger subunit, on the cell surface membrane of most cell types; although the same protein is produced in all tissues, differences in the sugar moieties allow that only the liver GGT is detectable in serum.[3] Most serum GGT is bound to carriers, such as and lipoproteins and albumin.[3] Serum GGT activity is affected by genetic and environmental factors, with heritability estimated at 0.52.[4] The loss of a direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production.[5] A number of recent studies have suggested that abnormal hepatocellular function is associated with obesity, insulin resistance, and type 2 diabetes. Prospective studies have found that high levels of hepatic enzymes including ALT[6] and GGT[7] are associated with later development of diabetes. At the same time, ultrasonographic and pathological series have shown that excess deposition of fat in liver, usually termed nonalcoholic fatty liver disease, has strong cross-sectional associations with obesity, insulin resistance, and type 2 diabetes.[8] The aim of the present study is to measure the levels of liver enzymes among normal subjects and then compare them in known type 2 diabetic subjects. The study also compared raised blood sugar levels with waist circumference, BMI, systolic, diastolic blood pressure and serum lipids as these are the risk factors for the development of metabolic syndrome.[9]

Patients and Methods

The study was conducted in the Department of Physiology, B.M.S.I., J.P.M.C, Karachi. The patients were recruited from outpatient department of Medicine J.P.M.C. Karachi. The study was done during the period of December 2006 to October 2007.

Grouping of Subjects:

The present study was cross-sectional. The subjects were divided into two groups. Group (A) included 100 healthy normal subjects. Group (B) included 50 type 2 diabetic subjects with uncontrolled blood sugar levels. Height and weight was measured with the help of height and weight scale in ZT-120. Weight was measured, while subjects were minimally clothed without shoes. Height was measured in standing position without shoes while the shoulder was in a

normal position. BMI was calculated as weight in kilograms divided by height in meters squared. BMI > 23.0 to 24.9 kg/m2 taken as overweight and >25.0 kg/m2 as obese.[8]

Among the measures of abdominal obesity, high WC was defined as >90 cm in males and >80 cm in females. High total cholesterol, high triglyceride, high low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol were defined as TC ≥ 200mg/dL, TG ≥ 150mg/dL, LDL-C ≥ 130mg/dL, and HDL-C <40mg/dL according to the criteria of APT III.[9] ALT, AST, ASOT and GGT were assessed with Bioscience Kinetic UV. IFCC rec. Reference ranges for ALT and AST upto 36 in females and upto 45 in males, AlkPhosphatase 65-306 in females and 80-306 in males and for GGT values up to 38 U/l in females and 55 U/l males.

Diabetes mellitus was defined according to the criteria set by the report on expert committee on the diagnosis and classification of diabetes.[10] Hypertension was defined according to the criteria set by JNC VII classification of hypertension.[11]

A stringent criterion was observed to include patients in the study. We excluded patients with acute or chronic liver, kidney and heart disease, history of alcohol addiction, patients taking drugs affecting liver enzymes, patients suffering from cancer, and pregnant women. We also excluded subjects with hepatitis C virus antibody and hepatitis B virus surface antigen and patients with aspartate amino transferase (SGOT) and alanine amino transferase (SGPT) and Gamma Glutamyltransferase (GGT) levels more than three times the normal and subjects with total leukocyte count more than 10,000/µl. A written consent of the patients was taken after explaining the procedure. All participants were asked to fast at least 12 hours and to avoid heavy physical activity for at least 2 hours before the examination. After a 5 minute rest blood pressure was measured in sitting position. All participants went through a clinical examination with measurement of; resting blood pressure, height, weight and waist and hip circumference. Daily physical activity, addiction history, history of previous illnesses and types of medication use was also recorded. Eight milliliter of venous blood was drawn in a disposable syringe. Complete Blood Count was done by Automated cell counter SYSMEX KX 21. Blood sugar was estimated by GOD-PAP Enzymatic Colorimetric Method. Hepatitis C virus antibodies were detected by chromatographic immunoassay (LG Quick card). Hepatitis B surface antigen was detected by qualitative immunoassay (Abbot Laboratory). Gamma GT was measured by according to the Szasz method.

Statistical Analysis:

Analysis was done on SPSS version 14. The subjects were analyzed by dividing them into normal and diabetic groups. General characteristics were done using descriptive analysis. The blood sugar level was analyzed by dividing them into normal and high sugar levels and then liver enzymes and lipid profile was compared with them using independent t test. Pearson correlation 2 tailed was done with GGT and blood sugar levels and with GGT and blood pressure. The value of "r" was calculated in normal and type 2 diabetes subjects.

Results

In this study 100 normal subjects were taken as control and their values of BMI, waist circumference, lipid profile, blood sugar levels and blood pressure were compared with 47 type 2 diabetic patients.

In Table-1 comparison of anthropometric measurements and blood pressure was done in normal and type 2 diabetic subjects. The levels of BMI,

Table-1: Comparison of Anthropometric Measurement, blood pressure and blood sugar levels in Diabetics and Control subjects.

Anthropometric measurements	Diabetic (n=47) Mean ± SEM	Control (n=100) Mean ± SEM	P-value
Age (years)	46 ± 2.08	47 ± 1.54	0.644
BMI (kg/m2)	23.3 ± 0.43	21.1 ± 0.15	**0.001
Waist circumference	95.73 ± 4.4	79.77 ± 7.43	**0.001
	Blood Pressure		
SBP mm Hg	145 ± 3.44	122 ± 1.4	**0.001
DBP mm Hg	86 ± 1.21	78 ± 0.72	**0.001
FBS mg/dl	158 ± 5.2	89±1.2	**0.001
RBS mg/dl	235± 8.5	121±1.4	**0.001

n= number of subjects, SEM : standard error mean
SBP : systolic blood pressure, DBP: diastolic blood pressure
FBS : fasting blood sugar level, RBS : random blood sugar level
** Significant Correlation (p<0.01).

Table-2: Comparison of Lipid Profile and Liver enzymes between Type 2 Diabetics and normal subjects.

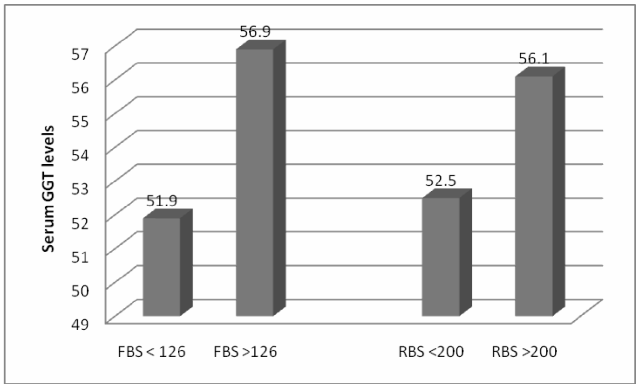
Laboratory Investigation	Diabetic (n=47) Mean ± SEM	Control (n=100) Mean ± SEM	P-value
Total Lipid mg/dl	1006 ± 23.1	681 ± 5.5	**0.001
Cholesterol mg/dl	276 ± 6.66	179 ± 1.64	**0.001
Triglyceride mg/dl	226 ± 6.50	161 ± 1.25	**0.001
HDL cholesterol mg/dl	31.6 ± 0.34	40.1 ± 0.21	**0.001
LDL cholesterol mg/dl	211 ± 6.91	107 ± 1.4	**0.001
Liver Enzymes			
GGT I.U/L	57 ± 1.44	18 ± 0.60	**0.001
SGPT I.U/L	10.3 ± 0.22	10.2 ± 0.19	0.690
SGOT I.U/L	7.1 ± 0.11	7.1 ± 0.10	0.910
Alkaline Phosphatase I.U	131 ± 2.53	128 ± 1.03	0.371

n= number of subjects, SEM : standard error mean
HDL: high density lipoproteins, LDL : low density lipoproteins.
GGT: gamma glutamyl transferase
SGPT: serum glutamic pyruvic transaminase
SGOT : serum glutamic Oxaloacetic transaminase
* Significant Correlation (p<0.05) ** Significant Correlation (p<0.01).

Table-3: Pearson's Correlation Coefficient between diabetes and normal subjects.

	Diabetics n = 47	Controls n = 100
Gamma GT Vs FBS	r = 0.54 **	r = 0.05
Gamma GT Vs RBS	r = 0.14	r = 0.15
Gamma GT Vs BP Systolic	r = 0.40 *	r = 0.13
Gamma GT Vs BP Diastolic	r = 0.50 **	r = 0.19

Gamma GT: gamma glutamyltransferase.
FBS: fasting blood sugar RBS : random blood sugar
BP Systolic : systolic blood pressure, BP Diastolic : Diastolic blood pressure.
Correlation coefficient (r) has been determined by Pearson correlation method
* Significant Correlation ($p<0.05$)
** Significant Correlation ($p<0.01$).



Fasting BS : fasting blood sugar, Random BS : random blood sugar
< 126: less then 126 mg/dl, ?126 : greater then 126 mg/dl
< 200: less then 200 mg/dl, ? 200: greater then 200 mg/dl.
GT : gamma glutamyltransferase
Serum GGT: serum levels of gammaglutamyltransferase in I.U.

Figure: Comparison of Gamma GT with increased Blood Sugar Levels in type 2 Diabetic Subjects.

waist/circumference, systolic and diastolic blood pressure were found to be increased in diabetics.

In Table-2 the comparison of lipid profile and liver enzymes was done between normal subjects and type 2 diabetics. The table is showing significantly increased levels of total lipids, cholesterol, triglycerides, LDL and decreased HDL among diabetic subjects. The table also compared the levels of liver enzymes between normal and type 2 diabetics and showed significant increase in GGT, SGPT, SGOT, and alkaline phosphatase in diabetics.

In Table-3 Pearson correlation two tailed study the value of GGT and blood sugar levels and blood pressure values were compared between normal and in diabetics. The regression value "r" in diabetic was significant with FBS, systolic and diastolic blood pressure.

Figure is comparing the values of fasting blood sugar and random blood sugar with serum levels of GGT. The fasting and random blood sugar levels were divided into normal and high according to WHO criteria. The table showed that as the levels of blood sugar were increased both in fasting and random conditions the levels of GGT were also raised.

Discussion

This study was done with the purpose to identify the effects of raised blood sugar levels on liver enzymes. In the present study comparison of high sugar levels was done with BMI, waist hip ratio, liver enzymes, lipid profile and blood pressure. The significant correlation with GGT, lipid profile, systolic and diastolic blood pressure was found with increase in blood sugar levels. Similar studies on the relationship between liver enzyme and diabetes in both sexes in general population[12,13] have found higher levels of gamma GT. A significant positive associations of GGT and ALT with diabetes were seen with, BMI, waist hip ratio, and alcohol consumption. Study on diabetic individuals and patients of metabolic syndrome[14] shows that the values of waist circumference, total cholesterol, Triglycerides, fasting glucose, AST, ALT, fasting insulin increased according to the increase level of serum GGT in both genders. Recent studies on diabetic middle aged men and women[15-17] have showed increased levels of GGT when compared with age, ALT, AST, alcohol consumption, and BMI. GGT was also correlated with insulin resistance-markers, waist-circumference, Triglycerides, Fasting plasma glucose, HbA1c, systolic and diastolic blood pressure.

Our study is in total agreement with this study however we have excluded subjects with any history of alcohol. Previous study[18] on patients with type 2 diabetes after a three year follow-up period had showed that raised gamma GT was correlated with the central obesity, increased fasting glucose, Triglycerides, and blood pressure in both sexes. In another study when results of GGT, FPG, and Triglycerides were compared,[19] the concentrations of FPG and triglycerides markedly increased among the higher GGT categories. Similarly, the frequency of FPG and hypertriglyceridemia increased steadily with levels of GGT.

Our results suggest that liver enzymes are closely associated with the risk of metabolic syndrome and type 2 diabetes and that among these enzymes serum GGT is the most powerful risk indicator for developing the metabolic syndrome and type 2 diabetes. Our results are consistent with those of previous studies[8,20] and indicate that elevated serum GGT is associated with an increased risk of the metabolic syndrome and type 2 diabetes. One explanation for our findings is that the elevation of liver enzymes could be expression of excess deposition of fat in liver, which is regarded as a feature of the insulin resistance syndrome.[21,22] There is clear evidence that cellular GGT level is closely related to oxidative stress indicators in vivo, either as an

antioxidant or a prooxidant, depending on circumstances.[23] Elevated GGT could reflect subclinical inflammation, which would represent the underlying mechanism. In addition, certain mechanisms related to oxidative stress might play a role because cellular GGT has a central role in glutathione homeostasis by initiating the breakdown of extracellular glutathione, a critical antioxidant defense for the cell.[1] Increases in serum GGT activity may be a response to oxidative stress, making increased transport of glutathione into cells. Supporting a role of serum GGT in the inflammation and oxidative stress. Among the list of countries with the highest numbers of estimated diabetics in the year 2000 Pakistan was 6th among the world with 5.2 million people with diabetes.[24] It is expected with its high growth rate that at 2030 Pakistan will have 13.9 million people with diabetes. It is therefore strongly suggested that GGT is advised in patients who are suspected to develop metabolic syndrome. Although the study does not elaborate mechanism of how serum GGT is associated with a higher risk of diabetes and how obesity may modify or strengthen this associations but their significance is certainly highlighted.

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