



CODEN [USA]: IAJPBB

ISSN: 2349-7750

## INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

<http://doi.org/10.5281/zenodo.1165097>
Available online at: <http://www.iajps.com>*Research Article*

### CORRELATION OF GAMMA GLUTAMYL TRANSFERASE AND HIGH DENSITY LIPOPROTEIN IN TYPE 2 DIABETIC SUBJECTS

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**Abstract:**

**Background:** Considering that serum gamma-glutamyl transferase (GGT) activity could reflect several different processes relevant to diabetes pathogenesis and the increasing rate of type 2 diabetes worldwide, the aim of this study was to assess the association between serum GGT concentrations and High Density Lipoprotein In Type 2 Diabetic Subjects

**Methods:** The present observational case control study was conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital Hyderabad/Jamshoro from October 2014 to September 2016. The materials for the present study were the diagnosed cases of type 2 DM. 100 diagnosed cases of T2DM and 100 non-diabetic subjects- taken as control, were selected by non-probability (purposive) sampling according to inclusion and exclusion criteria. Inclusion criteria were – diagnosed cases of type 2 DM, of >5 years duration, not taking anti- hyperlipidemic drug agent, age ≥40 years without history of cardiovascular disease. Diabetic subjects with urinary tract infections (UTI), Cardiac failure, pregnancy, diuretics, alcohol, chronic kidney disease (CKD), liver disease and smokers were excluded.

**Results:** Age of controls and cases was noted as  $52.23 \pm 6.21$  and  $51.29 \pm 4.97$  years respectively ( $P=0.94$ ) (table 1). Of 100 controls and 100 cases, male were 62 and 61 and female were 38 and 39 respectively ( $X^2 = 0.21$ ,  $P=0.51$ ). Body weight, blood pressure, random blood glucose, HbA1c, serum creatinine, cholesterol, triglycerides, LDLc, HDLc and GGT

**Conclusions:** The present study shows positive association of gamma glutamyl transferase with cholesterol, triglycerides and low density lipoprotein (LDLc) but negative association with high density lipoprotein (HDLc).

**Keywords:** Gamma-Glutamyltransferase, High Density Lipoprotein, Diabetes Mellitus, Type 2

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Please cite this article in press as Muhammad Ayoob Memon et al., Correlation of Gamma Glutamyl Transferase and High Density Lipoprotein in Type 2 Diabetic Subject , Indo Am. J. P. Sci, 2018; 05(01).

## INTRODUCTION:

Prevalence of Diabetes mellitus (DM) is multiplying exponentially. DM is a non-communicable disease metabolic disorder of glucose. It is characterized by chronic hyperglycemia caused by relative or absolute insulin insufficiency. Type 2 DM (T2DM) constitutes for 90% of total diabetic cases the World over. Male are affected more than female [1]. World prevalence of DM was estimated as 2.8% in 2000, and is estimated to rise 4.4% by the year 2030. By the year 2035, the total diabetic population is projected to 592 million. Pakistan has much prevalence and incidence of DM. The Asian countries are considered as the “Diabetes capital” [2,3]. Diabetic subjects are suffering from hyperlipidemia, hypercholesterolemia and dyslipidemia. Dyslipidemia are major risk for the coronary artery disease (CAD) in the diabetic subjects. A change in the lipid sub-fractions is a hallmark of DM and is a predictor of CAD [4,5]. Hyperglycemia and dyslipidemia make the person prone to atherosclerosis in diabetics. Type 2 diabetics are prone to CAD with atherogenic dyslipidemia [5,6]. Cross linking of collagen fibers and matrix proteins of arterial wall are glycosylated by persistent hyperglycemia, this leads to the endothelial dysfunction and accelerated atherosclerosis. CAD is a cause of morbidity and mortality. CAD is associated with hypertriglyceridemia, hyper-LDLc, hypercholesterolemia, and hypo-HDLc and postprandial hyperlipidemia. This pattern of blood lipid profile in T2DM subjects is termed as “diabetic dyslipidemia” [6]. The Y-transferase (GGT) is a plasma enzyme which catalyzes the extracellular glutathione [7]. GGT is present in the liver, gall bladder, biliary canaliculi, cardiac muscles, kidneys, brain, pancreas, lungs, etc. In case of disease of these organs, the GGT is elevated in the blood [7,8]. The GGT is produced by various tissues, but the most detectable GGT is of liver origin. Previous studies [8,9] reported the hepatocellular dysfunction is associated with type 2 DM, insulin resistance, and obesity. Loss of suppressive effects of insulin on the gluconeogenesis and glycogenolysis is responsible for the glucose over production. It is reported that the elevated liver enzymes reflect the chronic ectopic fat deposition [8-10]. Serum GGT is a simple and reliable marker of liver fat deposition and steatohepatitis. Fatty liver is a marker of insulin resistance and long term insulin resistance is a sign of type 2 DM [10]. As the Pakistan is suffering an epidemic of DM, similarly the hyperlipidemia and dyslipidemia are on incline in the diabetics, hence there is need to establish cost effective and easy marker for screening, diagnosis and prognosis at the earlier stages. In this context, the present study was

conducted to determine of correlation of gamma (Y) glutamyl transferase (GGT) with blood lipids in particular the high density lipoprotein (HDLc) in type 2 diabetic subjects

## SUBJECTS AND METHODS:

The present observational case control study was conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital Hyderabad/Jamshoro from October 2014 to September 2016. The materials for the present study were the diagnosed cases of type 2 DM. 100 diagnosed cases of T2DM and 100 non-diabetic subjects- taken as control, were selected by non-probability (purposive) sampling according to inclusion and exclusion criteria. Inclusion criteria were – diagnosed cases of type 2 DM, of >5 years duration, not taking anti- hyperlipidemic drug agent, age ≥40 years without history of cardiovascular disease. Diabetic subjects with urinary tract infections (UTI), Cardiac failure, pregnancy, diuretics, alcohol, chronic kidney disease (CKD), liver disease and smokers were excluded. Volunteers were communicated and interviewed. Willing participants were informed about the purpose of study, merits and demerits, benefit and loss. It was informed to participants that the present research will benefit the diabetic subjects. They were informed the research blood sampling only that will be used for biochemical testing. A detailed clinical history of patients and drugs intake and associated morbidities were enquired. Subjects were taken into confidence to come fasting during next visit for blood sampling. An 8-12 hour fasting was mandatory for blood lipids estimation. Biochemical analysis was performed on the Cobas analyzer (e 411), Roche Diagnostics (GmbH, Mannheim, Germany). Age, body weight, blood pressure, blood glucose, HbA1c, serum creatinine, triglycerides, cholesterol, LDLc, HDLc and GGT were noted. Jaffe’s method was used for serum creatinine estimation. Cholesterol and triglycerides were analyzed by enzymatic colorimetric method and HDLc by precipitant method. LDLc was calculated by Friedewald’s formula [11]. Blood glucose and Gamma- glutamyl transferase was detected by glucose oxidase<sup>12</sup> and IFCC method<sup>13</sup> respectively. Informed written consent proforma was signed by all volunteers. Research protocol was approved by ethical review committee of the institute. A predesigned proforma was used for data collection. SPSS 22.0 (IBM, Incorporation) and Graph Pad Prism were used for statistical analysis. Student’s t-test, Chi square tests and Pearson’s correlation

were used for the continuous data, categorical data and correlation. Statistical significance was defined at 95% confidence interval ( $P \leq 0.05$ ).

## RESULTS:

Age of controls and cases was noted as  $52.23 \pm 6.21$  and  $51.29 \pm 4.97$  years respectively ( $P=0.94$ ) (table 1). Of 100 controls and 100 cases, male were 62 and 61 and female were 38 and 39 respectively ( $X^2 = 0.21$ ,  $P=0.51$ ). Body weight, blood pressure, random blood glucose, HbA1c, serum creatinine, cholesterol, triglycerides, LDLc, HDLc and GGT

are shown in table 1. The GGT values differ significantly between controls and cases ( $P=0.001$ ). GGT in controls and cases was noted as  $20.45 \pm 5.73$  and  $36.89 \pm 6.26$  U/L respectively ( $P=0.001$ ). Pearson's correlation showed positive correlation of GGT with cholesterol ( $r=0.652$ ,  $p=0.0001$ ), triglycerides ( $r=0.758$ ,  $p=0.0001$ ) and LDLc ( $r=0.665$ ,  $p=0.0001$ ) but negative correlation with HDLc ( $r=-0.547$ ,  $P=0.0001$ ). Graph 1-3 show the scatter plots of GGT with cholesterol, LDLc and HDLc respective.

**Table 1. Characteristics and biochemical findings of study subjects**

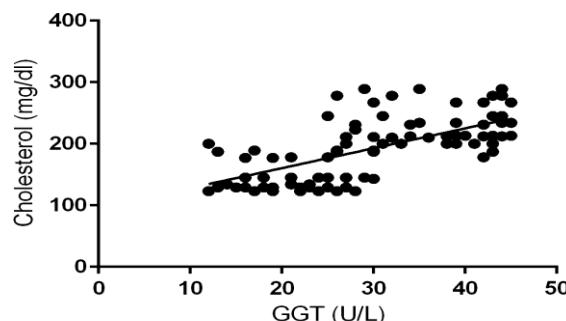
	Controls (n=100)	Cases (n=100)	P-value
Age (years)	$52.23 \pm 6.21$	$51.29 \pm 4.97$	0.94
Body weight (kg)	$70.35 \pm 5.42$	$71.65 \pm 8.07$	0.18
Systolic BP (mmHg)	$132.52 \pm 9.50$	$153.90 \pm 22.8$	0.0001
Diastolic BP(mmHg)	$69.05 \pm 5.30$	$85.15 \pm 14.07$	0.0001
RBG (mg/dl)	$133.74 \pm 8.64$	$272.78 \pm 47.72$	0.0001
HbA1c (%)	$5.43 \pm 0.80$	$10.69 \pm 2.31$	0.0001
S. Creatinine (mg/dl)	$0.87 \pm 0.17$	$1.06 \pm 0.26$	0.0001
S. Cholesterol (mg/dl)	$149.08 \pm 27.98$	$227.93 \pm 34.76$	0.0001
Triglycerides (mg/dl)	$187.94 \pm 29.76$	$423.53 \pm 101.10$	0.0001
LDL-c (mg/dl)	$90.50 \pm 25.91$	$191.17 \pm 32.85$	0.0001
HDL-c (mg/dl)	$46.67 \pm 3.02$	$30.19 \pm 10.61$	0.0001
GGT (U/L)	$20.45 \pm 5.73$	$36.89 \pm 6.26$	0.0001

BP- blood pressure, RBG- random blood glucose, HbA1c- glycated HbA1, LDL- low density lipoprotein, HDL- high density lipoprotein, GGT- gamma glutamyl transferase

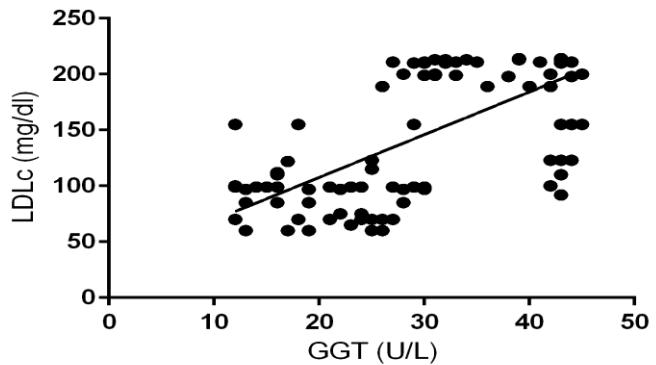
**Table 2. Correlation of Gamma glutamyl-transferase**

	Cholesterol (mg/dl)	Triglycerides (mg/dl)	LDLc (mg/dl)	HDLc (mg/dl)
r-value	0.652**	0.758**	0.665**	-0.547**
P-value	0.0001	0.0001	0.0001	0.0001

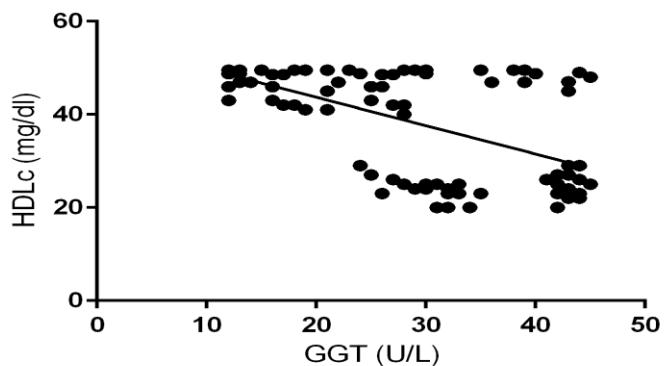
\*\*. Correlation is significant at the 0.01 level (2-tailed).



**Graph 1: Scatter plot showing correlation of cholesterol and GGT**



**Graph 2.** Scatter plot showing correlation of LDLc and GGT



**Graph 3:** Scatter plot showing correlation of HDLc and GGT

#### DISCUSSION:

The present case control study analyzed the association of GGT and lipid sub-fractions in particular the high density lipoprotein (HDLc) and low density lipoprotein (LDLc). An imbalance between HDLc and LDLc is a risk factor of coronary artery disease (CAD). The present study analyzed the association of GGT with HDLc, LDLc and cholesterol to utilize it as an inexpensive alternative biomarker of CAD. Positive association of GGT with cholesterol, triglycerides and low density lipoprotein (LDLc) but negative association with high density lipoprotein (HDLc) is worth clinical finding that may be exploited as an alternative biomarker atherogenesis in type 2 diabetic subjects. The GGT in cases was significantly raised in type 2 diabetics compared to control, the findings corroborate with previous studies [13,14]. Other clinical and animal studies have reported similar finding of elevated GGT in the type 2 diabetic's subjects [13-15]. Kashinakunti et al [13] and Desai et al [16] reported positive correlation of GGT with triglycerides, cholesterol and LDLc, but only triglycerides proved statistically significant ( $r=0.58$ ,  $p=0.04$ ), while HDL

showed negative association with GGT ( $r=-0.44$ ,  $p=0.30$ ). The significant positive association of triglycerides with GGT is consistent while LDLc and cholesterol non-significant association with GGT of above studies [13,16] are in contrast to the present study as we found statistically significant association. In present study GGT shows significant positive correlation with cholesterol ( $r=0.652$ ,  $p=0.0001$ ), triglycerides ( $r=0.758$ ,  $p=0.0001$ ) and LDLc ( $r=0.665$ ,  $p=0.0001$ ) and negative correlation with HDLc ( $r= -0.547$ ,  $P=0.0001$ ). Inverse correlation of HDLc with GGT corroborates with above studies.<sup>13,16</sup> The findings of correlation of triglycerides and HDLc are in accordance to other previous studies [17,18]. Khan et al [17] reported GGT correlated positively with triglycerides ( $r=0.91$ ,  $p= 0.02$ ) and negatively with HDLc ( $r= -0.192$ ,  $p=0.018$ ), these findings support the present study. A study by Demir et al [18] from Turkey reported highly contrasting results of negative correlation of GGT with cholesterol and LDLc and significantly positive correlation with triglycerides and HDLc ( $r=0.293$ ,  $p=0.039$ ). The conflicting results might be due to different ethnicity, selection criteria, dietary habits, and research bias.

Latha et al [19] reported positive correlation of GGT with triglycerides, LDLC, VLDL and cholesterol and negative correlation with HDLc ( $r = -0.773$ ). The findings are in agreement with the present study. Another previous study [20] reported positive correlation of GGT and triglycerides ( $r=0.112$ ), LDLC ( $r=0.05$ ) and cholesterol ( $r=0.027$ ) but negative correlation with HDLc. We also observed a significant negative correlation between serum GGT and HDL lipoprotein ( $r = -0.547$ ), which corroborate with the above study. Rise in serum GGT is supposed to be due to the increased reactive oxygen species (ROS) because the type 2 diabetics are carrying high oxidative load and damage with compromised anti oxidant mechanisms [21]. Raised GGT indicates a compensatory response to increased oxidative load because it is anti oxidant agent [22]. Raised GGT is seen in the sub clinical inflammation pointing towards the oxidative damage [22,23]. The GGT rises proportionately in response to the oxidative stress; this is because it plays central role in glutathione homeostasis. It breaks down the extracellular glutathione to combat against ROS to save the cell [23-25]. The major limitations of present study are a small sample size and particular ethnicity; hence findings should be cautiously interpreted. Future large scale studies are recommended.

### **CONCLUSION:**

The present study shows positive association of gamma glutamyl transferase with cholesterol, triglycerides and low density lipoprotein (LDLC) but negative association with high density lipoprotein (HDLc). Hence, it is concluded that the gamma glutamyl transferase may be used as an atherogenic biomarker in type 2 diabetic subjects.

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