

ASSOCIATION OF GAMMA GLUTAMYL TRANSFERASE AND BLOOD LIPID
LEVELS IN TYPE 2 DIABETIC SUBJECTSPoonam Bai*¹, Fnu Sandeep², Sateesh Kumar³, Sheena Shiwlani⁴, Roopa Kumari² and Jitesh Kumar⁵¹MBBS, MD, Peoples University of Medical and Health Sciences.²MBBS, Dow University of Medical and Health Sciences.³MBBS, Jinnah Postgraduate Medical Center.⁴MBBS, ISRA University.⁵MBBS, Jinnah Postgraduate Medical Center.***Corresponding Author: Dr. Poonam Bai**

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ABSTRACT

Objective: The present study analyzed the correlation of γ -glutamyl transferase (GGT) with the high density lipoprotein and low density lipoprotein in type 2 diabetics. **Study Design:** Case control study. **Study setting & Duration:** Department of Medicine- LUMHS Jamshoro, from January 2016 to September 2016. **Subjects & Methods:** 100 type 2 diabetics and 100 controls were selected through non-probability (purposive) sampling. Clinical history, physical examination and blood biochemical findings were noted in proforma. Biochemical tests were performed as per standard criteria on Roche Hitachi Chemistry Analyzer. GGT was detected by IFCC method. Data was analyzed at 95% confidence interval on the statistical package SPSS 22.0 (IBM, Incorporation, USA) and Microsoft excel. **Results:** The GGT was noted as 20.44 ± 5.71 and 39.5 ± 5.56 U/L ($P=0.0001$) and the HDLc as 49.15 ± 3.67 and 30.19 ± 10.61 U/L in controls and cases respectively ($P=0.0001$). GGT showed positive correlation with systolic BP, diastolic BP, blood glucose, HbA1c, creatinine, cholesterol, triglycerides and LDLc. Negative correlation was found of GGT with the HDLc ($r = -0.676$, $P=0.0001$). **Conclusion:** The present study found negative correlation of GGT with HDLc but positive correlation with LDLc. Hence, the GGT may be exploited as a simple and inexpensive atherogenic biomarker instead of expensive lipid profile.

KEYWORDS: Gamma-Glutamyl Transferase, HDLc, LDLc, Diabetes Mellitus.**INTRODUCTION**

Exponential rise in the prevalence of Diabetes mellitus (DM) is a major threat to the humanity through the World. DM is multiplying exponentially. Although it is a non-communicable disease but both the incidence and prevalence are rising. DM is a metabolic disorder of blood glucose homeostasis. DM predominates in the male compared to female. Type 2 DM comprises 90% of total diabetic cases through the World. DM is defined as a metabolic disorder of glucose characterized by chronic hyperglycemia caused by insulin deficiency which may be relative or absolute.^[1,2] In 2000, the DM prevalence was 2.8% which is projected to rise by 4.4% by the year 2030. Future estimates show the type 2 DM will raise to 592 million by the year 2035. Current prevalence in Pakistan is worse. Both the incidence and prevalence of type 2 DM are on incline in the country. While the Asian countries are said to be future "Diabetes capital".^[2,3] Diabetics suffer not only from hyperglycemia, but also the hyperlipidemia and dyslipidemia. Hypercholesterolemia, high low density lipoprotein cholesterol (LDLc) and low high density lipoprotein cholesterol (HDLc) put the patients at an increased risk

of coronary artery disease. Dyslipidemia is a major threat to the diabetics for it one of major risk factors of CAD, brain stroke, etc. Dyslipidemia is a change in the lipid fractions and predispose the patients to the CAD.^[4,5] Atherosclerosis is accelerated by the dyslipidemia combined with hypoglycemia. Dyslipidemia milieu is atherogenic, and increases the risk of atherosclerotic vascular disease through the body.^[5,6] Hypoglycemia accelerates the atherosclerosis by cross linking of collagen fibers and matrix proteins of arterial wall through the non-enzymatic glycosylation, this results in the endothelial dysfunction. Thus the hypertriglyceridemia, hyper - LDLc, hypercholesterolemia, and hypo-HDLc and postprandial hyperlipidemia are risk factors of atherosclerosis and CAD. Thus type 2 diabetics are at increased risk of CAD.^[6] The GGT is an enzymes involved in the catalysis of extracellular glutathione.^[7] GGT is located in various organs such as the cardiac muscles, biliary canaliculi and gall bladder, lungs, brain, renal tissue, lungs, liver, etc. In pathological conditions of these organs, its plasma levels are elevated.^[7,8] However, the liver is the major site of GGT activity as it handles the detoxification processes

by utilizing the glutathione. Hepatic dysfunctioning has been closely associated with the type 2 DM, obesity and insulin resistance.^[8,9] Insulin resistance is responsible for the chronic ectopic fat deposition within the hepatocytes, resulting in liver problems (steatohepatitis), and this in turn increases the GGT activity.^[8-10] Estimated serum GGT is a reliable biomarker of steatohepatitis.^[10] As the DM is increasing in Pakistan, there is urgent need to establish cost effective biomarker for screening, diagnosis and prognosis of hyperlipidemia, CAD and liver dysfunction in type 2 diabetics. The present study analyzed the predictive correlation of GGT for the dyslipidemia in general and its association with HDLc in particular. The present study hypothesized that the correlation doesn't exist between the GGT and HDLc if any causal correlation is found; it will benefit the diabetic subjects for an early intervention to prevent diabetic atherosclerosis complications.

SUBJECTS AND METHODS

The present observational case control study analyzed any casual correlation of GGT and HDLc conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital Hyderabad/Jamshoro from January 2016 to September 2016. A research proposal for conducting the study was applied for permission from the ethical review committee of institute and it was approved. Whole protocol of research was planned and researchers were assigned to abide by the protocol and particular responsibilities. 100 normal healthy – age, body weight and gender matched subjects were selected as *control*. While 100 diagnosed cases of type 2 DM were selected for the study purpose. Cases were selected according to pre set inclusion and exclusion criteria. Diagnosed cases of type 2 DM of age ≥ 40 years, diabetes duration >5 years and not taking lipid lowering drugs and willing voluntarily were included. Diabetic with coronary artery disease, chronic renal disease, heart failure, taking diuretics, taking minerals and multivitamin supplements, pulmonary tuberculosis, and smokers were excluded carefully by clinical history. Consent form was mandatory to sign by the volunteer subjects before they were informed about the benefits and losses. They were taken into confidence that the blood samples will be used for biochemical testing only. They were also informed that the personal information and biochemical tests will be kept confidential. Clinical

history was noted on a pre structured patient proforma. Patients were requested to come fasting on the day of blood sampling. After blood sampling they were provided breakfast arranged by the authors. Blood samples for lipids were taken from those having 8-12 hour fasting, this protocol was followed strictly. Biochemical tests were performed as per standard procedure on the Cobas analyzer (e 411), Roche Diagnostics (GmbH, Mannheim, Germany). LDLc (Friedewald's formula),^[11] Blood glucose (glucose oxidase method),^[12] HbA1c, serum creatinine (Jaffe's method), triglycerides and cholesterol (enzymatic colorimetric method), HDLc (precipitant method) and GGT (IFCC method).^[13] Proforma was designed for data collection. Statistical was performed on the software SPSS 22.0 (IBM, Incorporation, USA) and Microsoft excel were used. Data was analyzed using appropriate statistical tests such as; continuous data (Student's t-test), categorical data (Chi square test) and continuous variable correlation (Pearson's correlation) at 95% confidence interval ($P \leq 0.05$).

RESULTS

The present study analyzed 100 controls and cases each. The subjects were age, body weight and gender matched ($P > 0.05$) (table 1). Male and female in controls and cases were noted as 64% & 65% and 36% & 35% respectively ($X^2 = 0.0001$, $P = 0.91$). Systolic BP, Diastolic BP, Blood glucose (Random), Glycated HbA1 (HbA1c) (%), serum creatinine, serum cholesterol, serum triglycerides, low density lipoprotein cholesterol (LDLc), high density lipoprotein cholesterol (HDLc) and gamma glutamyl transferase (GGT) revealed statistically significant differences between controls and cases ($P < 0.05$) (table 1). GGT was noted as 20.44 ± 5.71 and 39.5 ± 5.56 U/L in controls and cases respectively ($P = 0.0001$). Similarly HDLc was noted as 49.15 ± 3.67 and 30.19 ± 10.61 U/L in controls and cases respectively ($P = 0.0001$). Correlation of γ -glutamyl transferase (GGT) with systolic BP, diastolic BP, blood glucose, HbA1c, creatinine, cholesterol, triglycerides, LDLc and HDLc are shown in table 2. GGT showed positive correlation with above parameters except for HDLc. HDLc showed negative correlation with GGT ($r = -0.676$, $P = 0.0001$). Scatter plots 1-4 show the graphical presentation of correlation of GGT with cholesterol, LDLc, HDLc and triglycerides respectively.

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

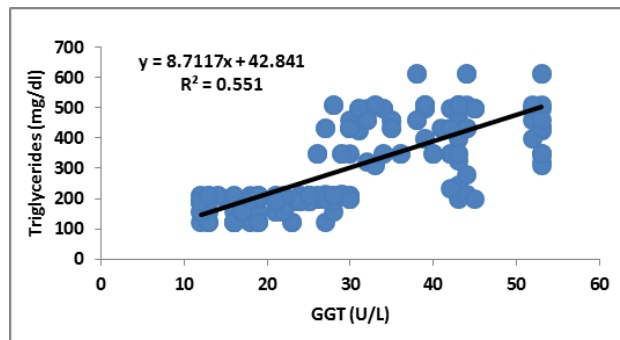
| | Controls (n=100) | Cases (n=100) | P-value |
|-------------------------|-------------------|--------------------|---------|
| Age (years) | 45.5 \pm 7.49 | 44.7 \pm 7.96 | 0.4300 |
| Body weight (kg) | 68.85 \pm 4.70 | 68.5 \pm 5.78 | 0.8900 |
| Systolic BP (mmHg) | 121.0 \pm 3.99 | 141.7 \pm 23.98 | 0.0001 |
| Diastolic BP (mmHg) | 69.0 \pm 5.30 | 78.95 \pm 14.25 | 0.0320 |
| RBG (mg/dl) | 132.1 \pm 8.22 | 243.23 \pm 71.06 | 0.0001 |
| HbA1c (%) | 4.38 \pm 0.89 | 10.33 \pm 2.62 | 0.0001 |
| S. Creatinine (mg/dl) | 0.85 \pm 0.23 | 1.01 \pm 0.28 | 0.0110 |
| S. Cholesterol (mg/dl) | 148.0 \pm 27.13 | 231.3 \pm 34.97 | 0.0001 |
| Triglycerides (mg/dl) | 184.5 \pm 31.13 | 423.8 \pm 99.67 | 0.0001 |
| LDL-cholesterol (mg/dl) | 99.6 \pm 32.16 | 225.72 \pm 78.13 | 0.0001 |

| | | | |
|----------------------------------|------------|-------------|--------|
| HDL- cholesterol (mg/dl) | 49.15±3.67 | 30.19±10.61 | 0.0001 |
| GGT (U/L) | 20.45±5.73 | 39.5±5.56 | 0.0001 |
| GGT- Gamma glutamyl transferase. | | | |

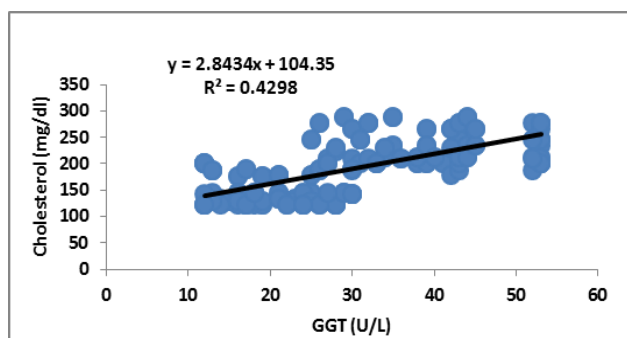
Table. 2: Correlation of Gamma glutamyl-transferase.

| | r-value | p-value |
|--------------------------|-----------|---------|
| Systolic BP (mmHg) | 0.517** | 0.0001 |
| Diastolic BP (mmHg) | 0.430** | 0.0001 |
| RBG (mg/dl) | 0.607** | 0.0001 |
| HbA1c (%) | 0.771** | 0.0001 |
| S. creatinine (mg/dl) | 0.340** | 0.0001 |
| S. cholesterol (mg/dl) | 0.656** | 0.0001 |
| S. triglycerides (mg/dl) | 0.742** | 0.0001 |
| Serum LDLc (mg/dl) | 0.394** | 0.0001 |
| Serum HDLc (mg/dl) | - 0.676** | 0.0001 |

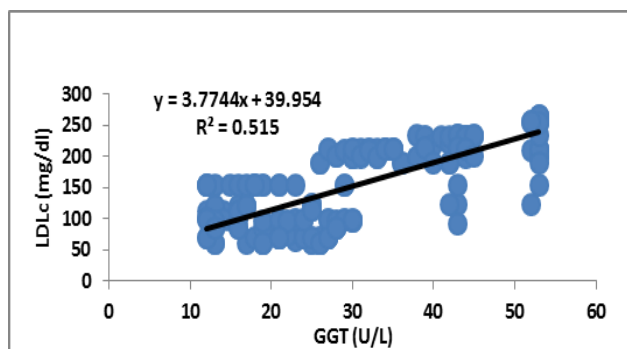
**Correlation is significant at the 0.01 level (2-tailed).



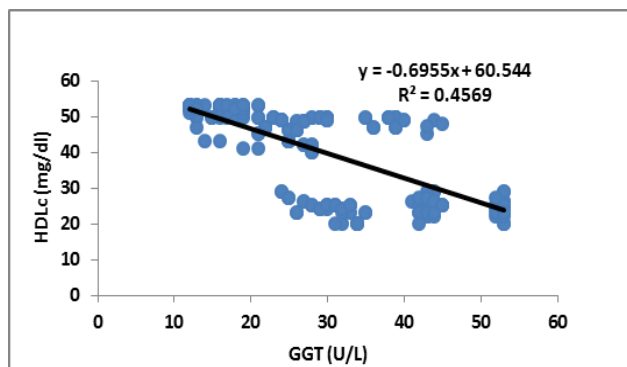
Graph. 4: Scatter plot showing correlation of GGT and triglycerides.



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



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



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

DISCUSSION

The present is the first research which analyzed the correlation of GGT, HDLc and LDLc as an atherogenic risk factor for coronary artery disease in diagnosed cases of type 2 DM at our tertiary care hospital. Correlation of GGT with lipid sub-fractions was analyzed in particular the high density lipoprotein (HDLc) and low density lipoprotein (LDLc). Altered HDLc and LDLc ratio is an established risk factor for the coronary artery disease. The present research investigated the GGT as predictor of HDLc and LDLc and as inexpensive, reliable and alternative biomarkers for CAD.

The GGT was significantly elevated in type 2 diabetics compared to normal healthy controls. In the present study, the GGT was noted as 20.44±5.71 and 39.5± 5.56 U/L in controls and cases respectively (P=0.0001). The finding is consistent with previous studies.^[13,14] The raised serum GGT of present study is supported by previous clinical and animal studies,^[13-15] they reported GGT was found elevated either in type 2 diabetic subjects or in diabetic animal models. Previous studies^[13,16] reported similar correlation of GGT with the triglycerides, LDLc and cholesterol, but only triglycerides proved significant correlation. Similar study^[13] reported negative correlation of GGT with the HDLc. In present study, the HDLc was very low in the cases 30.19± 10.61 mg/dl compared to controls 49.15±3.67 mg/dl (P=0.0001). In present study GGT shows significant positive correlation with cholesterol (r=0.656), triglycerides (r=0.758) and LDLc (r=0.394) and negative correlation with HDLc (r= - 0.676), all correlations were statistically significant (P=0.0001). Correlation is shown graphically in the scatter plots 1-4. Significant positive correlation of triglycerides with GGT of above studies^[13,16] is a consistent finding, while non-significant results of cholesterol and LDL cholesterol is inconsistent with the present study as significant positive correlation was found. Positive correlation of triglycerides and LDL cholesterol corroborate with other previous study also.^[17,18] HDLc revealed negative correlation (r= - 0.676, P=0.0001) with

GGT. Negative association of HDLc with GGT supports above studies.^[13,16] A previous study^[17] reported triglycerides ($r=0.91$, $p=0.02$) correlated positively with GGT while HDLc ($r=-0.192$, $p=0.018$) correlated negatively with GGT. A study from Turkey by Demir *et al.*^[18] observed positive correlation of HDLc with GGT ($r=0.293$, $p=0.039$), but negative association with the cholesterol and LDL cholesterol. These findings disagree with present and previous studies.^[13,16,17] The highly conflicting observations of above study might be due to geographical areas, different dietary habits and ethnicity and study population, however, research bias are seemingly responsible for such controversial results. A study by Latha *et al.*^[19] reported observations of positive correlation of GGT with VLDL, LDL cholesterol and inverse association with HDL cholesterol ($r=-0.773$). These findings corroborate with our present and previous studies.^[13,16,17] Findings by another previous study^[20] significantly corroborate with the present study. They reported GGT and triglycerides ($r=0.112$), LDLc ($r=0.05$) and cholesterol ($r=0.027$) but inverse association with HDLc. In present study the HDL cholesterol showed moderately negative correlation ($r=-0.676$) with GGT which corroborates with the above study.^[20] Elevated serum GGT in type 2 diabetics indicates the oxidative stress in these subjects with a concomitant rise in the antioxidant enzymes.^[21] Reactive oxygen species (ROS) are neutralized by glutathione (GSSH), the reaction is catalyzed by different enzymes, and GGT is one of them. Elevated GGT denotes compensatory rise in the anti oxidant mechanisms against the oxidative stress of diabetics.^[22] This has been reported by other previous studies.^[22,23] The GGT plays pivotal role in the glutathione homeostasis to combat the oxidative stress by neutralizing the ROS.^[23] Small sample size and diabetics of particular ethnicity are the limitations of present research, hence results be interpreted cautiously for other settings. The finding of positive correlation of GGT with LDLc (bad cholesterol) and negative correlation with HDLc (good cholesterol) is a worth finding which may be exploited for clinical prediction of blood lipid profile, tendency of atherogenesis, atherosclerosis and CAD.

CONCLUSION

The present study found negative correlation of GGT with HDLc but positive correlation with LDLc. Hence, the GGT may be exploited as a simple and inexpensive atherogenic biomarker instead of expensive lipid profile. However, further large scale studies are recommended.

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