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GAMMA GLUTAMYL TRANSFERASE AND ITS CORRELATION WITH HIGH DENSITY LIPOPROTEIN IN TYPE 2 DIABETIC SUBJECTS

[1]Om Parkash, [2]Ravi Kumar, [3]Mahmood Khan, [4]Fayaz Hussain Khoso, [5]Kanchan Devi, [6]Rizwan Talpur

[1]Medical officer, Taluqa Hospital, Diplo,Sindh, [2]Sindh Medical College, Karachi, Sindh, [3]Medical officer, Taluqa Hospital, Matli,Sindh, [4]Research Scholar, Department of Pharmacology, University of Sindh Jamshoro, [5] Sindh Medical College Karachi Pakistan, [6]Assistant professor, Department of Physiology, Isra University Hyderabad.

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 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±6.21 and 51.29±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).

Corresponding author:

Om Parkash,

Medical officer, Taluqa Hospital, Diplo,Sindh.

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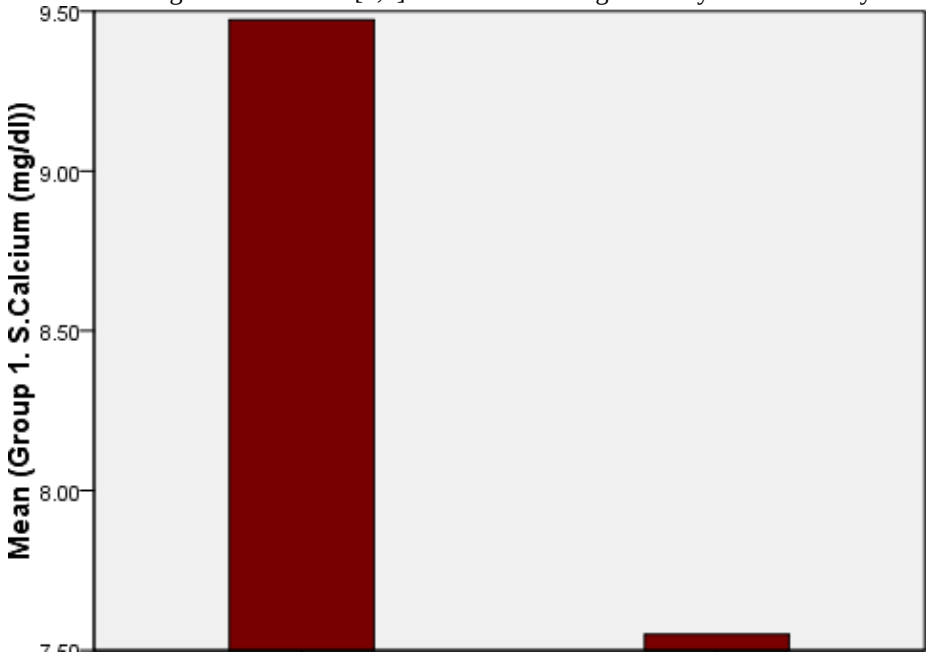
INTRODUCTION:

Diabetes mellitus is one of the most prevalent chronic non-communicable illnesses. It is caused by an error in glucose metabolism. Diabetes mellitus is characterized by persistent hyperglycemia due to absolute or relative deficiency of insulin. Type 2 Diabetes contributes for 90% of total worldwide diabetic case burden. Male gender is affected more than the female. [1] Prevalence of Diabetes estimated in year 2000 was 2.8% worldwide, and it is estimated that it will affect 4.4% of the world population by the year 2030. By the year 2035, total diabetic population is estimated to reach 592 million. Asian countries are thought to be the "Diabetes capital". Prevalence rate and incidence rate of Diabetes is alarming in Pakistan. [2,3] Diabetic subjects are having co-morbid conditions like hypertriglyceridemia, hypercholesterolemia and dyslipidemia. Dyslipidemia is one of the major risk factor in development of coronary artery disease (CAD) in known diabetic patients. Disturbances in the lipid profile is a hallmark of Diabetes mellitus and strong predictor of CAD. [4,5] Hyperglycemia associated with dyslipidemia makes the person prone to atherosclerosis. Coronary artery disease due to atherogenic dyslipidemia is more common in type 2 diabetic subjects. [5,6] Hyperglycemia for longer duration leads to glycosylation of cross linkages in arterial wall collagen fibers and matrix proteins which leads to dysfunction of vascular endothelium and atherosclerosis is accelerated affecting coronary vessels mainly.



Coronary artery disease is commonly associated with hypercholesterolemia, hypertriglyceridemia, hyper-LDLc, and hypo-HDLc along with postprandial hyperlipidemia. This pattern of serum lipid profile in diabetic subjects is commonly known as "diabetic dyslipidemia". [6] The ϒ-transferase (GGT) is a plasma enzyme that catalyzes extracellular glutathione. [7] GGT is present in most of the organs including liver, gall bladder, biliary canaliculi, cardiac muscles, pancreas, kidneys, lungs, brain, etc. GGT is released in blood in state of injury to any of these organs. [7,8] Despite various tissues capable of producing GGT, the commonly detectable GGT in blood is of liver in origin. [8,9] Type 2 Diabetes is associated with hepatocellular dysfunction, insulin resistance, and obesity. Insulin insensitivity on the gluconeogenesis and glycogenolysis pathways is responsible for accelerated glucose production. Studies have reported that raised plasma liver enzymes are associated with chronic fatty changes in liver. [8-10] Serum GGT is a basic and reliable marker for fat deposition in liver and steatohepatitis. Fatty liver is a sign of insulin resistance and long-term insulin resistance is a common feature in type 2 Diabetes. [10] Pakistan is affected by an epidemic of Diabetes mellitus, simultaneously hyperlipidemia and dyslipidemia are also commonly found in the diabetics, hence there is need to explore a cost effective, sensitive and relevant marker of diabetes for screening, diagnosis and prognosis at an earlier stage. In this regard, this study was conducted to explore of correlation of gamma (ϒ) glutamyl transferase (GGT) with serum lipids particularly the

high-density lipoprotein (HDLc) in type 2 diabetic cases.

SUBJECTS AND METHODS:

This is an observational case control study design, which was conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital Hyderabad/Jamshoro from October 2014 till September 2016. The materials for the study were known patients of type 2 DM. 100 known cases of diabetes and 100 non-diabetic subjects- taken as control, were selected through non-probability (purposive) sampling as per inclusion and exclusion criteria. Inclusion criteria was – known cases of type 2 DM, of duration greater than 5 years, which were not having any lipid lowering drug, aged more than or equal to 40 years without any cardiovascular illness. Diabetic subjects having urinary tract infections (UTI), chronic kidney disease (CKD), liver disease, heart failure, pregnancy, alcohol consumers, and smokers were excluded in this study. Consent form was produced in English, Urdu and Sindhi language, readable to various volunteers included in study, which explained the purpose of this study, its merits and demerits and uses of this study and then interviewed. Participants were informed that all pre-diabetic and diabetic subjects can be benefited from this research study. Participants were informed that blood sampling will only be used for biochemical testing mentioned in study. A detailed medical history of subjects and the history of drugs intake and co-morbidities were obtained. Subjects were informed to come 08 to 12 hour fasting in upcoming visit for blood sampling which is mandatory for serum lipid profile accuracy. Biochemical analysis was done on the Cobas analyzer (e 411) and Roche Diagnostics (GmbH, Mannheim, Germany). Age, body weight, blood pressure, fasting blood glucose, HbA1c, serum creatinine, triglycerides, total 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 was done by precipitant method. LDLc was calculated by Friedewald's formula [11]. Blood glucose and Gama- glutamyl transferase (GGT) were detected by glucose oxidase method [12] and IFCC method [13] respectively. Informed written consent was read and obtained by all the volunteers. Ethical approval was obtained from ethical review committee of the institute. A predesigned proforma was used for the data collection. SPSS version 22.0 (IBM, Incorporation) and Graph Pad Prism were used for the statistical analysis. Student`s t-test, Chi square tests and Pearson`s correlation were used for the continuous variables, categorical variables and correlation. Statistical significance was obtained at 95% confidence interval ($P \leq 0.05$).

RESULTS:

A total of 200 volunteers were included in this study and were divided into 2 groups. Group A contains 100 non-diabetic subjects taken as control, while group B contains 100 known diabetic subjects fit in inclusion criteria taken as cases. Mean age of the subjects was noted as 52.23±6.21 years in control and 51.29±4.97 years in cases (P=0.94) (table 1). Gender distribution in control (n=100) was 62 males and 38 female and in cases (n=100) it was 61 males and 39 females (X^2= 0.21, P=0.51). Body weight, blood pressure, fasting blood glucose, HbA1c, serum creatinine, total cholesterol, triglycerides, LDLc, HDLc and GGT are shown in table 1. GGT of the subjects was noted as 20.45±5.73 U/L in control and 36.8± 6.26 U/L in cases (P=0.001) which shows statistically significant difference between the 2 groups. Pearson's correlation showed the positive correlation of GGT with total cholesterol (r=0.652, p=0.0001), triglycerides (r=0.758, p=0.0001) and LDLc (r=0.665, p=0.0001) whereas; negative correlation has been found with HDLc (r= - 0.547, P=0.0001). Graph 1-3 is showing the scatter diagram of GGT with cholesterol, LDLc and HDLc respectively.

Table 1. Characteristics and biochemical findings of study subjects

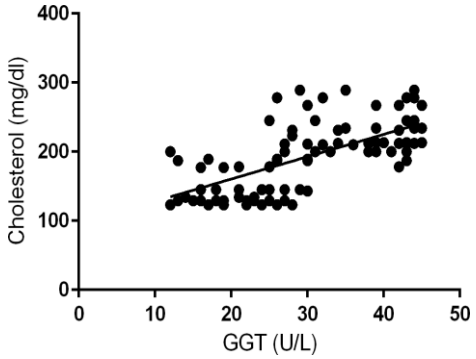
	Controls (n=100)	Cases (n=100)	P-value
Age (years)	52.23±6.21	51.29±4.97	0.94
Body weight (kg)	70.35±5.42	71.65±8.07	0.18
Systolic BP (mmHg)	132.52±9.50	153.90±22.8	0.0001
Diastolic BP(mmHg)	69.05±5.30	85.15±14.07	0.0001
FBG (mg/dl)	93.74±8.64	172.78±47.72	0.0001
HbA1c (%)	5.43±0.80	10.69±2.31	0.0001
S. Creatinine (mg/dl)	0.87±0.17	1.06±0.26	0.0001
S. Total Cholesterol (mg/dl)	149.08±27.98	227.93±34.76	0.0001
Triglycerides (mg/dl)	187.94±29.76	423.53±101.10	0.0001
LDL-c (mg/dl)	90.50±25.91	191.17±32.85	0.0001
HDL-c (mg/dl)	46.67±3.02	30.19±10.61	0.0001
GGT (U/L)	20.45±5.73	36.89±6.26	0.0001

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

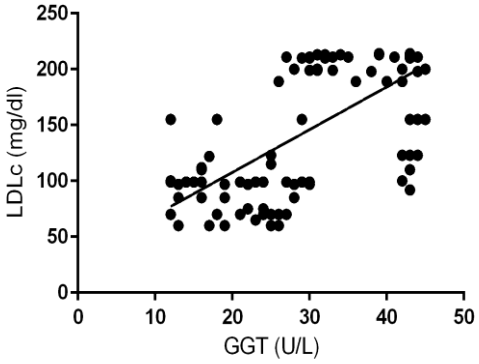
Table 2. Correlation of Gamma glutamyl-transferase

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

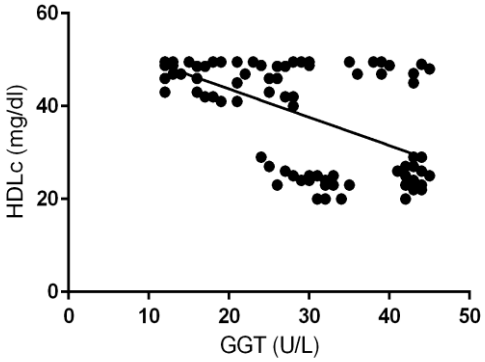
**. Correlation is significant at the 0.01 level (2-tailed).



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



Graph 2. Scatter plot showing correlation of LDLc and GGT



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

DISCUSSION:

The present observational case control study analyzed the association of GGT with lipid sub-fractions particularly the high-density lipoprotein (HDLc) and low density lipoprotein (LDLc). A mismatch between HDLc and LDLc is a known risk factor in development of coronary artery disease (CAD). This study analyzed the association of GGT with HDLc, LDLc and total cholesterol to use it as an inexpensive and reliable alternative biomarker of CAD. Positive correlation of GGT with cholesterol, triglycerides and low density lipoprotein (LDLc) and negative correlation with high density lipoprotein (HDLc) is a worthy clinical finding suggesting its use as an alternative biomarker for atherogenesis in type 2 diabetic subjects. The GGT levels were markedly increased in diabetic subjects as compared to the control, this finding is in accordance with previous studies. [13,14] Other clinical and animal experimental studies have also reported similar findings of raised GGT levels in the type 2 diabetic subjects. [13-15] Kashinakunti et al [13] and Desai et al [16] reported statistically significant positive correlation of GGT with triglycerides, while cholesterol and LDLc showed statistically insignificant positive correlation with GGT (r=0.58, p=0.04), whereas; HDLc showed negative corelation with GGT (r=-0.44, p=-0.30). These findings of significant positive association of GGT with triglycerides and negative association with HDLc are consistent with present study while non-significant association of GGT with LDLc and cholesterol are inconsistent with the present study as we found statistically significant association. [13,16] In present study we found statistically significant 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) and negative correlation with HDLc (r= - 0.547, P=0.0001). Inverse correlation of HDLc with GGT is in accordance with the above studies. [13,16] The findings of correlation of HDLc and triglycerides are in accordance to other previous studies. [17,18] Khan et al [17] reported the positive correlation of GGT with serum triglycerides (r=0.91, p= 0.02) and negative correlation with HDLc (r=- 0.192,

p=0.018), these findings are consistent with the present study. Demir et al [18] from Turkey reported contrasting results with highly significant negative correlation of GGT found with cholesterol and LDLc and significant positive correlation found with triglycerides and HDLc (r=0.293, p=0.039). These highly contrasting results might be due to change in ethnicity, dietary habits, selection criteria, and research bias. Latha et al [19] found positive correlation of GGT with LDLc, VLDL, cholesterol and triglycerides, while negative correlation reported with HDLc (r= -0.773). These findings are in agreement with the present study. Another study [20] reported similar findings with positive correlation of GGT with triglycerides (r=0.112), LDLc (r=0.05) and cholesterol (r=0.027) and negative correlation of GGT with HDLc. We also found a significant negative correlation of serum GGT with HDL lipoprotein (r = -0.547), which corroborate with the above study. Increase in serum GGT levels is supposed to be due to the tissue injury caused by increased reactive oxygen species (ROS) because the diabetes is associated with higher oxidative stress and damage with highly compromised anti- oxidant levels. [21] Compensatory raised GGT levels indicates a negative feedback response to increased oxidative stress due to its anti-oxidant properties. [22] Raised GGT levels are seen in the sub clinical inflammation also indicating towards continued oxidative damage. [22,23] The GGT is released proportionately in response to oxidative stress due to its central role in glutathione homeostasis. Extracellular glutathione is broken down by GGT to combat against ROS to save the cell life. [23-25] The major limitations of the present study are small sample size and particular ethnicity; hence findings should be interpreted cautiously and larger scale studies in future are suggested.

CONCLUSION:

The present study shows gamma glutamyl transferase (GGT) is positively associated with cholesterol, triglycerides and low density lipoprotein (LDLc) and negatively associated with high density lipoprotein (HDLc). Hence, the gamma glutamyl transferase (GGT) may be used as an atherogenic biomarker in type 2 diabetic subjects.

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