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Association of serum gamma glutamyl transferase and high sensitivity C-reactive protein levels with glycemic control in type 2 diabetes mellitus patients

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Abstract
Background and Objectives: Type 2 Diabetes Mellitus has emerged as a difficult health issue due to its rising incidence and rate of complications. Research on Diabetes Mellitus (DM) has mostly focused on understanding the role of oxidative stress and inflammation as underlying mechanisms for pathogenesis and preventing long-term consequences. The study aims to study the association of serum gamma-glutamyl transferase (GGT) and high sensitivity C-Reactive Protein (hs-CRP) levels with glycemic control (HbA1c) in type 2 Diabetes Mellitus patients with controlled Diabetes Mellitus type 2, uncontrolled Diabetes Mellitus type 2 and nondiabetic groups. The correlation between GGT and hs-CRP with glycemic control (HbA1c) was also studied in this research.
Material & Methods: A Hospital based observational study was conducted on 108 subjects which consisted of three groups of whom 36 subjects were type 2 DM patients with HbA1c level less than 7% (Group 1) ,36 subjects were type 2 DM patients with HbA1c level more than 7% (Group 2) and group 3 consisted of age and sex matched healthy subjects. Serum GGT, serum hs-CRP, Fasting Blood Sugar (FBS) and glycated hemoglobin (HbA1c) levels were measured in this study.
Results: The levels of mean serum GGT and serum hs-CRP were significantly raised in type 2 DM patients with poor glycemic control when compared to patients with good glycemic control and normal healthy subjects; p-value <0.001. There is a significant positive correlation between GGT and hs-CRP with HbA1c and also between GGT and hs-CRP.
Conclusions: The present study suggests that serum GGT and hs-CRP concentration is significantly increased in type 2 Diabetes Mellitus. This study suggests that oxidative stress and inflammation plays a crucial role in the pathogenesis and development of complications in type 2 DM patients.

Keywords: Type 2 diabetes mellitus, oxidative stress, inflammation, gamma glutamyl transferase, high sensitivity C- reactive protein

Introduction

Type 2 Diabetes Mellitus is a complicated etiology that includes the interplay of environmental and genetic variables. It involves beta-cell dysfunction and insulin resistance in the liver and muscles, which are the main pathophysiological abnormalities in type 2 Diabetes [1]. Hyperglycemia, which also acts as the disease's definition, is the primary source of the condition's noticeable symptoms as well as its long-term complications. Moreover, there are changes in the metabolism of lipids, carbohydrates, and proteins [2].

Low-grade chronic inflammation is also linked to this risk. Reactive oxygen species production is enhanced by inflammation, which is stimulated by oxidative stress to produce inflammatory mediators [3].

The majority of cells have an outer layer that contains the enzyme gamma-glutamyl transferase (GGT), which facilitates the uptake of glutathione, a crucial part of internal antioxidant defenses. The foundation of intracellular antioxidant defenses is the function of serum GGT in regulating the extracellular glutathione (GSH) transport pathway. Oxidative stress is linked to several pathogenic disorders, such as atherosclerosis, aging, carcinogenesis, inflammation, and reperfusion injury [4, 5].

Serum gamma-glutamyl transferase (GGT) concentrations have been linked to several risk factors for cardiovascular disease or elements of insulin resistance syndrome. Serum GGT leakage has several potential causes, including endothelial cell damage, glycosylation, oxidative stress, and protein breakdown. Thus, people with a little but continuous rise in oxidative and other cellular stress may be identified by elevated serum GGT levels [6].

CRP, a common inflammatory biomarker generated in the liver, is controlled by proinflammatory cytokines originating from adipocytes, such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6). High sensitivity C-Reactive Protein, an acute phase protein that rises with chronic inflammation. The pentraxin family of proteins includes 5 identical non-glycosylated polypeptide subunits that make up CRP [7].

The capacity to represent the cumulative glycemic history of the two to three months prior, the HbA1c is a significant indicator of long-term glycemic management. In individuals with or without diabetes, elevated HbA1c has also been identified as an individual risk factor for coronary heart disease and stroke. A single HbA1c test can yield useful information, making it a dependable biomarker for diabetes diagnosis and prognosis [8].

To compare the serum levels of high sensitivity C-Reactive Protein (hs-CRP, a biomarker of inflammation) and gamma glutamyl transferase (GGT, a biomarker of oxidative stress) in type 2 Diabetes Mellitus patients with good and poor glycemic control and normal healthy individuals, a hospital-based observational study was planned.

Materials and Methods

A hospital based observational study was conducted in Department of Biochemistry, S.M.S Medical College and Hospital in collaboration with Department of General Medicine, SMS Medical College and Hospital from February 2023 to April 2024.

The subjects selected for study were grouped as follows:

Group I: Type 2 Diabetes Mellitus patients with good glycemic control (n=36). This group consisted of patients with type 2 Diabetes Mellitus of age group 45 to 65 years of either sex with duration less than 8 years, HbA1c level less than or equal to 7% (≤ 7%). They were on life style modifications and oral hypoglycemic drugs and free from clinical evidence of any complication of type 2 Diabetes Mellitus.

Group II: Type 2 Diabetes Mellitus patients with poor glycemic control (n=36). This group consisted of patients with type 2 Diabetes Mellitus of age group 45 to 65 years of either sex with duration more than 8 years, HbA1c level more than or equal to 7% (≥ 7%). They are on life style modifications, oral hypoglycemic drugs, insulin or combination of all three and associated with one or more micro-vascular or macro-vascular complication of Diabetes Mellitus.

Group III: Control group (n=36) This group consisted of age and sex matched healthy individuals.

Selection criteria

Inclusion criteria

Cases & Controls-

36 cases of uncontrolled type 2 Diabetes Mellitus patients were included on 1st come 1st basis (Group-II) and 36 reporting cases of controlled type 2 Diabetes Mellitus patients after that were also included (Group-I) and 36 age and sex matched healthy individuals were included as control group (Group- III).

Exclusion Criteria

- Type 1 Diabetes Mellitus.
- All alcoholics, patients with known liver or gastrointestinal diseases, acute coronary syndrome.
- Patients on corticosteroids, Anti Tubercular Treatment drugs, Anti-epileptic drugs, methotrexate, amiodarone, tamoxifen or other hepatotoxic drugs.
- Any chronic infection like tuberculosis and inflammatory diseases like sarcoidosis, etc.
- Hemolytic anemia.

Ethical considerations

Approval by the institutional ethical committee was obtained. The objectives of the study were explained to all eligible subjects included in the study. Informed consent was taken from all participants.

Sample collection and storage

- After obtaining the consent, required data from the patient were obtained. By using aseptic precautions blood was collected from antecubital vein after 8 to 12 hours of fasting.
- 2ml blood was taken in EDTA vial for CBC and ESR.
- 2ml blood was taken in EDTA vial for glycated hemoglobin estimation (HbA1c).
- 5ml blood was taken in plain vial and left for clotting for one hour. It is then centrifuged at 3500 rpm for 10 minutes. Serum was separated and stored at 2-8^{0}C temperature. The remaining investigations biochemistry were performed with the serum.

Following parameters were estimated-

- Serum Gamma Glutamyl Transferase (GGT)
- Serum high sensitivity C-Reactive Protein (hs-CRP)
- Fasting blood sugar (FBS)
- Glycated hemoglobin (HbA1c)

Sample Analysis

- Serum Gamma Glutamyl Transferase levels were measured on AU 680 Analyzer by IFCC SZASZ method.
- Serum high sensitivity C-Reactive Protein (hs-CRP) levels were measured by antigen-antibody reaction by fluorescence immunoassay technology.
- Fasting Blood sugar levels were measured on AU 680 Analyzer by Glucose Oxidase - Peroxidase (GOD-POD) method.
- Glycated Hemoglobin levels (HbA1c) were measured on AU 680 Analyzer by Latex Turbidometric assay.

Statistical Analysis

The data was analyzed by using SPSS software version 25.0. Data was entered in MS excel sheet. Continuous data was summarized in form of mean and standard deviation, difference in between means was anlaysed using ANOVA. The correlation of Gamma Glutamyl Transferase (GGT) and high sensitivity C-Reactive Protein(hs-CRP) with glycated hemoglobin (HbA1c) was analysed using Pearson's correlation coefficient. Qualitative data was depicted using bar chart. The level of significance was kept 95% for all statistical anlaysis.

Results

Our study shows the mean hs-CRP levels for individuals with good glycemic control and poor glycemic control were significantly raised when compared to the control group. There was a significant difference between the hs-CRP levels between the three groups, p-value <0.001.

Table 1: Comparison of mean hs-CRP (mg/L) between the 3 groups

Groups	N	Mean	Std. Deviation	p-Value (Significance)
Good Glycemic Control	36	2.406	0.9683	<0.001
Poor Glycemic Control	36	4.717	0.8843	<0.001
Control Group	36	1.028	0.2337	<0.001

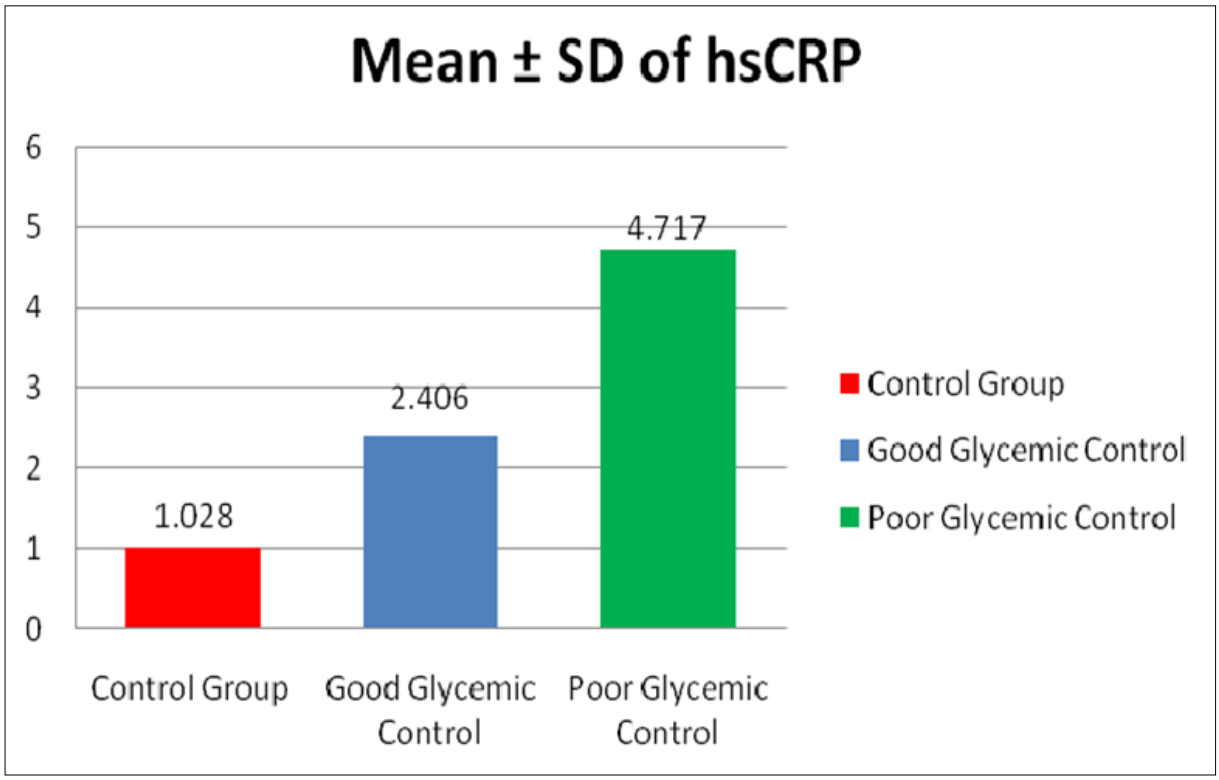

Fig 1: Graphical representation of Mean± SD of Serum hs-CRP in the 3 groups

The mean serum GGT levels were also increased in individuals with poor glycemic control and good glycemic control when compared to the control group. There was a significant difference between the serum GGT levels between the three groups, p value <0.001.

Table 2: Comparison of serum GGT (U/L) between the 3 groups

Groups	N	Mean	Std. Deviation	p-Value (Significance)
Good Glycemic Control	36	29.578	8.6932	<0.001
Poor Glycemic Control	36	40.536	9.5790	<0.001
Control Group	36	23.439	5.4025	<0.001

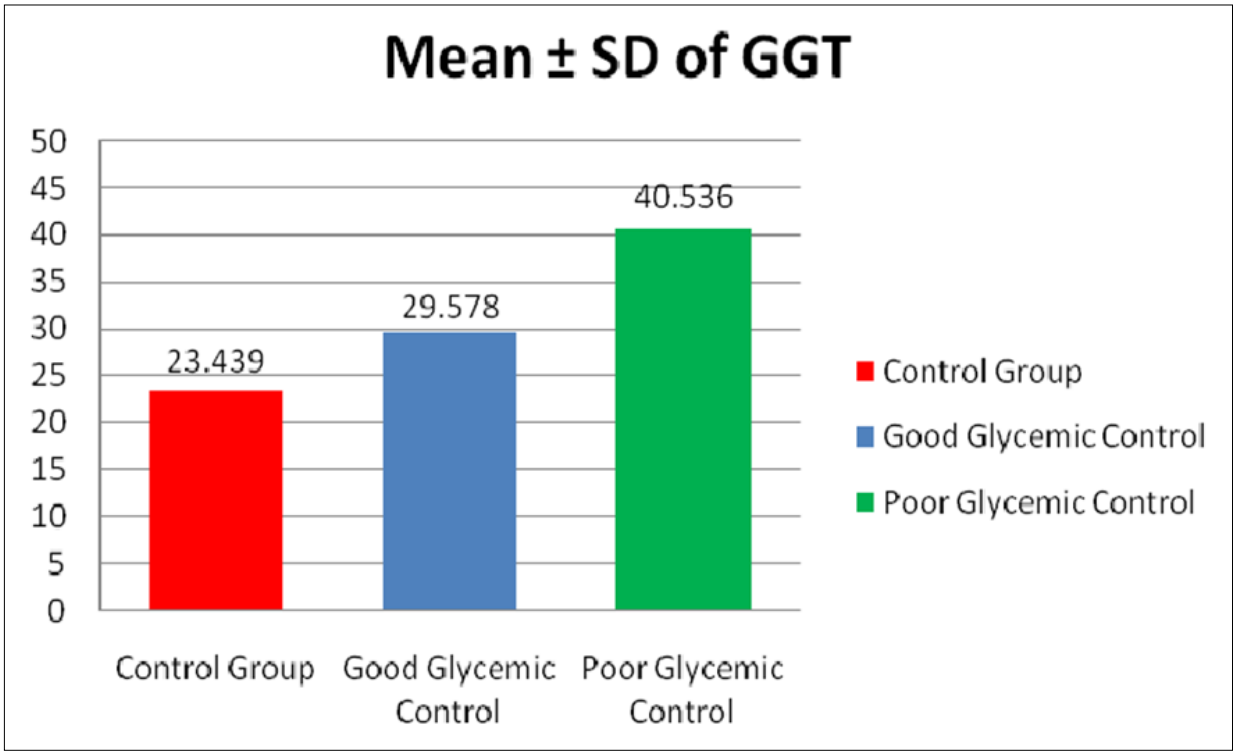

Fig 2: Graphical representation of Mean± SD of Serum GGT in the 3 groups

The mean serum HbA1c levels and fasting blood sugar levels (FBS) were also significantly raised in poor glycemic control and good glycemic control subjects when compared to normal healthy subjects, p-value < 0.001.

Table 3: Comparison of serum HbA1c (%) and fasting blood sugar (mg/dl) levels between the 3 groups

Parameters	Groups	N	Mean	Std. Deviation	P value (significance)
HbA1c	Good Glycemic Control	36	6.300	0.3942	<0.001
	Poor Glycemic Control	36	8.261	0.9141	<0.001
	Control Group	36	5.117	0.3291	<0.001
FBS	Good Glycemic Control	36	119.92	17.982	<0.001
	Poor Glycemic Control	36	190.36	63.021	<0.001
	Control Group	36	89.78	5.509	<0.001

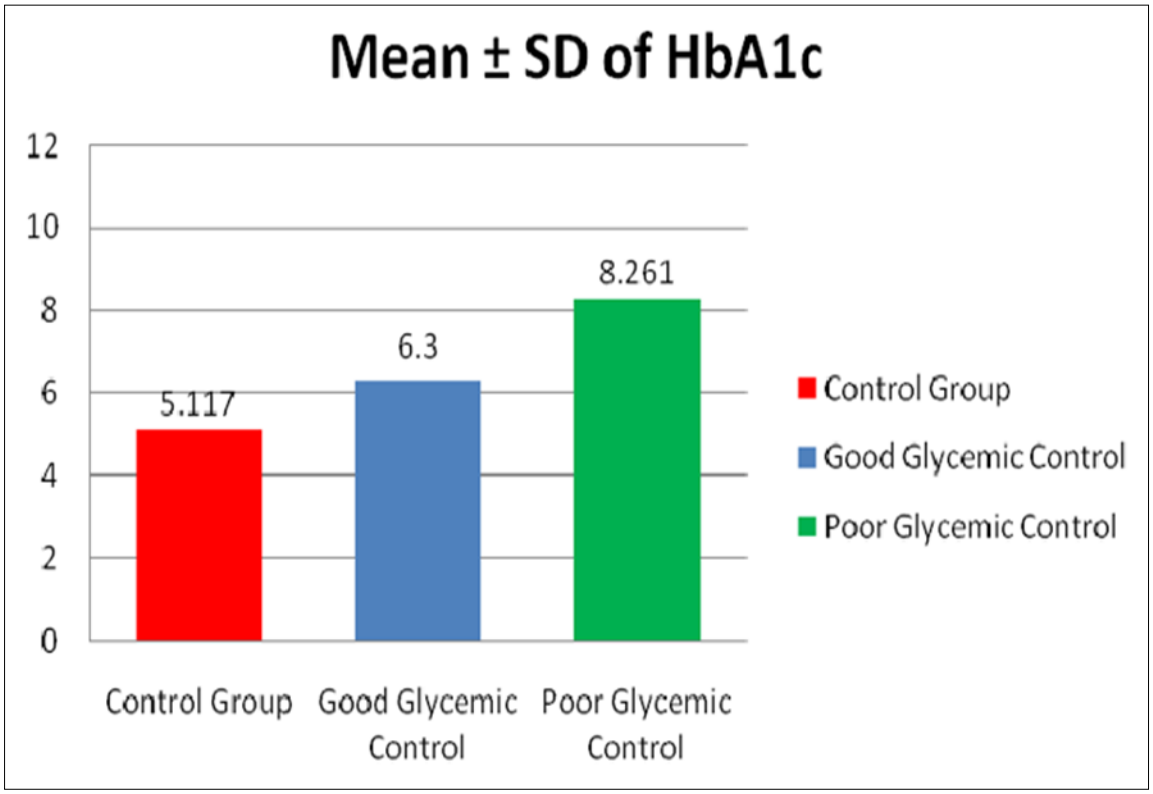

Fig 3: Graphical representation of Mean± SD of Serum HbA1c in the 3 groups

The Pearson correlation was applied to compare hs-CRP and GGT with HbA1c in diabetic patients, the positive correlation between hs-CRP and HbA1c was found to be significant and very strong (r value= 0.860), GGT and HbA1c was found to be significant and strong (r = 0.799) and correlation between hs-CRP and GGT was found to be significant and strong (r = 0.785) (p-value < 0.001).

Table 4: Table showing Pearson's correlation between GGT, hs-CRP and HbA1c

		hsCRP	GGT	HbA1c
hsCRP	Pearson Correlation Sig. (2-tailed) N	-108	0.785** 0.001 108	0 860** 0.001 108
GGT	Pearson Correlation Sig. (2-tailed) N	785** 0.001 108	-108	799** 0.001 108
HbA1c	Pearson Correlation Sig. (2-tailed) N	0 860** 0.001 108	0.799** 0.001 108	-108

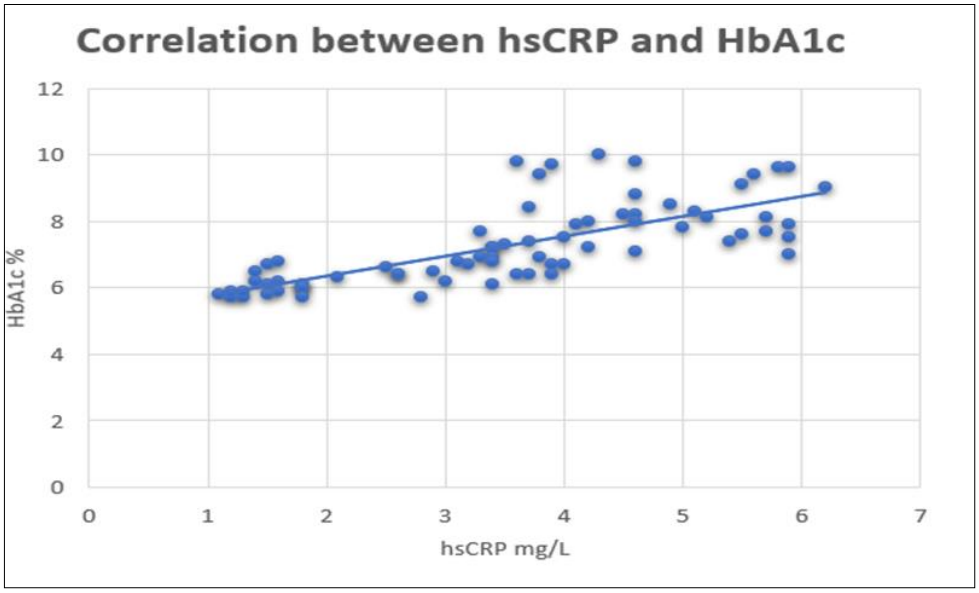

Fig. 4: Pearson's Correlation between hs-CRP and HbA1c

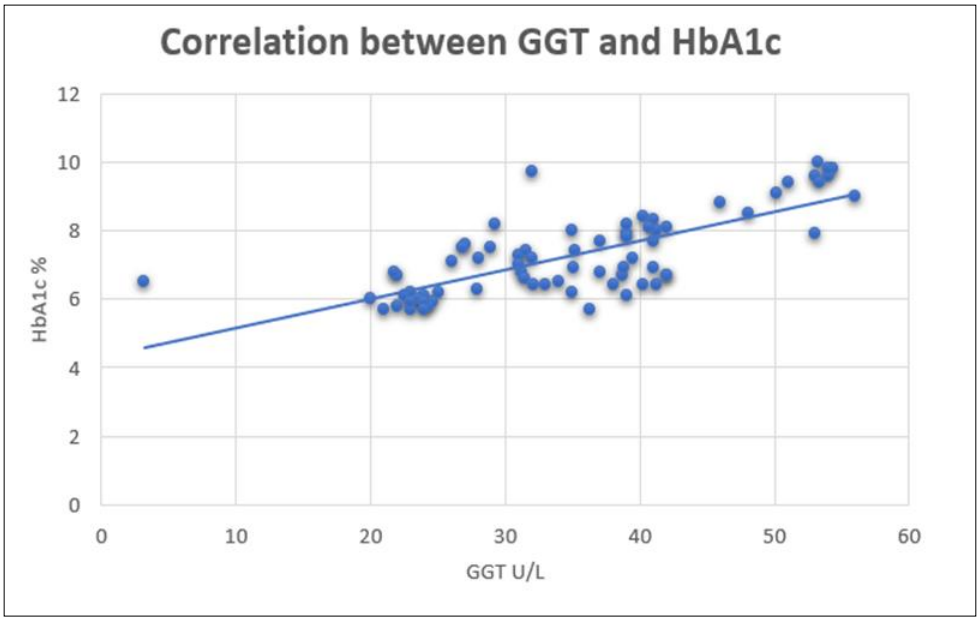

Fig 5: Pearson's Correlation between GGT and HbA1c

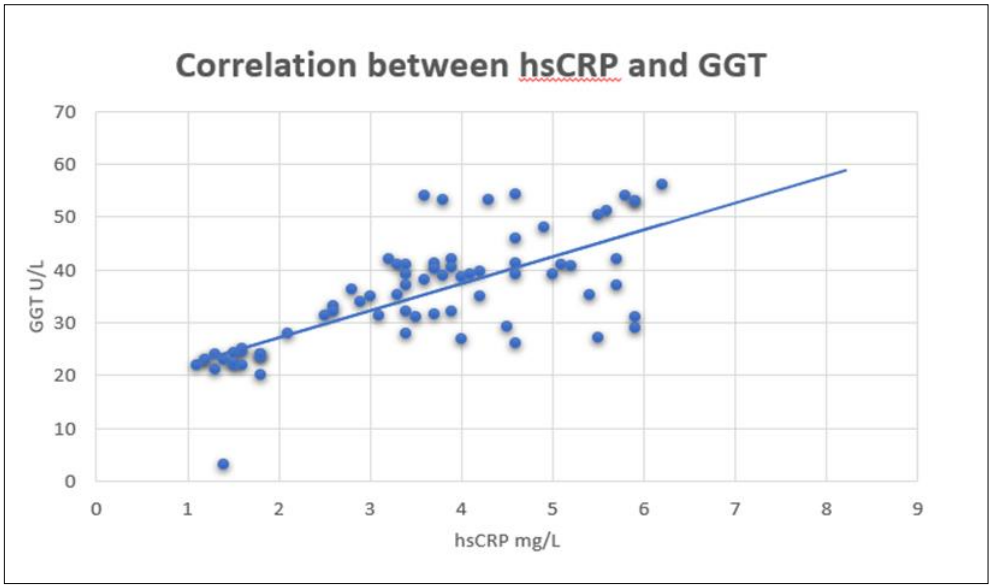

Fig 6: Pearson's Correlation between GGT and hs-CRP

Discussion

The present study was carried out to assess hs-CRP as an inflammatory marker and serum GGT as a measure of oxidative stress in type 2 diabetes patients with good glycemic control, poor glycemic control and normal healthy control group.

The present study shows a significant increase in GGT levels in patients with poor and good glycemic control compared to normal healthy control group, p-value < 0.001. In Sangappa Virupaxappa Kashina Kunti et al.'s study, the serum GGT level of diabetes patients was considerably greater than that of the healthy control group [9]. Arun Nanditha et al. demonstrated that incident diabetes cases had much higher baseline GGT, and came to the conclusion that GGT is an independent predictor of incident diabetes [10].

Gamma-glutamyl transferase may have a part in the pathogenesis and development of type 2 Diabetes Mellitus, according to research by D Rajarajeswari et al [11]. Serum GGT and FPG exhibited a strong association ($p<0.01$) in a study by Azhar Iqbal et al., suggesting that greater GGT is linked to a higher risk of type 2 diabetes and the metabolic syndrome [12]. GGT levels have been connected in the past to risk factors for cardiovascular disease, including physical inactivity, obesity, hypertension, and dyslipidemia [13].

The present study shows a significant increase in serum hsCRP levels in patients with poor glycemic control and good glycemic control when compared to normal healthy control group, p-value < 0.001. In their research, Anubha Mahajan et al. discovered that the median hs-CRP levels in men and women with diabetes were considerably greater than those in non-diabetics ($p<0.0001$) [14]. Sarinnapakorn V et al. discovered a correlation between HbA1c and hs-CRP levels, patients with hsCRP levels of 1 mg/dL or greater had significantly higher mean HbA1c levels ($p<0.001$) [15].

The median hs-CRP levels were found to be substantially higher in diabetic men and women than in non-diabetic individuals by Abha Gupta et al in their study, greater hs-CRP was found to be positively linked in their study with both greater HbA1c and fasting hyperglycemia. They came to the conclusion that increased hs-CRP levels may be a predictor of type 2 diabetes development [16].

Dilshad Ahmed Khan et al. found that, in comparison to controls, diabetes patients had significantly higher median values for HbA1c (7.9 vs. 4.9), hs-CRP (6.0 vs. 2.12) and GGT (29.50 vs. 22.50). HbA1c and hs-CRP and GGT exhibited a favorable connection ($p<0.001$) [17].

In the present study along with both HbA1c, there is a strong positive linear correlation between GGT and hs-CRP levels. These results point to a connection between oxidative stress (represented by elevated serum GGT concentration), inflammation (represented by elevated hs-CRP concentration), and glycemic control in type 2 diabetes patients.

Conclusion

The present study suggests that serum GGT and hs-CRP concentration are significantly increased in type 2 Diabetes Mellitus. Both are further increased in diabetic patients with poor glycemic control. There is a significant positive correlation between serum GGT activity and hs-CRP. Serum GGT level and hs-CRP concentration were independently and positively correlated with FBS and HbA1c (markers of glycemic control).

The increased levels of hs-CRP could lead to increased cardiovascular risk, thus monitoring of hs-CRP levels would help in early detection of diabetic complications in patients. Estimation of GGT in diabetic patients can reflect the oxidative stress in patients, which is the underlying mechanism for diabetes and diabetic complications.

Thus, this study could serve as a diagnostic instrument in the management of patients suffering with type- 2 diabetes mellitus by early recognition of the patient′s condition and prevention and progression of complications.

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