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Original Research Article

STUDY OF SERUM GGT ACTIVITY LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH GOOD AND POOR GLYCEMIC CONTROL

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ABSTRACT

Background

Diabetes is a chronic condition caused by either an absolute lack of insulin or a relative lack of insulin due to impaired insulin secretion and action. Insulin resistance and glucose intolerance results in chronic hyperglycemia and alterations in lipid and protein metabolism. Serum GGT is cell surface protein which has antioxidant property and catabolises extracellular glutathione. Recent prospective studies have suggested that an elevated level of GGT enzyme is associated with subsequent development complications of Diabetes.

Material and Methods

This is a Prospective and observational study. Patients with clinical features of diabetes mellitus admitted in medicine department, KIMS will be taken for study. Total 210 patients presenting with history ,characterstic clinical signs and symptoms of diabetes mellitus are taken into study and the following investigation will be done in selected patients. Group I – Control group (n=70) This group consists of age and sex matched healthy subjects. They are taken from general population. Group II – Type 2 DM patients with good glycemic control (n=70) This group consists of patients with type 2 DM with duration less than 8 years, HbA1c level less than 7%. They are on life style modifications and oral hypoglycemic drugs and free from clinical evidence of any complication of diabetes mellitus. Group III – Type 2 DM patients with poor glycaemic control (n=70).This group consists of patients with type 2 DM with duration more than 8 years, HbA1c level more than 7.1%. They are on life style modifications, oral hypoglycemic drugs, insulin or combination of all three and associated with one or more microvascular or macrovascular complication of diabetes mellitus.

Result

There were 41 males and 29 females in Group I, 39 males and 31 females in Group II, and 36 males and 34 females in Group III. There were 2 patients in age group of 21-30 years, 14 patients in age group of 31-40 years, 37 patients in age group of 41-50 years, 86 patients in age group of 51-60, 62 patients in age group of 61-70 years and 9 patients in age group of 71-

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80 years. There was no statistically significant difference between the Groups and hence they were comparable in demographic parameters. Mean GGT in Group 1 was 20.93 4.39 U/L, in Group 2 was 36.05 6.53 U/L, in Group 3 was 47.06 6.09 U/L.

Conclusion

There was positive correlation between FBS, PPBS, HbA1c and GGT,FBS, PPBS, HbA1c, indicating increasing oxidative stress and inflammation in patients poor glycemic control in Diabetes Mellitus. There was positive correlation between GGT and hsCRP in Diabetes Mellitus indicating linear relation between oxidative stress and inflammation.

Keywords: hsCRP, GGT, Oxidative stress, Diabetes Mellitus Type 2

INTRODUCTION

The rising prevalence of Diabetes poses a medical challenge globally and especially in developing countries as almost 80% of diabetes occur in these countries. [1] Diabetes is attaining pandemic proportions in India. [2] India has the largest diabetes population thus becoming Diabetes capital of the world, with an estimated 42 million patients comprising 6% of adult population and this number is expected to reach 79.4 million in 2030. [3]

Diabetes is a chronic condition caused by either an absolute lack of insulin or a relative lack of insulin due to impaired insulin secretion and action. [4] Insulin resistance and glucose intolerance results in chronic hyperglycemia and alterations in lipid and protein metabolism. [5] These metabolic anomalies can lead to consequences like cardiovascular disease, retinopathy, nephropathy, and neuropathy in the long run. [6-9] Diabetes mellitus (DM) is very common in all age groups, worldwide. In 2015, 415 million individuals worldwide were diagnosed with diabetes, and by 2040, that figure is predicted to climb to 642 million. [10]

The type II DM epidemic globally is result of changing lifestyles &societal influences. Pathologically, Type 2 Diabetes results from the interaction between a genetic predisposition, behavioral and environmental risk factors. [11] Although the genetic basis of type 2 diabetes has yet to be identified, there is strong evidence that such modifiable risk factors such as obesity and physical inactivity are the main non-genetic determinants of the disease. [12]

Understanding the pathogenesis and preventing long term complications have been major goals of research in Diabetes Mellitus. [13] Oxidative stress and inflammation appears to be a key component of many reactions associated with poor glycemic control and further pathogenesis of Diabetes and its complications. [14]

Understanding serum markers linked to diabetes, such as GGT, becomes critical in this situation. Serum GGT is an antioxidant protein that catabolizes extracellular glutathione. protein and GGT enzyme is linked to diabetes complications in life. [15] The goal of this study is to look at the levels of serum GGT in Type 2 Diabetic patients and see if there's a link between good glycemic management and inflammatory markers.

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METHODOLOGY

This is a Prospective and observational study. Patients with clinical features of diabetes mellitus admitted in medicine department, KIMS will be taken for study

Methods of collecting data : 210 patients presenting with history ,characterstic clinical signs and symptoms of diabetes mellitus are taken into study and the following investigation will be done in selected patients. The following examination findings are noted in these patients.

- Blood pressure and BMI.
- Complete hemogram
- RFT, serum electrolytes
- Liver function test
- HIV, HBsAg
- ECG
- 2DEcho
- Lipid profile
- LFT
- Serum GGT
- Serum hsCRP

Inclusion criteria

– The subjects selected for study were grouped as follows:

- **Group I** – Control group (n=70) This group consists of age and sex matched healthy subjects. They are taken from general population.
- **Group II** – Type 2 DM patients with good glycemic control (n=70) This group consists of patients with type 2 DM with duration less than 8 years, HbA1c level less than 7%. They are on life style modifications and oral hypoglycemic drugs and free from clinical evidence of any complication of diabetes mellitus.
- **Group III** – Type 2 DM patients with poor glycaemic control (n=70).This group consists of patients with type 2 DM with duration more than 8 years, HbA1c level more than 7.1%. They are on life style modifications, oral hypoglycemic drugs, insulin or combination of all three and associated with one or more microvascular or macrovascular complication of diabetes mellitus.

Exclusion criteria

1. Type 1 diabetes mellitus
2. All alcoholics, patients with known liver or gastrointestinal diseases, Acute coronary syndrome
3. Patients on corticosteroids, ATTdrugs, Antiepileptic drugs, methotrexate, amiodarone other hepatotoxic drugs
4. Any chronic infection like tuberculosis & inflammatory diseases like sarcoidosis etc.

Sample size : A study consists of 210 subjects,out of them 70 patients having type 2 DM with good glycemic control (Group 2),70 patients with type 2 DM with poor glycemic control and 70 normal healthy control (Group1) were selected.

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Statistical analysis : Continuous variables were presented as mean for parametric data and median if the data is non parametric or skewed. Student t test was applied for calculation of statistical significance whenever the data followed normative distribution. Mann whitney test was applied whenever data followed non normative distribution. Categorical variables was expressed as frequencies and percentages. Nominal categorical data between the groups was compared using Chi-square test or Fisher's exact test as appropriate.

RESULTS

Table.1 Association Between Group and Age

Age	Group				Chi-Squared Test	
	1	2	3	Total	$\chi 2$	P Value
21-30 Years	2 (2.9%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	46.727	<0.001
31-40 Years	12 (17.4%)	2 (2.8%)	0 (0.0%)	14 (6.7%)		
41-50 Years	21 (30.4%)	12 (16.9%)	4 (5.7%)	37 (17.6%)		
51-60 Years	23(32.8%)	30 (42.3%)	34 (48.6%)	86 (41.0%)		
61-70 Years	10 (14.5%)	24 (34.2%)	27 (38.6%)	62 (29.5%)		
71-80 Years	2 (2.9%)	2 (2.8%)	5 (7.1%)	9 (4.3%)		
Total	70 (100.0%)	70 (100.0%)	70 (100.0%)	210 (100.0%)		

There were 2 patients in age group of 21-30 years, 14 patients in age group of 31-40 years, 37 patients in age group of 41-50 years, 86 patients in age group of 51-60, 62 patients in age group of 61-70 years and 9 patients in age group of 71-80 years. There was no statistically significant difference.

Table.2 Association Between Group and Gender

Gender	Group				Chi-Squared Test	
	1	2	3	Total	$\chi 2$	P Value
Male	41 (59.4%)	39 (54.9%)	36 (51.4%)	116 (55.2%)	0.902	0.637
Female	29 (40.6%)	31 (45.1%)	34 (48.6%)	94 (44.8%)		
Total	70 (100.0%)	70 (100.0%)	70 (100.0%)	210 (100.0%)		

59.4% of the participants in the group [Group: 1] had [Gender: Male]. 40.6% of the participants in the group [Group: 1] had [Gender: Female]. 54.9% of the participants in the group [Group: 2] had [Gender: Male]. 45.1% of the participants in the group [Group: 2] had

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[Gender: Female]. 51.4% of the participants in the group [Group: 3] had [Gender: Male]. 48.6% of the participants in the group [Group: 3] had [Gender: Female].

Table.3 Comparison of the 3 Subgroups of the Variable Group in Terms of Duration Of Diabetes (Years)

Duration Of Diabetes (Years)	Group			Kruskal Wallis Test	
	1	2	3	χ2	p value
Mean (SD)	NaN (NA)	5.88 (1.69)	13.00 (3.52)	98.063	<0.001
Median (IQR)	NA (NA-NA)	6 (5-7)	13 (10-16)		
Range	Inf - -Inf	3 - 15	6 - 21		

The mean (SD) of Duration Of Diabetes (Years) in the Group: 1 group was NaN (NA). The mean (SD) of Duration Of Diabetes (Years) in the Group: 2 group was 5.88 (1.69). The mean (SD) of Duration Of Diabetes (Years) in the Group: 3 group was 13.00 (3.52). The median (IQR) of Duration Of Diabetes (Years) in the Group: 1 group was NA (NA-NA). The median (IQR) of Duration Of Diabetes (Years) in the Group: 2 group was 6 (5-7). The median (IQR) of Duration Of Diabetes (Years) in the Group: 3 group was 13 (10-16). The Duration Of Diabetes (Years) in the Group: 1 ranged from Inf - -Inf. The Duration Of Diabetes (Years) in the Group: 2 ranged from 3 - 15. The Duration Of Diabetes (Years) in the Group: 3 ranged from 6 - 21. There was a significant difference between the 3 groups in terms of Duration Of Diabetes (Years) ($\chi2$ = 98.063, p = <0.001), with the mean Duration Of Diabetes (Years) being highest in the Group: group.

Table.4 Comparison of the 3 Subgroups of the Variable Group in Terms of S. GGT (U/L)

S. GGT (U/L)	Group			Kruskal Wallis Test	
	1	2	3	χ2	p value
Mean (SD)	20.93 (4.37)	36.05 (6.53)	47.06 (6.09)	160.831	<0.001
Median (IQR)	21 (17.8-23.5)	36.56 (34.26-38.8)	47.15 (43.2-52.25)		
Range	12.5 - 33.2	15.7 - 55.6	24.7 - 57.8		

The mean (SD) of S. GGT (U/L) in the Group: 1 group was 20.93 (4.37). The mean (SD) of S. GGT (U/L) in the Group: 2 group was 36.05 (6.53). The mean (SD) of S. GGT (U/L) in the Group: 3 group was 47.06 (6.09). The median (IQR) of S. GGT (U/L) in the Group: 1 group was 21 (17.8-23.5). The median (IQR) of S. GGT (U/L) in the Group: 2 group was 36.56 (34.26-38.8). The median (IQR) of S. GGT (U/L) in the Group: 3 group was 47.15 (43.2-52.25). The S. GGT (U/L) in the Group: 1 ranged from 12.5 - 33.2. The S. GGT (U/L) in the Group: 2 ranged from 15.7 - 55.6. The S. GGT (U/L) in the Group: 3 ranged from 24.7 - 57.8. There was a significant difference between the 3 groups in terms of S. GGT (U/L) ($\chi2$ = 160.831, p = <0.001), with the median S. GGT (U/L) being highest in the Group: 3 group.

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Table.5 Comparison of the 3 Subgroups of the Variable Group in Terms of HbA1c (%)

HbA1c (%)	Group			Kruskal Wallis Test	
	1	2	3	$\chi 2$	p value
Mean (SD)	5.37 (0.38)	6.63 (0.34)	9.07 (1.28)	181.645	<0.001
Median (IQR)	5.32 (5.1-5.61)	6.66 (6.44-6.88)	8.88 (8.05-9.65)		
Range	4.54 - 6.78	5.98 - 7.9	6.51 - 13.45		

The mean (SD) of HbA1c (%) in the Group: 1 group was 5.37 (0.38). The mean (SD) of HbA1c (%) in the Group: 2 group was 6.63 (0.34). The mean (SD) of HbA1c (%) in the Group: 3 group was 9.07 (1.28). The median (IQR) of HbA1c (%) in the Group: 1 group was 5.32 (5.1-5.61). The median (IQR) of HbA1c (%) in the Group: 2 group was 6.66 (6.44-6.88). The median (IQR) of HbA1c (%) in the Group: 3 group was 8.88 (8.05-9.65). The HbA1c (%) in the Group: 1 ranged from 4.54 - 6.78. The HbA1c (%) in the Group: 2 ranged from 5.98 - 7.9. The HbA1c (%) in the Group: 3 ranged from 6.51 - 13.45. There was a significant difference between the 3 groups in terms of HbA1c (%) ($\chi 2 = 181.645$, p = <0.001), with the median HbA1c (%) being highest in the Group: 3 group.

Table.6 Correlation between S. GGT (U/L) and HbA1c (%)

Correlation	Spearman Correlation Coefficient	P Value
S. GGT (U/L) vs HbA1c (%)	0.8	<0.001

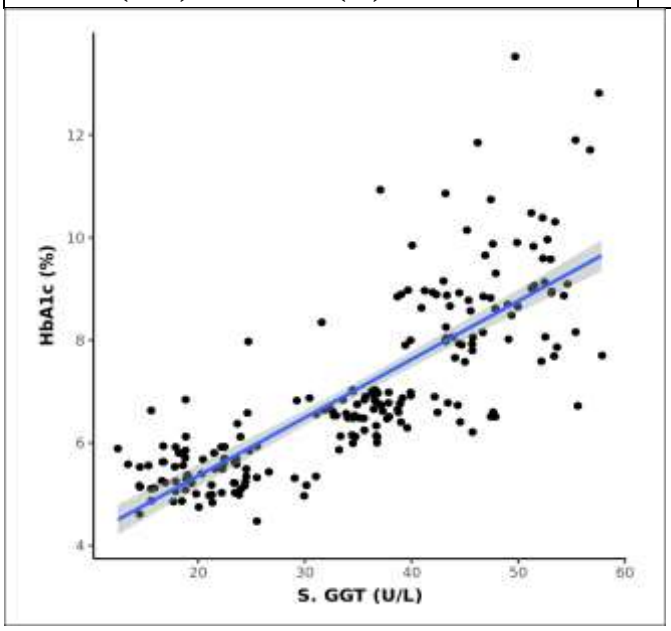

Fig.18 Correlation between S. GGT (U/L) and HbA1c (%)

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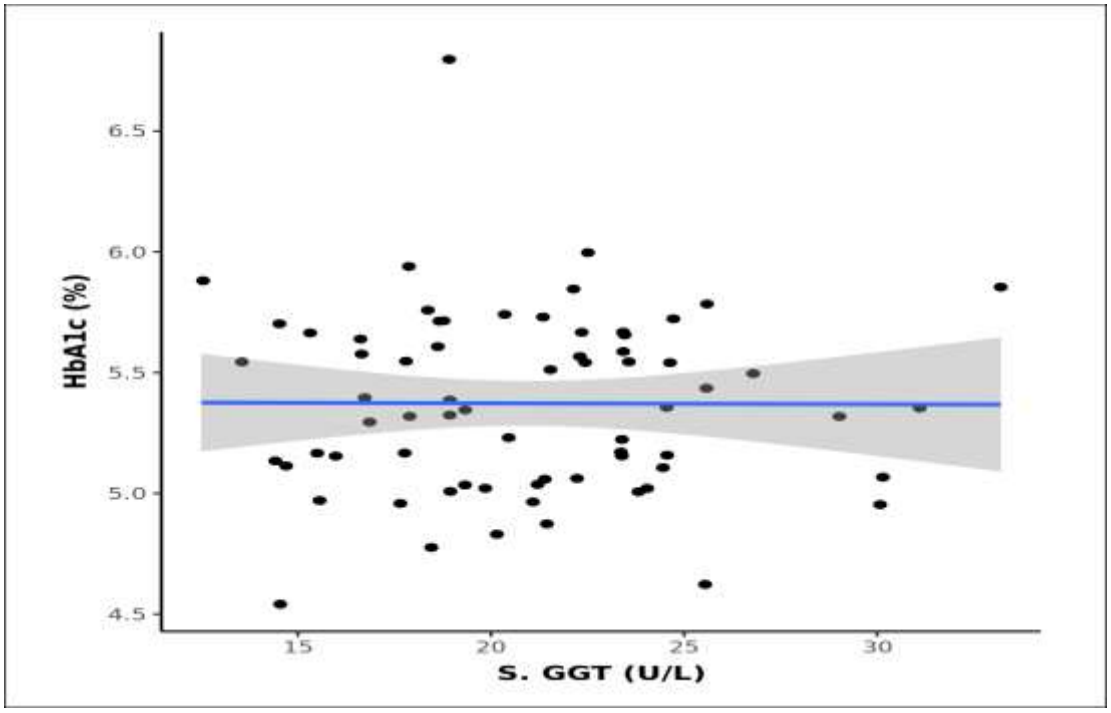
The above scatterplot depicts the correlation between S. GGT (U/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline. Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a strong positive correlation between S. GGT (U/L) and HbA1c (%), and this correlation was statistically significant (rho = 0.85, p = <0.001).
For every 1 unit increase in S. GGT (U/L), the HbA1c (%) increases by 0.11 units.
Conversely, for every 1 unit increase in HbA1c (%), the S. GGT (U/L) increases by 5.60 units.

Table.7 Correlation between S. GGT (U/L) and HbA1c (%) in (Group: 1)

Correlation	Spearman Correlation Coefficient	P Value
S. GGT (U/L) vs HbA1c (%)	0.0	0.776



The above scatterplot depicts the correlation between S. GGT (U/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline. Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally

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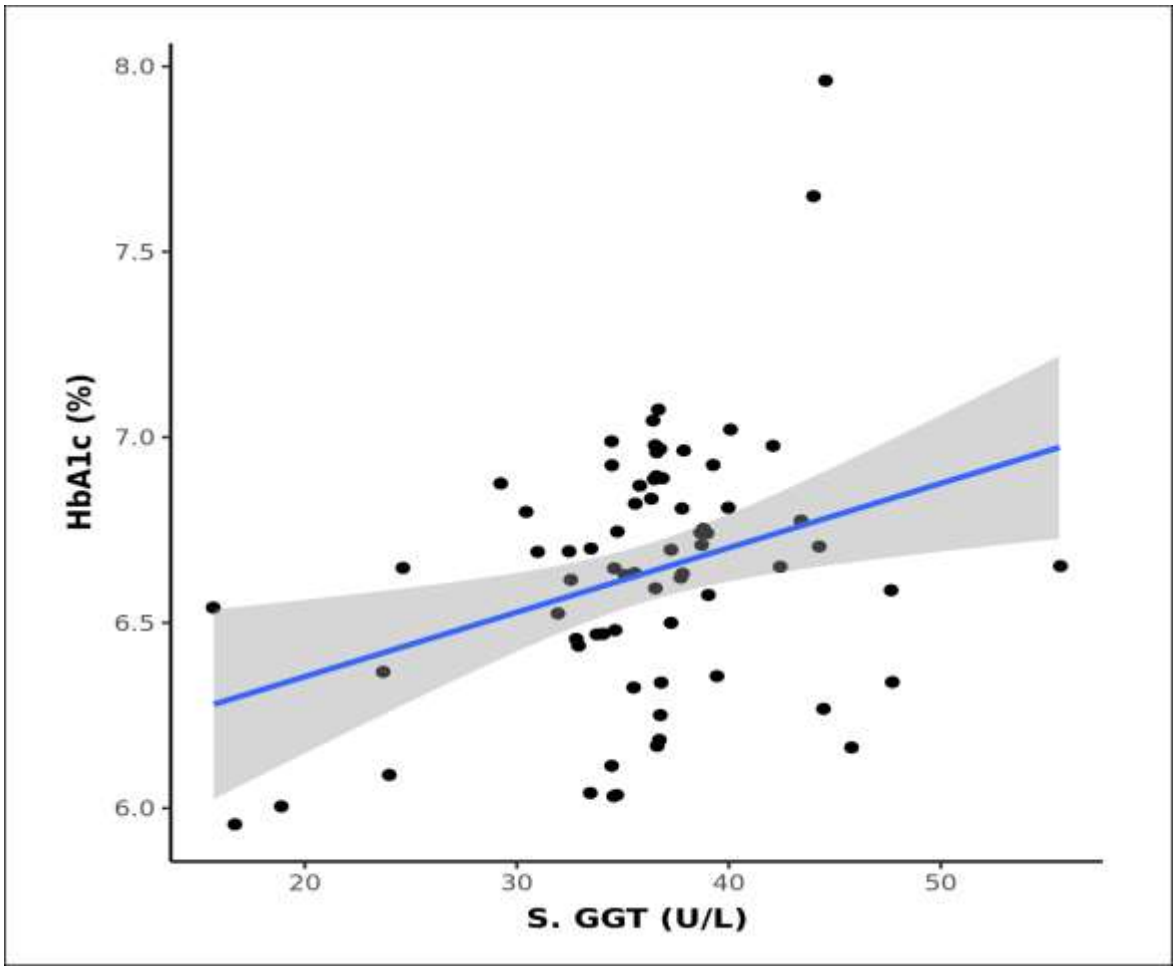
distributed. There was a weak positive correlation between S. GGT (U/L) and HbA1c (%), and this correlation was not statistically significant (rho = 0.03, p = 0.776).

Table.8 Correlation between S. GGT (U/L) and HbA1c (%) in (Group: 2)

Correlation	Spearman Correlation Coefficient	P Value
S. GGT (U/L) vs HbA1c (%)	0.3	0.019



The above scatterplot depicts the correlation between S. GGT (U/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a positive correlation between S. GGT (U/L) and HbA1c (%), and this correlation was statistically significant (rho = 0.28, p = 0.019).

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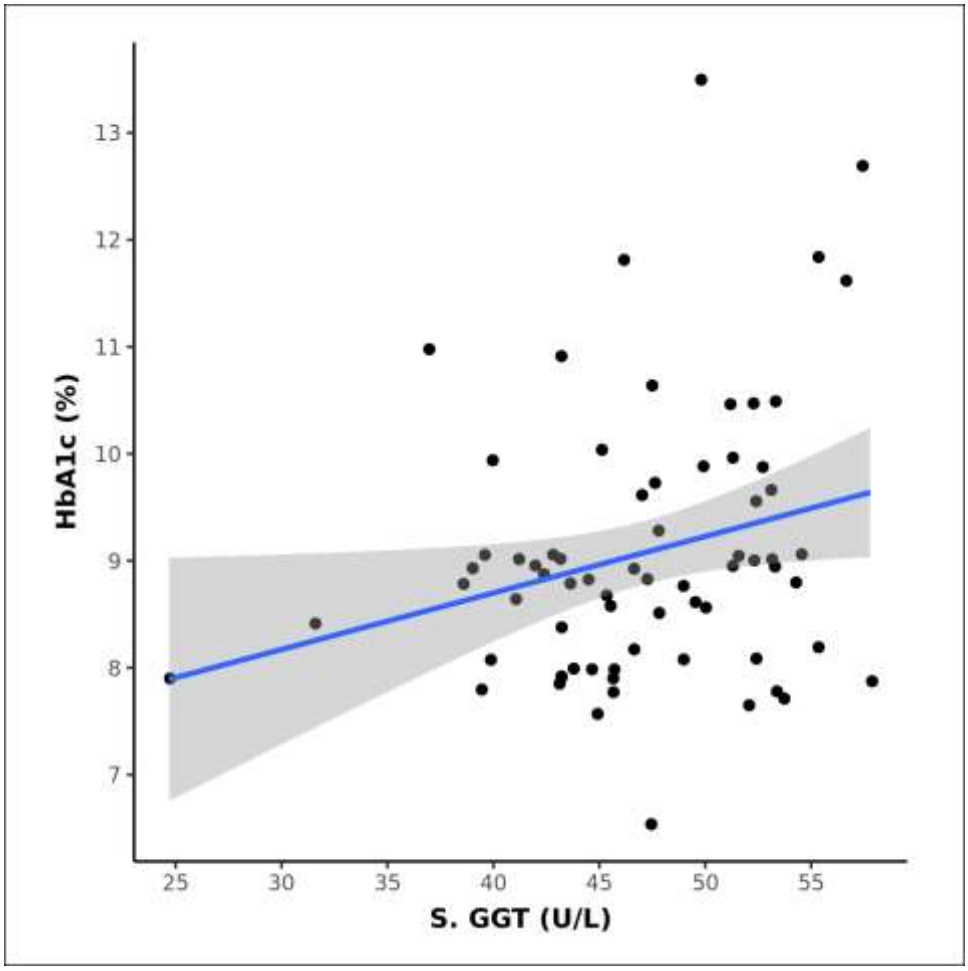
For every 1 unit increase in S. GGT (U/L), the HbA1c (%) increases by 0.02 units. Conversely, for every 1 unit increase in HbA1c (%), the S. GGT (U/L) increases by 6.24 units.

Table 9. Correlation between S. GGT (U/L) and HbA1c (%) in (Group: 3)

Correlation	Spearman Correlation Coefficient	P Value
S. GGT (U/L) vs HbA1c (%)	0.2	0.111



The above scatterplot depicts the correlation between S. GGT (U/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

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There was a positive correlation between S. GGT (U/L) and HbA1c (%), and this correlation was not statistically significant (rho = 0.19, p = 0.111).

DISCUSSION

There was significant difference between mean GGT of study groups. Mean GGT was higher in subsequent groups (Group III > Group II > Group I).This indicates poor the glycemic control, higher will be the oxidative stress which reflects in higher mean GGT in different study groups. Results of present study was comparable with study by Gohel MG et al. [16]

When trend of GGT was compared with HbA1c as across the group, there was statistically significant correlation across the study groups. Hence, higher the HbA1c, higher was GGT. This further strengthens the hypothesis that poor the glycemic control, higher the oxidative stress and they share mutual linear relationship. Similar observation was found in other studies as mentioned and present study closely comparable to gohel MG et al. [17]

In our study, there was statistically significant correlation between GGT and BMI. Clinical studies suggest that oxidative stress plays a major role in the pathogenesis of obesity and its complications. Hence the association between GGT and BMI. present study closely comparable with Adams LA et al.

In our study, there was a statistically significant correlation between GGT and Hypertension. Study by Cheung et al[18] have emphasised, role of GGT in the pathogenesis of hypertension. They found GGT as an independent predictor of new-onset hypertension. In another research project by Jung et al involving 10,988 participants, GGT showed strong positive correlations with systolic blood pressure and diastolic blood pressure.

In our study, there was a statistically significant correlation between GGT and Total cholesterol. GGTcatalyzes the oxidation of low-density lipoprotein (LDL), a process involved in the pathogenesis of atherosclerosis. This explains possible linear relation between the two. In a study by Emiroglu MY et al, they found GGT strongly associated with LDL -C in causing IHD. [19]

CONCLUSION

There was a positive correlation between FBS,PPBS,HbA1c and GGT,FBS,PPBS,HbA1c and hsCRP, indicating increasing oxidative stress and inflammation in patients poorer glycemic control in Diabetes Mellitus. Higher the levels of HbA1c and GGT, stronger was the correlation between them.

BIBILOGRAPGY

1. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. The Lancet. 2011 Jul 9;378(9786):182-97.
2. Nolan CJ, Ruderman NB, Kahn SE, Pedersen O, Prentki M. Response to Comments on Nolan et al. Insulin Resistance as a Physiological Defense Against Metabolic

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Stress: Implications for the Management of Subsets of Type 2 Diabetes. Diabetes 2015; 64: 673–686. Diabetes. 2015 Oct 1;64(10):e38-9.

3. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. The Journal of clinical investigation. 2016 Jan 4;126(1):12-22.
4. Kim NH, Pavkov ME, Knowler WC, Hanson RL, Weil EJ, Curtis JM, Bennett PH, Nelson RG. Predictive value of albuminuria in American Indian youth with or without type 2 diabetes. Pediatrics. 2010 Apr 1;125(4):e844-51..
5. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, Melzer D. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. Jama. 2008 Sep 17;300(11):1303-10.
6. Rother KI. Diabetes treatment—bridging the divide. The New England journal of medicine. 2007 Apr 12;356(15):1499.
7. McCarthy MI. Genomics, type 2 diabetes, and obesity. New England Journal of Medicine. 2010 Dec 9;363(24):2339-50.
8. Cerf ME. Beta cell dysfunction and insulin resistance. Frontiers in endocrinology. 2013 Mar 27;4:37.
9. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology. 2018 Feb;14(2):88-98.
10. Fu Z, R Gilbert E, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Current diabetes reviews. 2013 Jan 1;9(1):25-53.
11. Boland B.B., Rhodes C.J., Grimsby J.S. The dynamic plasticity of insulin production in beta-cells. *Mol. Metab.* 2017;6:958–973. doi: 10.1016/j.molmet.2017.04.010.
12. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. The Journal of clinical investigation. 2011 Jun 1;121(6):2118-25.
13. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nature medicine. 2017 Jul;23(7):804-14.
14. Wilcox G. Insulin and insulin resistance. Clinical biochemist reviews. 2005 May;26(2):19.
15. Vaxillaire M, Froguel P. Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. Endocrine reviews. 2008 May 1;29(3):254-64.
16. Vaxillaire M, Bonnefond A, Froguel P. The lessons of early-onset monogenic diabetes for the understanding of diabetes pathogenesis. Best practice & research Clinical endocrinology & metabolism. 2012 Apr 1;26(2):171-87.
17. Gibson G. Rare and common variants: twenty arguments. Nature Reviews Genetics. 2012 Feb;13(2):135-45.
18. Stranger BE, Stahl EA, Raj T. Progress and promise of genome-wide association studies for human complex trait genetics. Genetics. 2011 Feb 1;187(2):367-83.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 09, 2023

19. Yang Y, Bailey C, Loewenstein A, Massin P. Intravitreal corticosteroids in diabetic macular edema: pharmacokinetic considerations. Retina (Philadelphia, Pa.). 2015 Dec;35(12):2440.