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Original Research Article

STUDY OF SERUM hsCRP ACTIVITY LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH GOOD AND POOR GLYCAEMIC CONTROL.

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Abstract

Background

Diabetes mellitus comprises a group of common metabolic disorders which share common phenotype of hyperglycemia.CRP which has both proinflammatory and anti-inflammatory property and is a direct contributor to atherosclerosis with introduction of high sensitive CRP assays which is a most potent independent predictor of atherosclerosis and coronary artery disease.CRP level, which significantly increases in acute coronary syndromes, has a prognostic value in patients with cardiovascular complications and in apparently healthy individuals.The importance of CRP in the pathophysiology of atherosclerosis, including the potential mechanisms of action in circulation as well as the potential impact of genetic variations within the CRP gene, The ability of human CRP to activate/regulate complement could be a crucial characteristic that connects CRP and inflammation to atherosclerosis.

METHODOLOGY

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

Result

The mean (SD) of hsCRP (mg/L) in the Group: 1 group was 2.04 (1.51). The mean (SD) of hsCRP (mg/L) in the Group: 2 group was 5.20 (10.93). The mean (SD) of hsCRP (mg/L) in the Group: 3 group was 16.91 (19.12). The median (IQR) of hsCRP (mg/L) in the Group: 1 group was 1.86 (1.2-2.68). The median (IQR) of hsCRP (mg/L) in the Group: 2 group was 2.54 (1.79-3.26). The median (IQR) of hsCRP (mg/L) in the Group: 3 group was 5.85 (3.44-29.6). The hsCRP (mg/L) in the Group: 1 ranged from 0.34 - 9.1. The hsCRP (mg/L) in the Group: 2 ranged from 0.45 - 66. The hsCRP (mg/L) in the Group: 3 ranged from 2.12 - 76.8.

There was a significant difference between the 3 groups in terms of hsCRP (mg/L) ($\chi 2 = 90.513$, $p = <0.001$), with the median hsCRP (mg/L) being highest in the Group: 3 group.

Conclusion

There was positive correlation between FBS, PPBS, HbA1c and GGT,FBS, PPBS, HbA1c and hsCRP, indicating increasing oxidative stress and inflammation in patients poor glycemic

control in Diabetes Mellitus. There was positive correlation between GGT and hsCRPin Diabetes Mellitus indicating linear relation between oxidative stress andinflammation.

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

Introduction

Diabetes mellitus comprises a group of common metabolic disorders which share common phenotype of hyperglycemia.[1] Defective beta-cell function and insulin resistance are the major pathologies in type 2 diabetes mellitus, resulting in elevated blood glucose levels. [2]The degree of hyperglycemia and diabetes duration is associated with an increased risk of the development of mainly micro and macrovascular complications. [3]

Some patients cannot be clearly classified as having type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. [4]Occasionally, patients who otherwise have type 2 diabetesmay present with

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ketoacidosis. Similarly, patients with type 1 diabetes may have a late onset and slow (but relentless) progression of disease despite having features of autoimmune disease. [5] Such difficulties in diagnosis may occur in children, adolescents and adults. The true diagnosis may become more obvious over time. [6]

The diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h value in the 75-g oral glucose tolerance test (OGTT) and the hbA1C test to diagnose diabetes, with a threshold of ≥6.5% and ADA adopted this criterion in 2010. [7] The diagnostic test should be performed using a method that is certified by the National Glycohaemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and ComplicationsTrial (DCCT) reference assay. [8]

CRP is an acute phase reactant belongs to a pentraxin family of proteins synthesised mainly by hepatocytes, serum level of CRP will be elevated in reponse to various infections, inflammation and tissue damage.[9] Widely measured for rapid diagnosis infection or inflammation ,measured in serum,cerebrospinal fluid and urine it is the first acute phase protein to be described, is a sensitive systemic marker of inflammation and tissue damage. Precise response and ease of assay have made CRP an ideal marker of inflammation.[10]

CRP which has both proinflammatory and anti-inflammatory property and is a direct contributor to atherosclerosis with introduction of high sensitive CRP assays which is a most potent independent predictor of atherosclerosis and coronary artery disease.[11] CRP level, which significantly increases in acute coronary syndromes, has a prognostic value in patients with cardiovascular complications and in apparently healthy individuals.[12]The importance of CRP in the pathophysiology of atherosclerosis, including the potential mechanisms of action in circulation as well as the potential impact of genetic variations within the CRP gene, The ability of human CRP to activate/regulate complement could be a crucial characteristic that connects CRP and inflammation to atherosclerosis. [13]

CRP and IL6 levels are elevation can predict type 2 diabetes mellitus, This link suggests that inflammation may have a role in the development of diabetes.[14] CRP is a Powerful independent predictor of diabetes, after adjustment for obesity, clinical risk factors, and fasting insulin levels.[15]CRP elevation has also been linked to a number of genetic variations. Ethnicity, dietary patterns, and obesity are all factors that influence CRP and other genes.[16]

METHODOLOGY

Prospective 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.

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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.

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 Comparison of the 3 Subgroups of the Variable Group in Terms of BMI (kg/m²)

BMI (kg/m²)	Group			Kruskal Wallis Test	
	1	2	3	χ2	p value
Mean (SD)	24.86 (3.44)	28.24 (3.72)	29.71 (4.17)	50.106	<0.001
Median (IQR)	24.16 (22.49-26.98)	27.91 (25.77-30.84)	29.06 (27.22-31.24)		
Range	18.71 - 35.11	19.48 - 38.33	22.64 - 41.32		

The mean (SD) of BMI (kg/m²) in the Group: 1 group was 24.86 (3.44). The mean (SD) of BMI (kg/m²) in the Group: 2 group was 28.24 (3.72). The mean (SD) of BMI (kg/m²) in the Group: 3 group was 29.71 (4.17). The median (IQR) of BMI (kg/m²) in the Group: 1 group was 24.16 (22.49-26.98). The median (IQR) of BMI (kg/m²) in the Group: 2 group was 27.91 (25.77-30.84). The median (IQR) of BMI (kg/m²) in the Group: 3 group was 29.06 (27.22-31.24). The BMI (kg/m²) in the Group: 1 ranged from 18.71 - 35.11. The BMI (kg/m²) in the Group: 2 ranged from 19.48 - 38.33. The BMI (kg/m²) in the Group: 3 ranged from 22.64 - 41.32 and there was no stastically significant differences.

Table.2 Comparison of the 3 Subgroups of the Variable Group in Terms of Systolic BP (mmHg)

Systolic BP (mmHg)	Group			Kruskal Wallis Test	
	1	2	3	χ2	p value
Mean (SD)	118.19 (14.43)	128.70 (18.91)	134.54 (19.18)	26.887	<0.001
Median (IQR)	114 (108-128)	122 (114-145)	136 (116.5-150)		
Range	90 - 156	100 - 180	100 - 174		

The mean (SD) of Systolic BP (mmHg) in the Group: 1 group was 118.19 (14.43). The mean (SD) of Systolic BP (mmHg) in the Group: 2 group was 128.70 (18.91). The mean (SD) of Systolic BP (mmHg) in the Group: 3 group was 134.54 (19.18). The median (IQR) of Systolic BP (mmHg) in the Group: 1 group was 114 (108-128). The median (IQR) of Systolic BP (mmHg) in the Group: 2 group was 122 (114-145). The median (IQR) of Systolic BP (mmHg) in the Group: 3 group was 136 (116.5-150). The Systolic BP (mmHg) in the Group: 1 ranged from 90 - 156. The Systolic BP (mmHg) in the Group: 2 ranged from 100 - 180. The Systolic BP (mmHg) in the Group: 3 ranged from 100 - 174.

There was a significant difference between the 3 groups in terms of Systolic BP (mmHg) ($\chi2 = 26.887$, $p = <0.001$), with the median Systolic BP (mmHg) being highest in the Group: 3 group.

Table.3 Comparison of the 3 Subgroups of the Variable Group in Terms of Diastolic BP (mmHg)

Diastolic BP (mmHg)	Group			Kruskal Wallis Test	
	1	2	3	χ2	p value
Mean (SD)	76.17 (8.90)	80.45 (11.36)	84.11 (11.21)	16.663	<0.001
Median (IQR)	74 (70-80)	78 (72-88)	84 (76-90)		
Range	60 - 100	60 - 118	68 - 110		

The mean (SD) of Diastolic BP (mmHg) in the Group: 1 group was 76.17 (8.90). The mean (SD) of Diastolic BP (mmHg) in the Group: 2 group was 80.45 (11.36). The mean (SD) of Diastolic BP (mmHg) in the Group: 3 group was 84.11 (11.21). The median (IQR) of Diastolic BP (mmHg) in the Group: 1 group was 74 (70-80). The median (IQR) of Diastolic BP (mmHg) in the Group: 2 group was 78 (72-88). The median (IQR) of Diastolic BP (mmHg) in the Group: 3 group was 84

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(76-90). The Diastolic BP (mmHg) in the Group: 1 ranged from 60 - 100. The Diastolic BP (mmHg) in the Group: 2 ranged from 60 - 118. The Diastolic BP (mmHg) in the Group: 3 ranged from 68 - 110.

There was a significant difference between the 3 groups in terms of Diastolic BP (mmHg) ($\chi2$ = 16.663, p = <0.001), with the median Diastolic BP (mmHg) being highest in the Group: 3 group.

Table.4 Comparison of the 3 Subgroups of the Variable Group in Terms of HbA1c (%)

HbA1c (%)	Group			Kruskal Wallis Test	
	1	2	3	$\chi2$	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 (%) ($\chi2$ = 181.645, p = <0.001), with the median HbA1c (%) being highest in the Group: 3 group.

Table.5 Comparison of the 3 Subgroups of the Variable Group in Terms of hsCRP (mg/L)

hsCRP (mg/L)	Group			Kruskal Wallis Test	
	1	2	3	$\chi2$	p value
Mean (SD)	2.04 (1.51)	5.20 (10.93)	16.91 (19.12)	90.513	<0.001
Median (IQR)	1.86 (1.2-2.68)	2.54 (1.79-3.26)	5.85 (3.44-29.6)		
Range	0.34 - 9.1	0.45 - 66	2.12 - 76.8		

The mean (SD) of hsCRP (mg/L) in the Group: 1 group was 2.04 (1.51). The mean (SD) of hsCRP (mg/L) in the Group: 2 group was 5.20 (10.93). The mean (SD) of hsCRP (mg/L) in the Group: 3 group was 16.91 (19.12). The median (IQR) of hsCRP (mg/L) in the Group: 1 group was 1.86 (1.2-2.68). The median (IQR) of hsCRP (mg/L) in the Group: 2 group was 2.54 (1.79-3.26). The median (IQR) of hsCRP (mg/L) in the Group: 3 group was 5.85 (3.44-29.6). The hsCRP (mg/L) in the Group: 1 ranged from 0.34 - 9.1. The hsCRP (mg/L) in the Group: 2 ranged from 0.45 - 66. The hsCRP (mg/L) in the Group: 3 ranged from 2.12 - 76.8.
There was a significant difference between the 3 groups in terms of hsCRP (mg/L) ($\chi2$ = 90.513, p = <0.001), with the median hsCRP (mg/L) being highest in the Group: 3 group.

Table.6 Correlation between hsCRP (mg/L) and HbA1c (%) (n = 210)

Correlation	Spearman Correlation Coefficient	P Value
hsCRP (mg/L) vs HbA1c (%)	0.6	<0.001

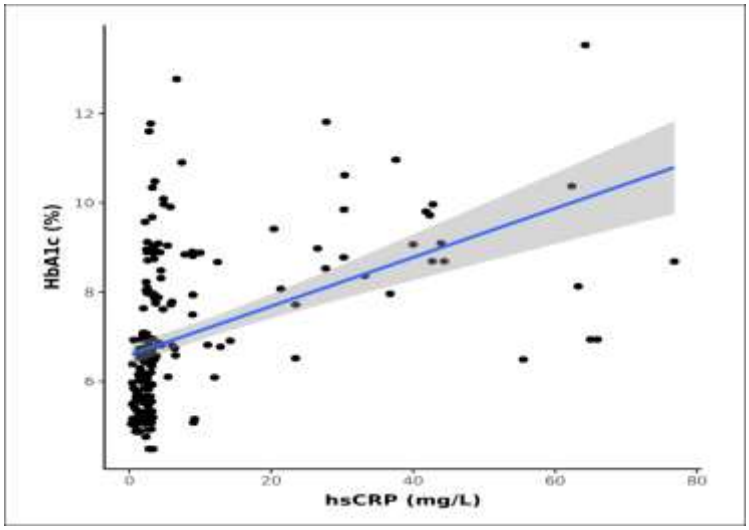

Fig.1Correlation between hsCRP (mg/L) and HbA1c (%) (n = 210)

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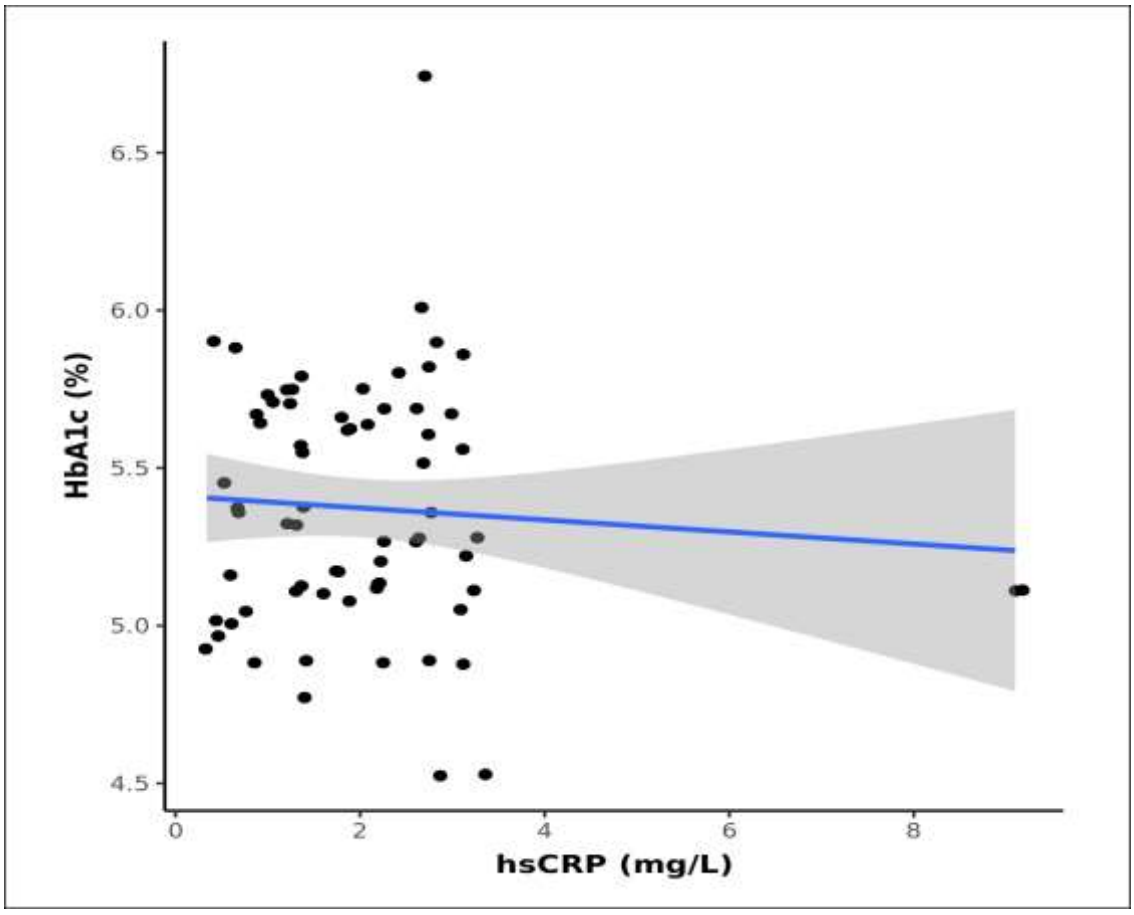
The above scatterplot depicts the correlation between hsCRP (mg/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.
Non-parametric 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 hsCRP (mg/L) and HbA1c (%), and this correlation was statistically significant (rho = 0.63, p = <0.001).
For every 1 unit increase in hsCRP (mg/L), the HbA1c (%) increases by 0.05 units.
Conversely, for every 1 unit increase in HbA1c (%), the hsCRP (mg/L) increases by 3.72 units.

Table.7 Correlation between hsCRP (mg/L) and HbA1c (%) in (Group: 1)

Correlation	Spearman Correlation Coefficient	P Value
hsCRP (mg/L) vs HbA1c (%)	-0.0	0.945



The above scatterplot depicts the correlation between hsCRP (mg/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 weak negative correlation between hsCRP (mg/L) and HbA1c (%), and this correlation was not statistically significant (rho = -0.01, p = 0.945).

Table.8 Correlation between hsCRP (mg/L) and HbA1c (%) in (Group: 2)

Correlation	Spearman Correlation Coefficient	P Value
hsCRP (mg/L) vs HbA1c (%)	0.2	0.047

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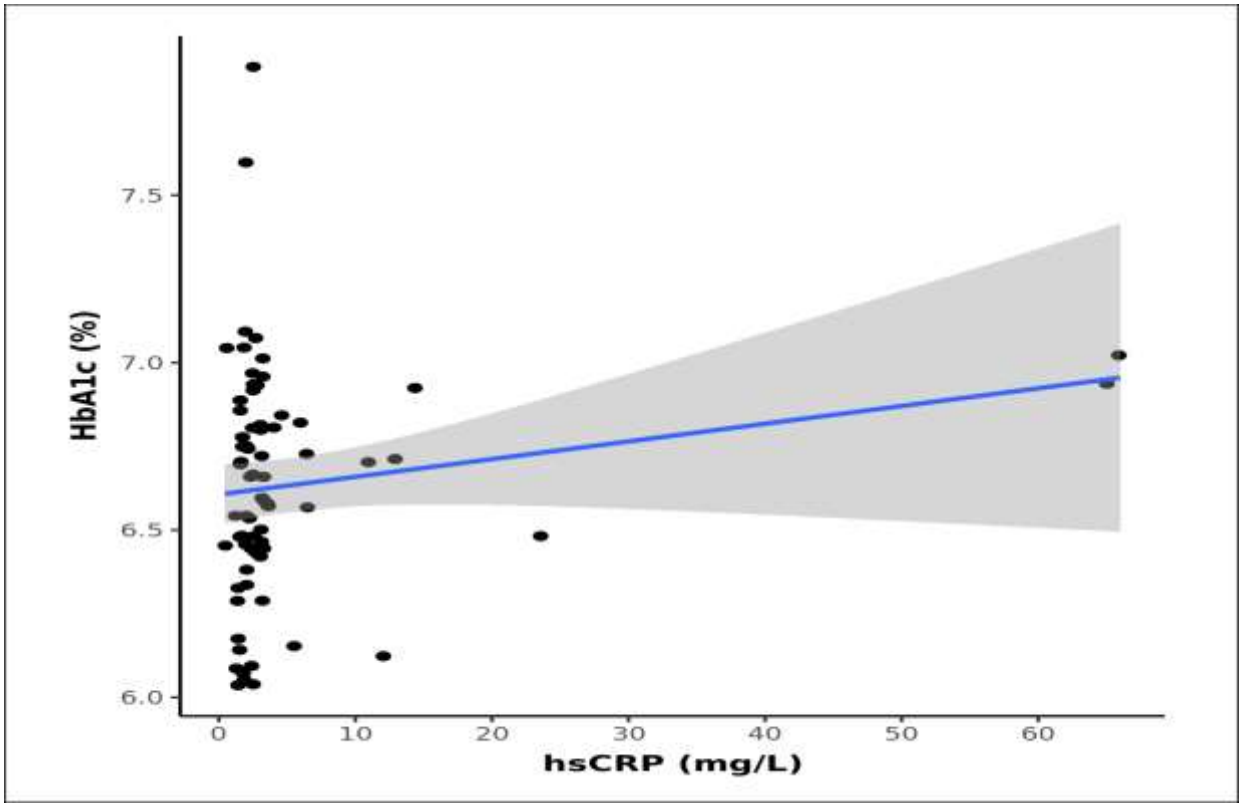

The above scatterplot depicts the correlation between hsCRP (mg/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

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 hsCRP (mg/L) and HbA1c (%), and this correlation was statistically significant (rho = 0.24, p = 0.047).

For every 1 unit increase in hsCRP (mg/L), the HbA1c (%) increases by 0.01 units.

Conversely, for every 1 unit increase in HbA1c (%), the hsCRP (mg/L) increases by 5.33 units.

Table.9 Correlation between hsCRP (mg/L) and HbA1c (%) in (Group: 3)

Correlation	Spearman Correlation Coefficient	P Value
hsCRP (mg/L) vs HbA1c (%)	0.1	0.477

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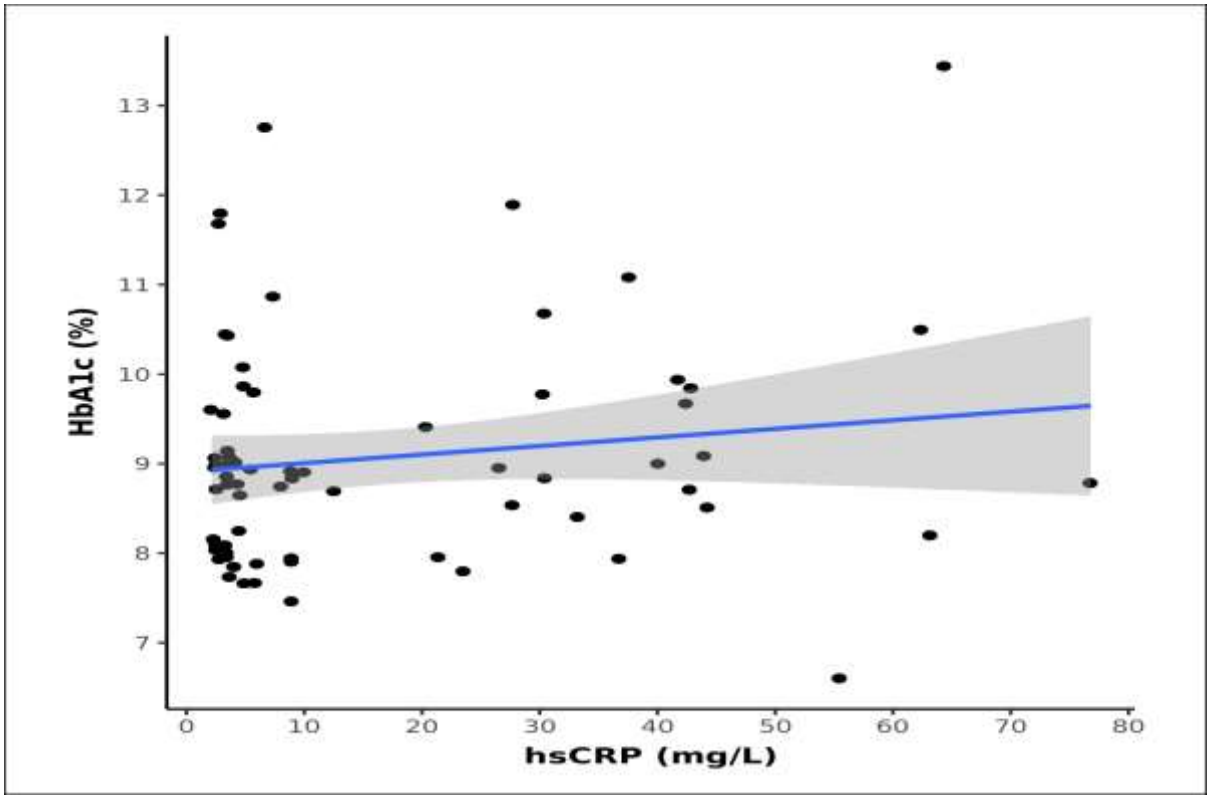

The above scatterplot depicts the correlation between hsCRP (mg/L) and HbA1c (%). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.
Non-parametric 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 hsCRP (mg/L) and HbA1c (%), and this correlation was not statistically significant (rho = 0.09, p = 0.477).

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.[17]

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. [18]

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 BMIpresent study closely comparable with Adams LA et al. [19]

In our study, there was a statistically significant correlation between GGT and Hypertension. Study by Cheung et al have emphasised, role of GGT in the pathogenesis of hypertension. [20] 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. [21]

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. [22]

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In our study, there was statistically significant difference found between mean hsCRP levels among study groups. Similar observation was made in other studies. The hsCRP is a protein of an acute phase secreted by the liver as well as by other tissues in response to any inflammatory condition. hsCRP has pro-inflammatory activity and considered one of the most important pro-atherosclerotic mediators.

In our study, correlation coefficient of hsCRP with Blood pressure was 0.14, indicating poor correlation between hsCRP with Blood pressure. In a study bySarinnapakorn V et al, they found similar poor correlation between hsCRP with Blood pressure. [23]

In our study, correlation coefficient of hsCRP with BMI was 0.06, indicating poor correlation between hsCRP with BMI.In a study bySarinnapakorn V et al, they found similar poor correlation between hsCRP with BMI. [24]

In our study, correlation coefficient of hsCRP with total cholesterol was 0.14, indicating poorcorrelation between hsCRP with total Cholesterol . In a study *by* Sarinnapakorn V et al, theyfound similar poor correlation between hsCRP total cholesterol.[25]

In our study, serum levels of GGT and hsCRP were positively correlated.Our findingsshows that serum GGT activity and hsCRP level were significantly increased in patientswith type 2 diabetes mellitus compared to healthy control.

Studies have pointed out that GGT could be the expression of subclinical inflammationwhich also contributes to the development of type 2 DM and insulin-resistantstate. Research also shows rise in levels of hsCRP and GGT in diabetic subjects andtheir significant association which might be a result of inflammation and oxidativestress in diabetes mellitus.

In a study by Dilshad Ahmed Khan et al they found that diabetic patients hadsignificantly elevated median of HbA1c, hsCRP and GGT as compared tocontrols.[27]Study by R Sharma et al also emphaisied similar findings.[28]Thus various studies have pointed connection between Glycemic control andinflammation marked by hsCRP. As Diabetes is state of inflammation which is linkedto various intracellular events, pro inflammatory markers are raised in Diabetics. Poorthe control of glycemia, higher is the inflammation.

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 poorerglycemic control in Diabetes Mellitus. There was positive correlation between GGT and hsCRP in Diabetes Mellitusindicating linear relation between oxidative stress and inflammation.

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