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hsCRP Levels And GLYCEMIC Control In Adults With Diabetes Mellitus

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Abstract:
Background:
In worldwide, type 2 diabetes prevalence is increasing in the all age group population. HSCRP indicates inflammation and Hba1c indicates hyperglycaemia. Both together establishes cardiac risks in individual with atherosclerosis. In diabetic patients, there will be development of macrovascular changes, when there is a poor control of glycaemic level. Increase levels of c-reactive protein is also linked in increased risk for development of diabetes in later stages.
Methodology:
Cross sectional observational study conducted in patients with diabetes mellitus.
Data analysed using SPSS 24.0 and Pearson's correlation test was used.
Results:
In our study, we observed positive correlation between hsCRP and FBS, hsCRP and PPBS, hsCRP and HbA1c, hsCRP and WBC as well as hsCRP and ESR
We observed significant positive correlation between hsCRP and HbA1c
($p<0.05$)
Conclusion:
hsCRP which are increased in T2DM and correlated well with the HbA1c, could be used as good diagnostic tool in prediction and prevention of complications of the disease
Raised levels ofhsCRP in subjects with Type2 DM,where HbA1C was above the target control level are prone for increased future relative risk of cardiovascular events and other complications. Hence Raised levels of hs-CRP indicates the role of ongoing inflammation in the management of diabetes.
Key words: *hsCRP, DM, glycemic control,HBA1c*

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I. Introduction

Diabetes mellitus (DM) is a heterogenous group of metabolic disorders recognized from ancient era which is characterized by chronic hyperglycaemia. The prevalence of diabetes especially type 2 DM is rapidly increasing worldwide over the past two decades. In 2010, there were 285 million individuals worldwide with type 2 diabetes.[1]

India had 41 million diabetics in 2006, according to the International Diabetic

Federation (IDF) and it is expected to increase to 70 million by the year 2025.[2] Diabetes was responsible for almost four million deaths in 2010 (6.8% of deaths) and is the fifth leading cause of mortality worldwide.[3] Cardiovascular complications especially coronary heart disease are the most common cause of morbidity and mortality in diabetics.[4]

A graded relationship also exists between glycaemic control (estimated by HbA1C level) and cardiovascular risk. Diabetes is now considered to be a proinflammatory and procoagulant state and low-grade chronic inflammation ('microinflammation') is a key factor in the genesis and rupture of atheromatous plaque.[5]Hyperglycaemia, oxidative stress, inflammation and dysregulation of hemostasis contribute to the increased risk of diabetic vasculopathies. Hence, the diabetes state per se confers an increased propensity to accelerated atherogenesis, which is compounded by other conventional cardiovascular risk factors.[6]

C reactive protein, measured as high sensitivity C reactive protein (hsCRP) and fibrinogen are acute phase reactants synthesized in the liver in response to proinflammatory cytokines. These markers of inflammation are found to be elevated in individuals with type 2 DM and are emerging as novel risk factors to

assess cardiovascular risk. They also have positive association with obesity, dyslipidemia, hypertension and poor glycaemic control.Once tissue damage or inflammation occurs, CRP activates complement classical pathway, as C-reactive protein is a acute phase reactant. C-reactive protein is largely regulated by circulating levels of interleukin-6 predicts coronary heart disease incidence in healthy subjects.[7]

After myocardial infarction and stroke, CRP levels rises significantly in the serum. This increase is observed within 6hours of inflammation and the level may be up to 2000 times normal.[8]Highly sensitive CRP is a measurement of CRP of lower concentration. It is a quantitative assay of CRP in plasma and it gives a new method for identification of rupture of plaque in high risk individuals.[9] For the diagnosis of future myocardial infarction and stroke in a healthy men and women, HSCRP plays an important independent predictor. It also has a role in primary prevention of cardiovascular disease.**10,11**

HSCRP indicates inflammation and Hba1c indicates hyperglycaemia. Both together establishes cardiac risks in individual with atherosclerosis. In diabetic patients, there will be development of macrovascular changes, when there is a poor control of glycaemic level. CRP is a significant risk factor for the development of cardiovascular disease. Increase levels of c-reactive protein is also linked in increased risk for development of diabetes in later stages. Hence the study has been taken up to know the relation between the Hba1c and CRP in type 2 diabetes mellitus.

With this background the present study was conducted in diabetes mellitus subjects to assess hsCRP levels which is a predictor of cardiovascular mortality.

II. Material and Methodology

Study setting:
Study population:
Both male and female with diabetes mellitus presenting to the OPD or getting admitted
Study design: Cross sectional observational study
Sample size:100
Calculation of sample size
Formula for sample size calculation:
(**Source for formula:** Source: Patrikar S. In Text book of Community Medicine. 1st Ed, 2009. Ed. Bhalwar R. Dept of Community Medicine. AFMC Pune. Publ. WHO India Office, New Delhi)

$$n = 2\frac{S^2(Z1 + Z2)^2}{(M1 \quad M2)^2}$$

Ref of article: Ramesh S S, Basavaraju M M, Shashikanth Y S. A study of high sensitivity c–reactive protein (hsCRP) in relation to HbA1C in type2 diabetes mellitus in tertiary care hospital, Mysore. International Journal of Contemporary Medicine Surgery and Radiology. 2019;4(1): A62-A64.

Variable considered for calculation of sample size: Mean HbA1c and its correlation with hSCRPis considered here for sample size calculation

M1	Mean test intervention	7.52
M2	Mean control intervention	8.15
S1	Standard deviation of M1	1.03
S2	Standard deviation of M2	1.15
S	Pooled SD	1.09
AH	One sided=1, Two sided =2	1
1-α	Set level of confidence. Usual values 0.95; 0.99	0.99
1-β	Set level of power of test. Usual values 0.8, 0.9	0.9
Z1	Z value associated with alpha **	2.32
Z2	Z value associated with beta	1.28
n	**Minimum sample size**	**79**

By using above formula and putting the values in it, minimum sample size came to 79.
But it was planned to include total 100 subjects fulfilling eligibility criteria in our study.

Sampling technique:
Inclusion criteria:

- Known patients of diabetes mellitus.
- Age > 18 years
- Those who are willing to participate in the study after consent

Exclusion criteria:

- Patients with other disease likely to increase C reactive protein like acute infection, coronary artery disease, rheumatological disorders.
- Patients who had used anti-inflammatory drugs within previous 30 days.
- Patients who had used cholesterol lowering drugs within previous 30 days.
- Age < 18 years
- Pregnant patients.
- Those who are not willing to participate in the study after consent

III. Results

Table 1: Distribution according to age

		Frequency	Percent
Age group in years	< 30	2	2.0
	31-40	18	18.0
	41-50	19	19.0
	51-60	33	33.0
	>60	28	28.0
	Total	100	100.0

We included total 100 patients in our study. Majority of them were from 51-60 years age group i.e. 33%, followed by 28% from above 60 years,19% from 41-50, 18% from 31-40 and least i.e. 2% from below 30 years age group. Mean age was
52.97±11.03 years

Fig. 1: Bar diagram showing Distribution according to age

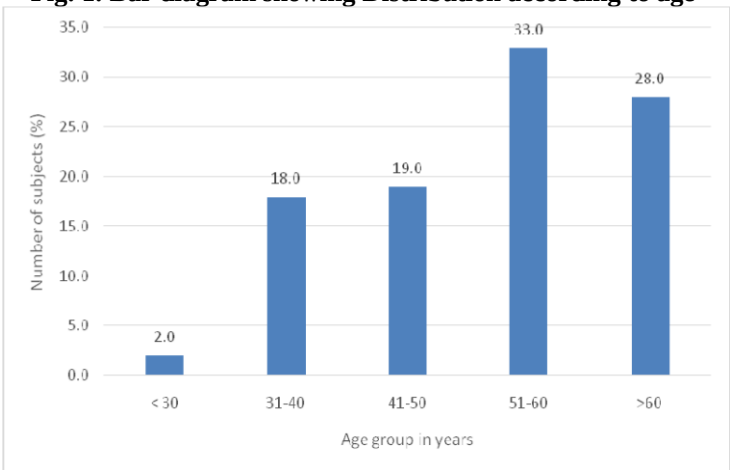

Table 2: Distribution according to gender

		Frequency	Percent
Gender	Male	49	49.0
	Female	51	51.0
	Total	100	100.0

Female patients were 51% whereas males were 49%. Male: female ratio was 0.96:1

Fig.2: Pie diagram showing Distribution according to gender

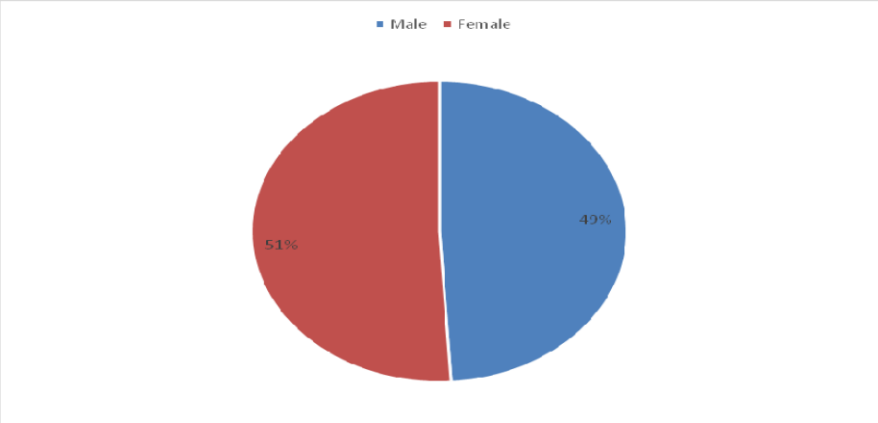

Table 3: Distribution according to age and gender

		Male		Female		Total
		Frequency	Percent	Frequency	Percent	
Age group in years	< 30	0	0.0	2	3.9	2
	31-40	12	24.5	6	11.8	18
	41-50	11	22.4	8	15.7	19
	51-60	18	36.7	15	29.4	33
	>60	8	16.3	20	39.2	28
	Total	49	100.0	51	100.0	100

Out of 49 males, majority were from 51-60 years age group i.e. 18(36.7%) followed by 12 (24.5%) from 31-40 years age group, 11(22.4%) from 41-50 years.
Out of 51 females, majority were from above 60 years age group i.e. 39.2% followed by 15 (29.4%) from 51-60 years age group, 8(15.7%) from 41-50 years

Fig. 3: Bar diagram showing Distribution according to age and gender

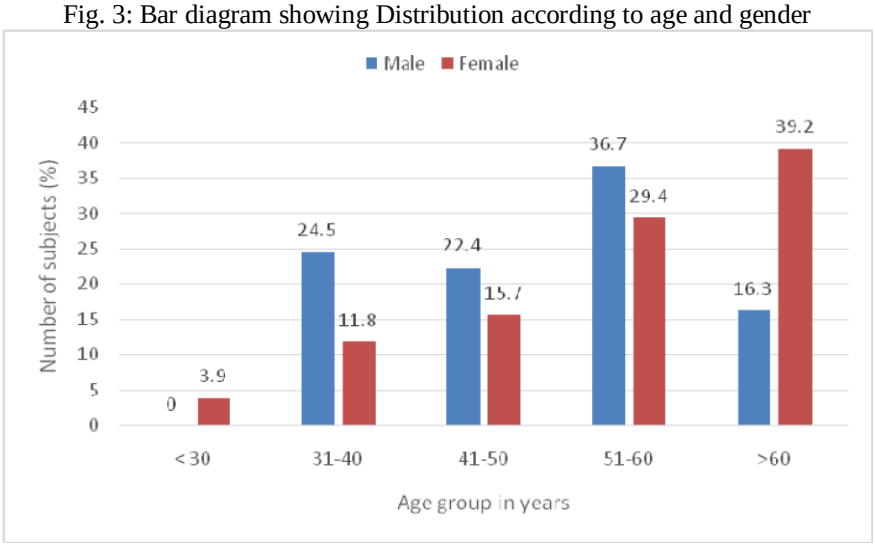

Table 4: Distribution according to BMI grades

		Frequency	Percent
BMI grading	Normal	72	72.0
	Overweight	28	28.0
	Total	100	100.0

Prevalence of overweight in our study was 28%

Fig. 4: Pie diagram showing Distribution according to BMI grades

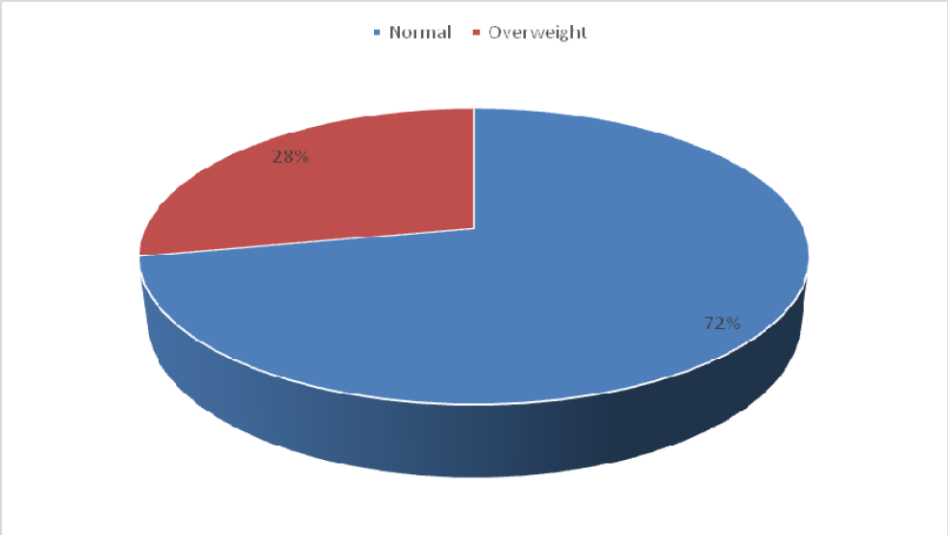

Table 5: Distribution according to hsCRP grades

		Frequency	Percent
hsCRP	< 1	21	21.0
	1 to 3	12	12.0
	> 3	67	67.0
	Total	100	100.0

hsCRP level above 3 was found in 67% patients. HsCRP between 1 to 3 was found in 12% and below 1 was seen in 21% patients

Fig.5: Pie diagram showing Distribution according to hsCRP grades

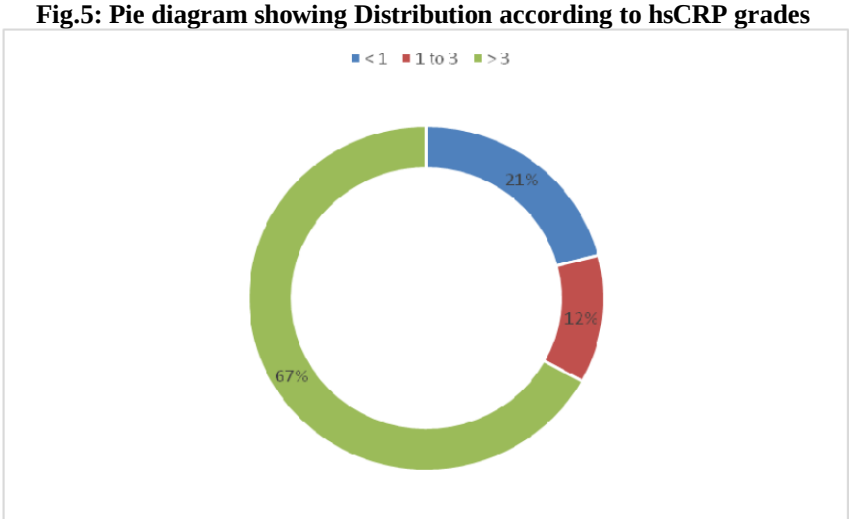

Table 6: Descriptive statistics of the variables

	N	Mean	Std. Deviatio n	Std. Error	Range	Minimu m	Maximu m
Age	100	52.97	11.03	1.10	53	27	80
FBS	100	138.61	22.27	2.23	117.6	70.4	188.0
PPBS	100	190.90	37.75	3.78	131.2	137.0	268.2
BMI	100	23.52	2.06	0.21	7.88	19.56	27.44
HBA1c	100	10.01	1.50	0.15	5.40	7.40	12.80
hsCRP	100	7.43	8.02	0.80	31.95	0.05	32.00
WBC	100	6295.0 0	1962.34	196.23	7500	3100	10600
ESR	100	22.31	8.90	0.89	33	10	43

Mean age was 52.97±11.03 years
Mean FBS was 138.61±22.27 mg/dl
Mean PPBS was 190.90±37.75 mg/dl
Mean BMI was 23.52±2.06
Mean HBA1c was 10.01±1.50
Mean hsCRP was 7.43±8.02
Mean WBC was 6295.00±1962.34
Mean ESR was 22.31±8.90 **Table 7: Correlation of hsCRP with other variables**

		FBS	PPBS	BMI	HBA1c	WBC	ESR
hsCR P	Pearson Correlatio n	0.066	0.118	0.116	.232*	0.020	0.120
	p	0.516	0.243	0.248	0.020	0.846	0.234
	Inference	Positive correlatio n	Positive correlatio n	Positive correlatio n	Positive correlatio n	Positive correlatio n	Positive correlatio n

In our study, we observed positive correlation between hsCRP and FBS, hsCRP and PPBS, hsCRP and HbA1c, hsCRP and WBC as well as hsCRP and ESR
We observed significant positive correlation between hsCRP and HbA1c ($p<0.05$)

Fig.6 a: Scatter diagram showing Correlation of hsCRP with FBS

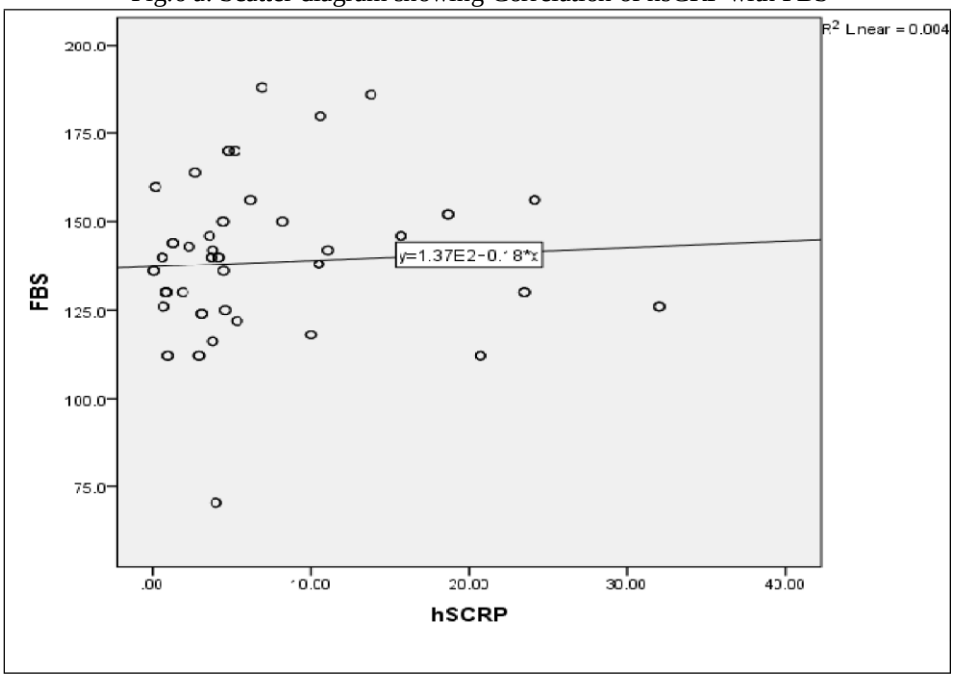

Fig. 6 b: Scatter diagram showing Correlation of hsCRP with PPBS

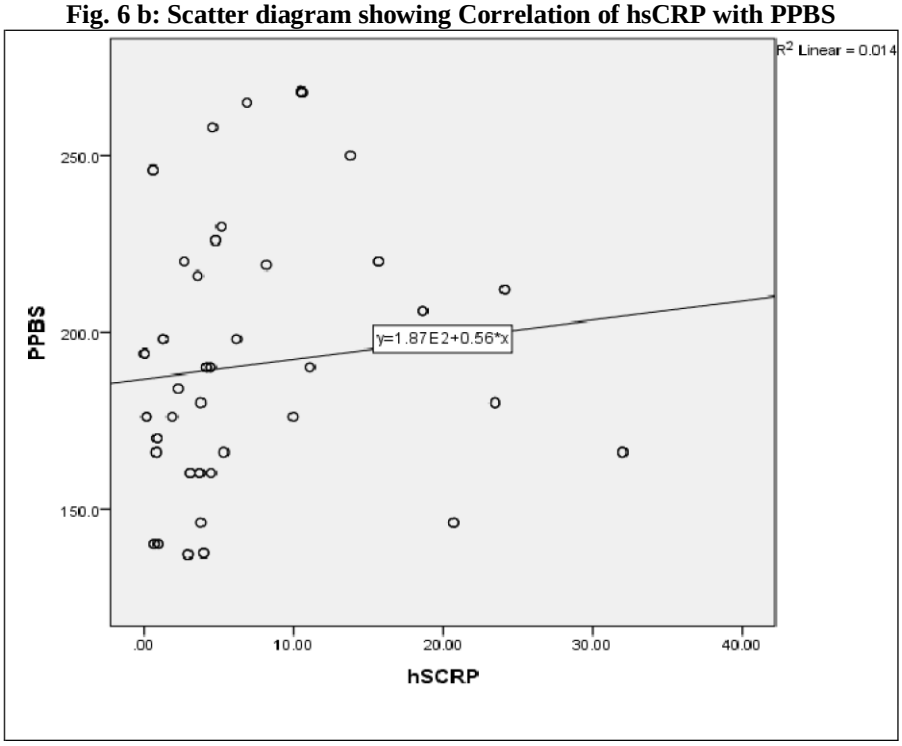

Fig.6 c: Scatter diagram showing Correlation of hsCRP with BMI

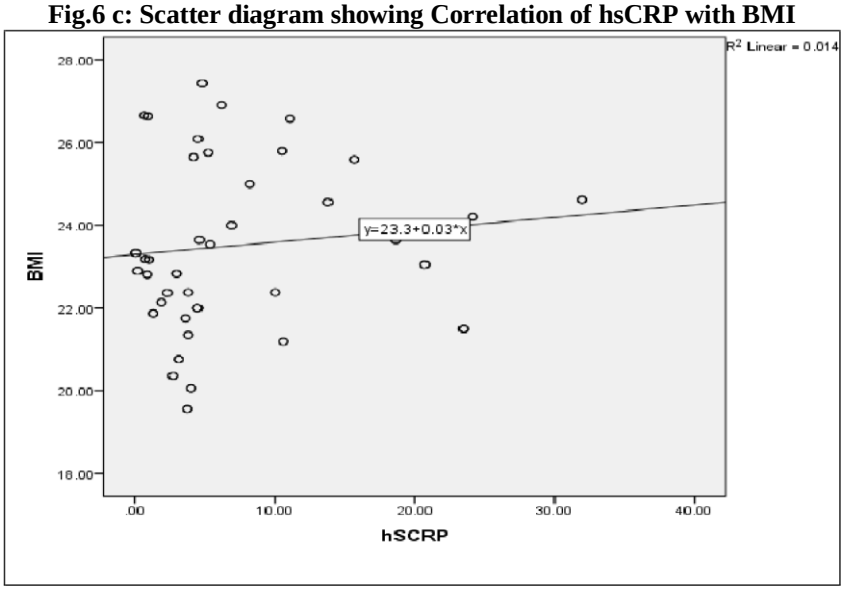

Fig.6 d: Scatter diagram showing Correlation of hsCRP with BMI

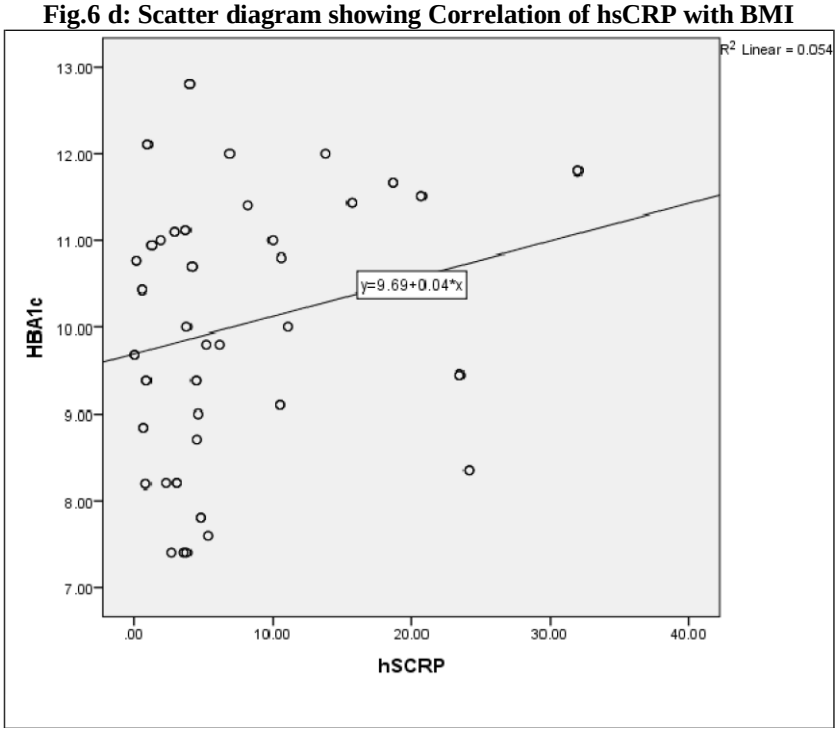

Fig.6 e:Scatter diagram showing Correlation of hsCRP with BMI

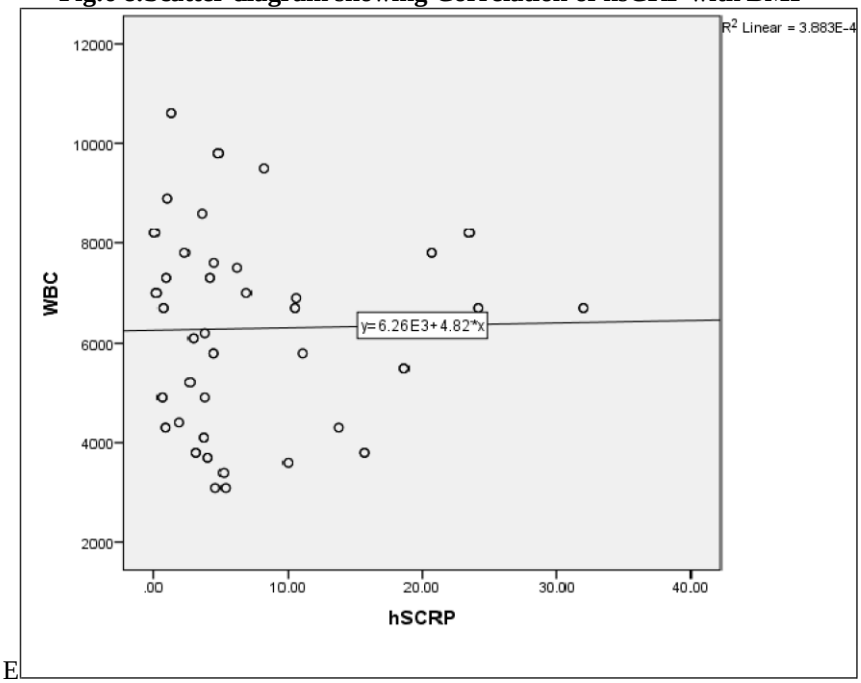

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Fig.6 f: Scatter diagram showing Correlation of hsCRP with BMI

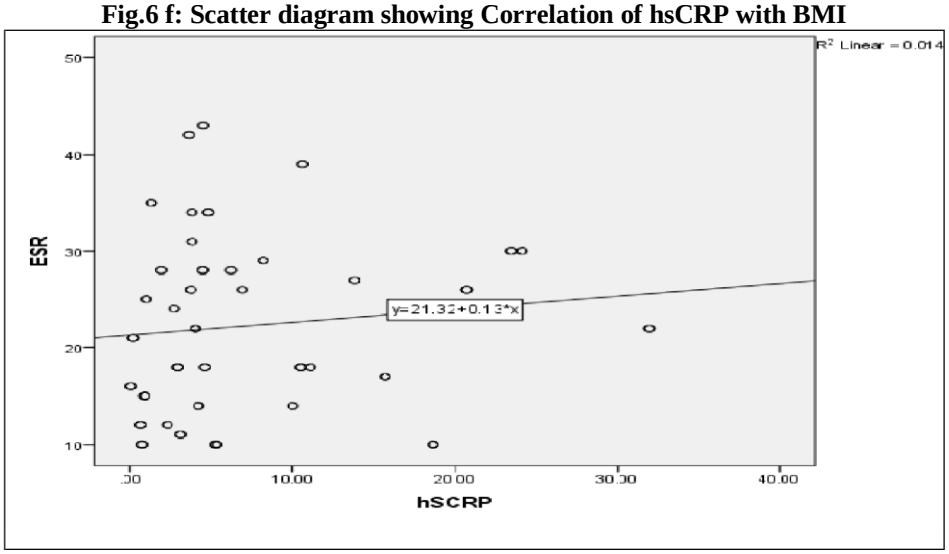


Table 8: Distribution according to age and hsCRP

		<1		1 to 3		> 3		Total
		No	%	No	%	No	%	
Age group in years	< 30	0	0.0	2	16.7	0	0.0	2
	31-40	3	14.3	2	16.7	13	19.4	18
	41-50	6	28.6	5	41.7	8	11.9	19
	51-60	12	57.1	0	0.0	21	31.3	33
	>60	0	0.0	3	25.0	25	37.3	28
	Total	21	100.0	12	100.0	67	100.0	100

Out of total 21 patients with hsCRP less than 1, majority were from 51-60 years age group i.e. 12(57.1%) whereas in 12 patients with hsCRP 1-3, majority were from 41-50 years i.e. 5(41.7%) and in 67 patients with hsCRP above 3, majority were from above 60 years i.e. 25(37.3%).

Fig. 7: Bar diagram showing Distribution according to age and hsCRP

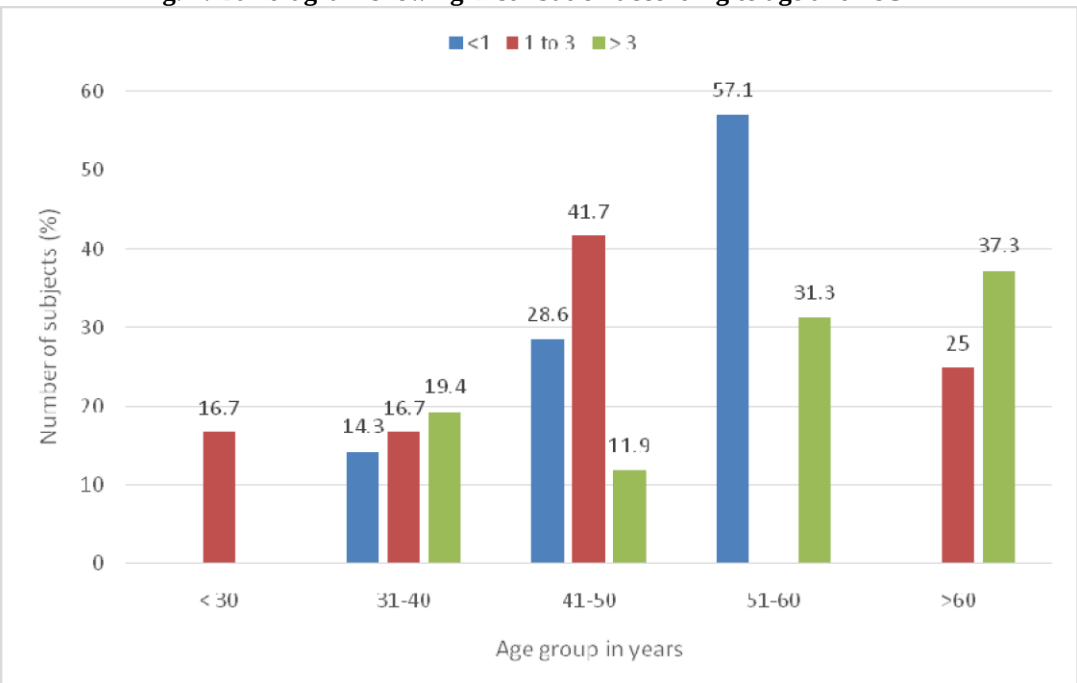


Table 9: Distribution according to gender and hsCRP

		<1		1 to 3		> 3		Total
		No	%	No	%	No	%	
Gender	Male	18	85.7	7	58.3	24	35.8	49
	Female	3	14.3	5	41.7	43	64.2	51
Total		21	100.0	12	100.0	67	100.0	100

Out of total 21 patients with hsCRP less than 1, majority were males i.e. 18(85.7%) whereas in 12 patients with hsCRP 1-3, majority were males i.e. 7(58.3%) and in 67 patients with hsCRP above 3, majority were females i.e. 43(64.2%).

Fig.8: Bar diagram showing Distribution according to gender and hsCRP

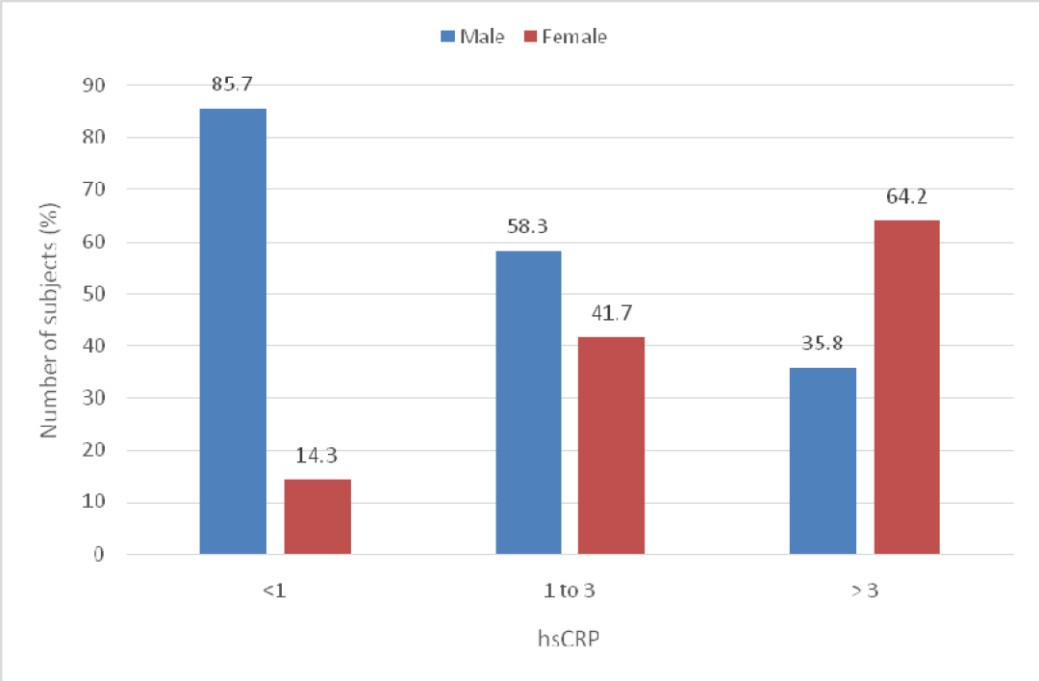


Table 10: Comparison of mean hsCRP level in different age groups

Age group in years	N	Mean hsCRP	SD	F	p	Inference
< 30	2	2.30	0.00	0.68	0.6 (>0.05)	Not significant
31-40	18	7.36	5.30			
41-50	19	5.42	8.44			
51-60	33	8.58	9.73			
>60	28	7.86	7.19			
Total	100	7.43	8.02			

Mean hsCRP in patients below 30 years was 2.30, between 31-40 years it was 7.36±5.30, between 41-50 was 5.42±8.44, between 51-60 was 8.58±9.73 and above 60 was 7.86±7.19.
When we compared the mean hsCRP between all groups, the difference in the mean hsCRP value was not found statistically significant (>0.05)

Fig.9: Bar diagram showing Comparison of mean hsCRP level in different age groups

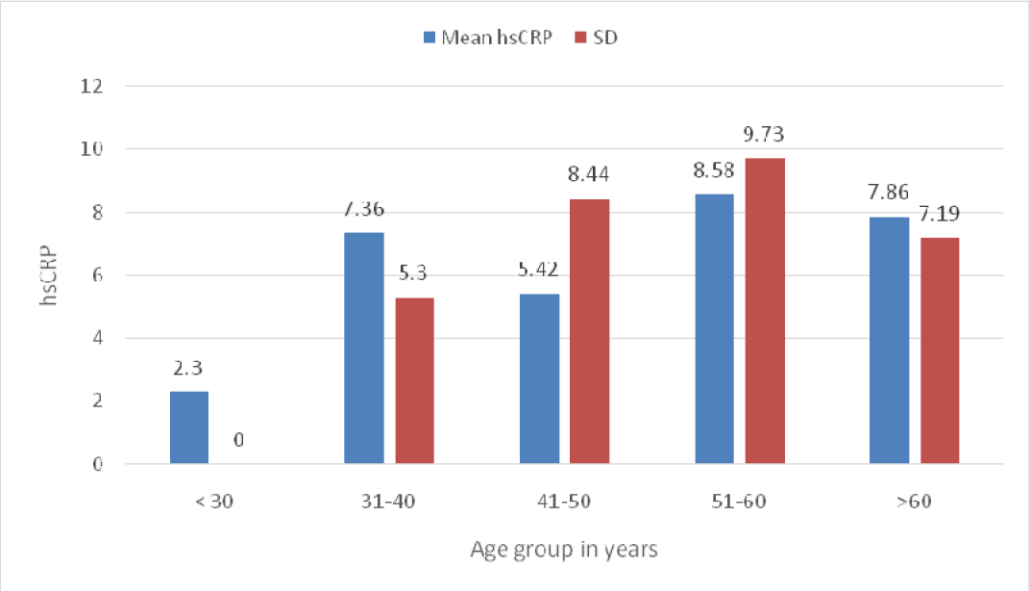
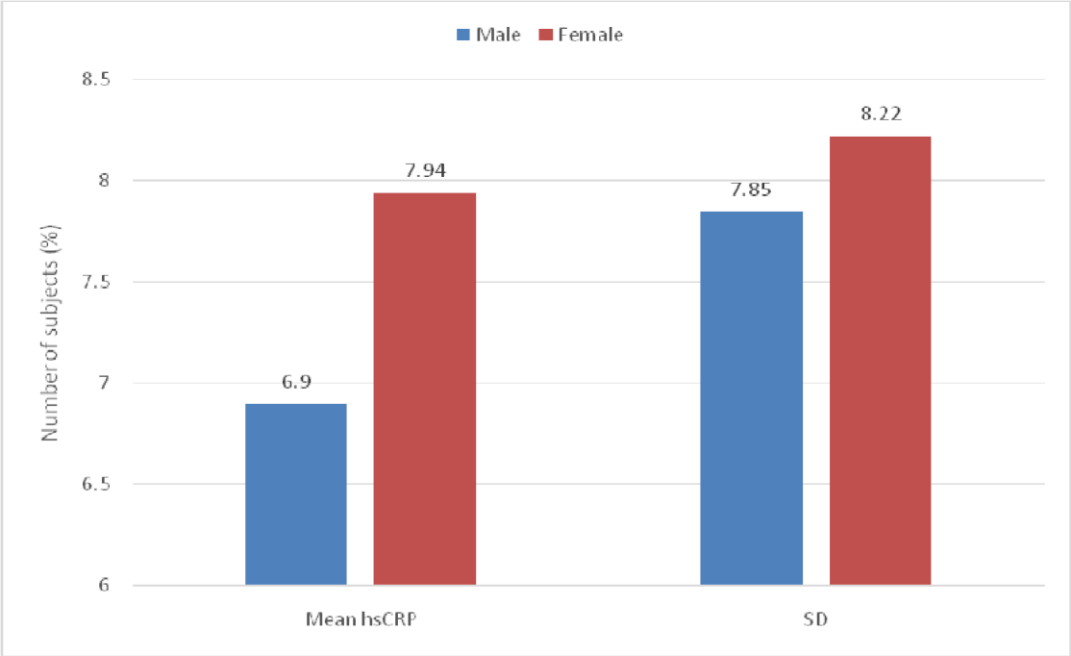


Table 11: Comparison of mean hsCRP level with respect to gender

Gender	N	Mean hsCRP	SD	F	P	Inference
Male	49	6.90	7.85	-0.64	0.51 (>0.05)	Not significant
Female	51	7.94	8.22			

Mean hsCRP in males was 6.90±7.85 and in females was 7.94±8.22. When we compared the mean hsCRP between two groups, the difference in the mean hsCRP value was not found statistically significant (>0.05)

Fig.10: Bar diagram showing Comparison of mean hsCRP level with respect to gender



IV. Discussion

Age and gender

We included total 100 patients in our study. Majority of them were from 51-60 years age group i.e. 33%, followed by 28% from above 60 years,19% from 41-50, 18% from 31-40 and least i.e. 2% from below 30 years age group.Mean age was
52.97±11.03 years
In our study, female patients were 51% whereas males were 49%. Male: female ratio was 0.96:1
Ramesh S Set al[12] observed that out of total of 77 cases that were included in which 12 (16%) subjects were in the age group of 36- 45 years, 31(40%) subjects in the age group of 46-55 years and 34 (44%) subjects in the age group of >56 years ie. most of our cases are in this age group. Of 77 subjects, 44 (57%) subjects were males and 33 (43%) subjects were females.
Petchiappan V et al[13] reported the mean age of the study subjects was 58.7±8.6 years.

The findings of above-mentioned authors are similar to our findings.

hsCRP in diabetes

In our study, hsCRP level above 3 was found in 67% patients. HsCRP between 1 to 3 was found in 12% and below 1 was seen in 21% patients. Mean hsCRP was
7.43±8.02 mg/l.
The mean hsCRP levels in the study population at baseline was 7.43±8.02 mg/l which is in accordance to that observed in another Indian study conducted in Bangalore (6.9±9.3 mg/l); while Saudi Arabian and Bangladesh studies had shown mean hsCRP
levels lower than that observed in the present study, 1.13 and 2.3 mg/L respectively.[14,15] The reason for this difference in CRP levels is unclear; further studies are needed to assess the differences in ethnic groups; standardisation of the techniques used for measurement of hsCRP.
Ramesh S Set al observed that 7 (9%) patients had low hs-CRP levels, 15 (20%) had intermediate and 55 (71%) had high hs-CRP levels which is consistent with our study findings.
The findings of above-mentioned authors are similar to our findings.

Correlation between hsCRP and HbA1c

In our study, we observed positive correlation between hsCRP and HbA1c.
We observed significant positive correlation between hsCRP and HbA1c ($p<0.05$)
A positive co-relation was observed between HbA1c and hsCRP levels at the baseline in the present study indicating that the change in HbA1c affects hsCRP levels in the same direction. There are other studies which support our results. In a crosssectional study conducted by **Gohel et al**[16] a significant positive linear relationship was observed between hsCRP and HbA1c.
Li et al[17]**, Khan DA et al**[18]**, and Sarinnapakorn V et al**[19]**,** also had made similar observation in their studies.
Kashinakunti et al[20], in their case control study noted significantly high hsCRP levels in diabetics than controls; also noted positive co-relation between hsCRP and HbA1c, although non-significant.
Low HbA1c levels strongly related to negative hs-CRP levels as observed by **Amanullah S. et al**[21]
Another study conducted in Sudan showed significant correlation between CRP levels with fasting plasma glucose and HbA1c.[22]
All the above-mentioned studies were cross-sectional observational studies which assessed the relationship between Hba1c and CRP.
The role of chronic low-grade inflammation contributing to the pathogenesis of diabetes and its related complications is well known. Chronic hyperglycaemia induces oxidative stress and chronic inflammatory state, which jointly contribute to the pathogenesis of atherosclerosis. C-reactive protein levels more than 3.0 mg/L is associated with worse cardiovascular outcome.[23]
Various studies had demonstrated significantly elevated serum hsCRP levels in diabetics than non-diabetics. Also, significant elevation was noted in those with poor glycaemic control compared to those with good glycaemic control.
Recent research has shown that HbA1c and CRP jointly contribute to the
increased cardiovascular risk in patients with advanced cardiovascular disease.[24]
Festa et al[25] demonstrated that people who developed DM(detected by an OGTT) had higher baseline serum CRP levels than those who did not develop DM [23]. There was a linear increasing trend in the incidence of DM as the baseline CRP quartile increased. In **Pizarra et al**[26] prospectivestudy, people with baseline hs-CRP ≥3mg/L (≥28.6 nmol/L)developed DM.

Correlation between hsCRP and FBS and PPBS

We observed positive correlation between hsCRP and FBS, hsCRP and PPBS as well as with BMI.
Ramesh S S et al[12] also reported positive correlation between hsCRP and FBS, hsCRP and PPBS.
Study done by **YildizTutuncu et al**[25] on comparison of hs- CRP levels in new Diabetes groups observed a positive correlation between hs-CRP levels and age, hsCRP with FBS and PPBS as well as with BMI which is similar to our study findings
The findings of above-mentioned authors are similar to our findings

V. Conclusion

hsCRP which are increased in T2DM and correlated well with the HbA1c, could be used as good diagnostic tool in prediction and prevention of complications of the disease
Raised levels of hsCRP in subjects with Type2 DM, where HbA1C was above the target control level are prone for increased future relative risk of cardiovascular events and other complications. Hence Raised levels of hs-CRP indicates the role of ongoing inflammation in the management of diabetes.

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