Research Article National Journal of Medical and Dental Research, July-Sep. 2016: Volume-4, Issue-4, Page 280-286

RELATION OF C - REACTIVE PROTEIN WITH CONTROL OF DIABETES & AS INFLAMMATORY MARKER OF DIABETES

Kishan Gopal Barupal[A], Amit Sagar[A], Manju Lata Verma[B]

[A] - *Assistant Professor, Department of General Medicine, Dr. S.N.Medical College, Jodhpur Rajasthan*

[B] - *Senior Resident, Department of Dermatology, Dr. S.N.Medical College, Jodhpur Rajasthan*

Medicine

Corresponding Author

Dr. Kishan Gopal Barupal,
Doctors Quarter no. 3/3,
Near UG Hostel,
MDM Hospital Campus,
Jodhpur, Rajasthan
Mobile : 9928009779

Abstract:

Background: Inflammatory reaction mediated by acute phase proteins and cytokine release can result in diabetes- preventing or diabetes-promoting effects. Recent evidence suggests that poor glycemic control is significantly associated with the development of complication of diabetes. Studies have indicated that C-reactive protein (CRP) is related with control of blood sugar in diabetic patients. HbA_{1c} level is important factor to assess the control of diabetes so ultimately C-reactive protein is also related to the level of HbA_{1c}..

Aims: To find out the Relation of C-reactive protein with control of diabetes and role of CRP as inflammatory marker of diabetes.

Settings and Design: Prospective study where, patients attending the MOPD/IPD of Mahatma Gandhi Hospital, Dr. S. N. Medical College were included. They were stratified into four category based on level of Hba_{1c}. Methods and Material- Fasting blood glucose was analyzed by the method devised by Astoor and King and C-Reactive Protein (CRP) by Immuno-nephelometry.

Results and Conclusions: C-reactive protein level were more in diabetic patients. Highly significant relation found between CRP level and HBA_{1C}.

Keywords- Diabetes, Acute phase proteins, Glycemic control, CRP, HbA_{1c}, Immuno-nephelometry.

Introduction

Diabetes is a global problem with devastating human, social and economic impact. The crude prevalence rate of diabetes in urban areas of India is about 9% and that the prevalence in rural areas has also increased to around 3% of the total population. Taking a urban-rural population distribution of 70:30 and an overall crude prevalence rate of around 4%, at a conservative estimate, India is home to around 40 million diabetics and this number is thought to give India the dubious distinction of being home to the largest number of diabetics in any one country.[1]

The presence of inflammation has recently been studied extensively in metabolic disorders such as diabetes mellitus (DM). Inflammatory reaction mediated by acute phase proteins and cytokine release can result in diabetes- preventing or diabetes-promoting effects. Inflammatory mediators such as cytokines and C-reactive protein (CRP) have been shown to be elevated in type 1 and type 2 DM.[2] They have been associated with the development and progression of diabetic complications in addition defects in the function of the mediators of the immune system could also be related to long-term complication of diabetes such as increased susceptibility to

infection and impaired wound healing.[3]

Recent evidence suggests that poor glycemic control is significantly associated with the development of complication of diabetes. Studies have indicated that C-reactive protein (CRP) is related with control of blood sugar in diabetic patients. HbA_{1c} level is important factor to assess the control of diabetes so ultimately C-reactive protein is also related to the level of HbA_{1c}.[4]

C-reactive protein was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with C-polysaccharide of pneumococcus.

CRP rise up to 50,000 fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hourse. Its half-life is constant and therefore its levels are mainly determined by the rate of production (and hence the severity of the precipitating cause). Serum amyloid A is a related acute-phase marker that responds rapidly in similar circumstances.[5] Normal concentration in healthy human serum is usually lower than 10mg/L, slightly increasing with ageing. Higher levels are found in late, pregnant women. Mild inflammation and viral infection (10-40 mg/L), active inflammation, bacterial infection (40-200 mg/L), severe bacterial infections and burns (>200 mg/L). Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes, hypertension and cardiovascular disease.[6]

Aim and Objective Of Study

To find out the Relation of C-reactive protein with control of diabetes and Role of CRP as inflammatory marker of diabetes.

Method

A observational prospective study was conducted in Patients attending the medical outpatient department of Mahatma Gandhi Hospital Dr. S. N. Medical College were included in the study. They were stratified as follows**:-** **Cat.1**-Non diabetic control group, **Cat.2**-Diabetic patients with controlled blood sugar –Hba1c < 7, **Cat.3**-Diabetic patients with uncontrolled blood sugar–Hba1c > 7 to 8.9**,** **Cat.4**- Hba1c > 9 . The details of the history and physical findings were recorded on a special Performa. All subjects were subjected to the following examination:-
Anthropometric Measurements, ECG, Fasting Blood Sugar ,Postprandial blood sugar , C-reactive protein quantitative test and Hba1c

Methodology

Fasting blood glucose was analyzed by the method devised by Astoor and King (1954),C-Reactive Protein (CRP) by Immunonephelometry with range Less than or equal to 3 mg/L.

Observations

This study was done in outdoor & indoor patients coming to Mahatma Gandhi Hospital, Dr. S.N. Medical College Jodhpur (Raj.). Following groups were made-

Group – I - Include 30 non diabetic control patients.
Group – II - Include 30 diabetic patients with $HbA_{1c} < 7$.
Group –III - Include 30 diabetic patients with HbA_{1c} 7-9.
Group – IV - Include 30 diabetic patients with $HbA_{1c} > 9$.

Table –1 Fasting blood sugar

Fasting blood sugar (mg/dl)	Male	Mean FBS±S.D.	Female	Mean FBS±S.D.
< 100	31	84.74±9.26	19	83.21±10.99
100-125	18	107.72±7.44	16	113.12±6.63
> 125	20	182.8±46.52	16	177.87±38.43

Table – 2 Comparison of HbA_{1c} in different age group

Group	Age	No. of patients	Mean HbA_{1C} ± SD.			
			Group I	Group II	Group III	Group IV
A	20-40	34	6.57±0.26	6.44±0.21	7.38±0.18	9.42±0.21
B	40-60	51	6.4±0.21	6.81±0.07	8.06±0.24	10.23±0.26
C	> 60	35	6.13±0.08	6.82±0.10	8.58±0.55	11.06±0.36
	Total	120				

Comparing the HbA_{1C} with age groups it was found that

	A &B		B&C		A&C	
Group I	<0.001	H.S.	<0.001	H.S	<0.001	H.S
Group II	<0.001	H.S	>0.7	N.S.	<0.01	S.
Group III	<0.001	H.S	<0.001	H.S	<0.001	H.S
Group IV	<0.001	H.S	<0.001	H.S	<0.001	H.S

Table – 3 Comparison of Fasting Blood Sugar with HbA1C

Group	Fasting Blood sugar (mg/dl)	Total number of the patients	Mean±S.D of FBS	Mean±S.D of HbA1c
A	< 100	N= 51	84.21±9.68	6.51±0.30
B	100-125	N= 35	110.17±7.28	8±1.01
C	> 125	N= 34	185.52±37.77	9.67±1.33

Comparison of mean HbA1C in different FBS group

Groups	P Value	Significance
A + B	<0.001	H.S
A+C	<0.001	H.S
B+C	<0.001	H.S

Applying the "standard error of difference between two means" test of significance, it was found that highly significant relation between fasting blood sugar and HbA_{1c} existed between group A & B, group A & C and B & C.

Table – 4 Study of C-reactive protein in different weight group ==

Gr.	Wight (kg/dl)	No. of patients	Mean CRP±SD.
A.	20-40	35 (29.17%)	6.61±4.41
B.	40-60	51 (42.50%)	7.22±5.62
C.	> 60	34 (28.33%)	10.12±7.23
	Total	120	

This table show that 35 patients were in weight group 20-40 had mean CRP 6.61 with Standard deviation 4.41, 51 patients were in 40-60 weight group had mean CRP 7.22 with Standard deviation 5.62 and 34 patients were in more than 60 kg weight group had mean CRP 10.12 with standard deviation 7.23.

Group	P Value	Significance
A&B	>0.6	N.S
A&C	<0.02	S.
B&C	>0.1	N.S.

Table – 5 Comparison of HbA_{1c} and CRP in different weight group

Group	Weight	No. of patients	Mean wt.±S.D.	Mean HbA_{1C}±S.D.	Mean CRP±S.D.
A	< 50	12	48.41±1.80	6.63±0.73	3.93±2.39
B	50-70	65	63.27±5.43	7.06±0.99	4.87±3.65
C	70-90	34	80.79±5.43	9.12±1.32	12.6±5.29
D	> 90	9	96.44±5.43	10.32±0.86	16.71±3.28

Applying the "standard error of difference between two means" test of significance, it was found that highly significant relation between the weight and HbA_{1c} existed between group A & C, group A & D, B & C and B & D. Significant relation between Group C & D and Non significant relation between A & B.

Comparison of CRP in different weight group

Groups	P.Value	Significance
A & B	> 0.3	Non Significant
A & C	< 0.001	Highly Significant
A & D	< 0.001	Highly Significant
B & C	< 0.01	Highly Significant
B & D	< 0.001	Highly Significant
C & D	< 0.01	Significant

Applying the "standard error of difference between two means" test of significance, it was found that highly significant relation between the weight and CRP existed between group A & C, group A & D, B & C and B & D. Significant relation between Group C & D and Non significant relation between A & B.

Table – 9 Comparison of Fasting Blood sugar with CRP in different group

Group	FBS	No. of patients	Mean FBS ±S.D.	Mean CRP ±S.D.
A	<100	51	84.21±9.68	3.01±0.77
B	100 -125	35	110.17±7.28	8.18±3.75
C	> 125	34	185.52±37.77	14.8±4.99

Comparison of mean CRP in different FBS group

Groups	P.Value	Significance
A & B	< 0.001	Highly Significant
A & C	< 0.001	Highly Significant
B & C	< 0.001	Highly Significant

This table showed that there was highly significant co-relation between CRP & Fasting blood sugar among group A & B, A & C and B & C.

Table – 10 Study of relation between HbA_{1C} and CRP

Group	HbA_{1C}	Total of pts.	Mean CRP	± S.D.
A	6-6.99	59	2.96	0.63
B	7-7.99	16	6.80	0.81
C	8-8.99	14	10.42	1.57
D	9-9.99	13	13.55	0.38
E	10-10.99	14	18.23	1.88
F	> 11	4	20.68	0.18

Applying the "standard error of difference between" the test of significance, it was found that highly significant relation between the CRP and HbA_{1C} existed between group A & B, A & C, A & D, A & E, A &F, B & C and B & D, B & E, B & F, C & D, C & D, C &E, C & F, D & E, D & F and E & F.

Discussion

The level of fasting blood sugar ,post prandial blood sugar, HbA1C and c-reactive protein were done and comparison done among group I, II, III and IV. Both type I and II diabetic patients were compared with non diabetic control patients.

In the study of mean C-reactive protein with fasting blood sugar, it was found that mean CRP were--

3.01±0.77 In normal Blood Sugar group
8.18±3.75 In Impair fasting blood sugar group
14.8±4.99 In diabetic group

The difference was statistically significant

In present study on comparing the fasting blood sugar with HBA_{1C} it was found that mean HBA_{1C} was 6.51± 0.30 for patients having blood sugar below 100 mg/dl (mean FBS± S.D.84.21± 9.68),8.0±101 for patients having blood sugar 100-125 mg/dl (mean FBS± S.D.110.17±7.28) and 9.67±1.33 for patients having blood sugar more than 125 mg/dl (mean FBS± S.D. 185.52±37.77). The difference was statistically significant Comparing the c reactive protein level with HBA_{1C} level it was found that 49.17% patients were in HBA_{1C} group 6- 6.99 had mean CRP 2.96±0.63,13.33% patients were in HBA_{1C} group 7-7.99 had mean CRP 6.80±0.81, 11.67% patients were in HBA1C group 8-8.99 had mean CRP 10.42±1.57, 10.83% patients were in HBA1C group 9-9.99 had mean CRP 13.55±0.38, 11.67% patients were in HBA_{1C} group 10-10.99 had mean CRP 18.23±1.88, 3.33% patients were in HBA_{1C} group > 11 had mean CRP 20.68±0.18. The difference was statistically significant (p value< 0.001).

King DE, Mainous AG 3rd, Buchanan TA, Pearson WS et al[7]. studied the relation between CRP and HbA(1c) in a large national sample of individuals with diabetes. A nationally representative sample of noninstitutionalized U.S. adults aged 17 years and over with nongestational diabetes was derived from the National Health and Nutrition Examination Survey III (1988-1994) (n= 1,018). Respondents with diabetes were stratified by HbA(1c) level. The main outcome measure was elevated (>0.30 mg/dl) CRP. In unadjusted analyses, respondents with diabetes who had elevated HbA(1c) levels (> or =9.0%) had a significantly higher percent of elevated CRP than people with low (<7%) HbA(1c) levels (P < 0.001). In adjusted regression analysis, after controlling for age, race, sex, smoking, length of time with diabetes, insulin, and BMI, HbA(1c) was significantly associated with an increased likelihood of elevated CRP for HbA(1c) >9.0% (OR 2.15, 95% CI 1.07-4.32) and for HbA(1c) >11.0% (4.40, 1.87-10.38). In this study, the likelihood of elevated CRP concentrations increased with increasing HbA(1c) levels. These findings suggest an association between glycemic control and systemic inflammation in people with established diabetes.

Our study also concluded that higher C-reactive protein is associated with increased HbA_{1C} level (P<0.001 highly significant).

Wen J, Liang Y, Wang F, Sun L, Guo Y, Duan X, Liu X, Wong TY, Lu X, Wang N et al[8] studied the association of C-reactive protein (CRP), gamma-glutamyl transferase (GGT) and type 2 diabetes in Chinese a population-based cross-sectional study.: CRP and GGT levels were significantly higher in participants with diabetes than in those without (P<0.001). Higher CRP levels were positively associated with prevalent type 2 diabetes after adjustment for age, sex, smoking, alcohol consumption, physical activity, family history of diabetes, body mass index, waist circumference, waist/hip ratio, education, systolic blood pressure, triglycerides, high density lipoprotein cholesterol, use of antihypertensive drugs, aspirin and lipid-lowering agents, with multivariable odds ratios (OR) of 1.55 (95% confidence interval (CI), 1.05-2.27, P trend=0.005, comparing quartile 4 to quartile 1). However, after further adjustment for GGT, the association

was completely attenuated (fourth quartile OR 1.23, 95% CI, 0.83-1.82, P trend=0.127). Moreover, the association of CRP and prevalent type 2 diabetes was stronger in subjects with GGT values above the median than in those with GGT values below the median. Increasing serum GGT quartiles were positively associated with prevalent type 2 diabetes after adjustment for potential confounding variables (P for trend <0.001). CRP may not be an independent risk factor for type 2 diabetes, at least in Chinese people but in our study CRP was associated with control of diabetes. Higher CRP were present in uncontrolled diabetes patients

GA[3]mez JM, Vila R, Catalina P, Soler J, Badim A[3]n L, Sah A[0]n M.et al[9] studied the several biomarkers of inflammation, of endothelial dysfunction, glycated haemoglobin in patients with type 2 diabetes mellitus and in their relatives, in order to demonstrate if relatives present markers as a form of precocious indicators of diabetes mellitus. In conclusion patients with uncomplicated type 2 diabetes, but not their relatives, have biochemical markers of sub-clinical inflammation in relationship with glycated haemoglobin and dysfunction of the endothelial cells markers .In our study also c reactive protein level were more in diabetic patients than control. The c reactive protein level were related to blood sugar control .Applying the "standard error of difference between two means" test of significance, it was found that highly significant relation between c reactive protein level and $HbA1_c$.

Conclusion

In the control group there were 21 (70%) male and 9 (30%) female patients. In type I diabetics out of total 25 patients 13(52%) were male and 12 (48%) were female. In the type 2 diabetics out of total 65 patients 35 (53.84%) were male and 30 (46.16) were female. The difference was found to be in statistically insignificant. In the study of relation between fasting blood sugar and mean $HbA1_C$ it was found that there was highly significant co-relation P <0.001 between fasting blood sugar and mean $HbA1_C$ in the different fasting blood sugar groups. On comparing mean $HbA1_C$ with different weight groups it was found that mean $HbA1_C$±S.D. was 48.41±1.8 mean weight group, 7.06±0.99 for 63.27±0.43 mean weight group, 9.12±1.32 for 80.79±5.43 mean weigh group and 10.32±0.86 for 96.44±5.43 weigh group patients. The difference was found to be in statistically highly significant.

In the study of mean C-reactive protein with fasting blood sugar, it was found that mean CRP were 3.01±0.77 in normal Blood Sugar group, 8.18±3.75in impair fasting blood sugar group, 14.8±4.99 in diabetic group. Comparing the mean C-reactive protein with different HbA_{1C} group it was found that mean C-reactive protein were 2.96±0.63 in 6-6.99 HbA_{1C} group, 6.80±0.81 in 7-7.99 HbA_{1C} group, 10.42±1.57 in 8-8.99 HbA_{1C} group ,13.55±0.38 in 9-9.99 HbA_{1C} group, 18.23±1.88 in 10-10.99 HbA_{1C} group, 20.68±0.18 in > 11 HbA_{1C} group. On comparison of different group statistically highly significant relation was found (P<0.001) between HbA_{1C} and C-reactive protein.

Finally we concluded that statistically significant difference was found in number of type 1 and 2 patients and highly significant relation was found between fasting blood sugar and HbA_{1c} both in control and diabetic patients. Statistically highly significant relation was found between mean C-reactive protein with fasting blood sugar and between mean C-reactive protein with HBA_{1C}.

References

1. Gupta A, Gupta R, Sarna M, Rastogi S, Gupta VP, Kothari K. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. Diabetes Res Clin Pract 2003; 61 : 69-76.

2. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin-6, and risk of developing type 2 diabetes mellitus. JAMA 286:327-334, 2001 .

3. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279:48487-90.

4. Hu FM, Meigs JB, Li Ty, Rifai N, Manson JE: Inflammatory markers and risk of developing type 2 diabetes in women Diabetes 53:693-700,2004..

5. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin- 6, and risk of developing type 2 diabetes mellitus. JAMA 286:327–334,2001

6. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an

American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112:2735-2752.

7. King DE, Mainous AG 3rd, Buchanan TA, Pearson WS et al. The relation between CRP and HbA(1c) .The National Health and Nutrition Examination Survey III (1988-1994) .

8. Wen J, Liang Y, Wang F, Sun L, Guo Y, Duan X, Liu X, Wong TY, Lu X, Wang N et al .The association of C-reactive protein (CRP), gamma-glutamyltransferase (GGT) and type 2 diabetes in Chinese a population-based cross-sectional study .

9. GA3mez JM, Vila R, Catalina P, Soler J, Badim A3n L, Sah A0n M.et al . The biomarkers of inflammation, of endothelial dysfunction, glycated haemoglobin in patients with type 2 diabetes mellitus and in their relatives, in order to demonstrate if relatives present markers as a form of precocious indicators of diabetes mellitus.