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Study of Highly Sensitive C - Reactive Protein (hs-CRP) In Type 2 Diabetes Mellitus and Its Correlation with Glycosylated Hemoglobin

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Abstract
Background: *Diabetes mellitus is one of the leading causes of morbidity and mortality. Studies have shown that hs-CRP is associated with insulin resistance, type 2 diabetes and higher HbA1c levels. This study was done to evaluate the correlation of hs-CRP with HbA_1C.*
Objectives: *The aim of this study is to determine the serum high sensitive C- Reactive Protein (hs-CRP) in patients with type 2 diabetes mellitus and to correlate with HbA_1C levels.*
Materials and Methods: *In this study 50 patients aged above 18 years with type 2 diabetes mellitus were enrolled and subjected to detailed history and examination. In all patients hs-CRP with HbA_1C were measured.*
Results: *In our study population 79% had hs-CRP levels ≥3.0 and 21% had hs-CRP levels <3.0. It concludes that higher prevalence of increase of hs-CRP in subjects with Type 2 diabetes. We found no statistically significant correlation among them except with duration of DM.*
Conclusion: *This study strongly warrants future investigations that probe the role of genetic variants and other environmental factors that influence the elevation of hsCRP levels in this high-risk group.*
Keywords: *HbA_1C, hs-CRP, Type 2 diabetes mellitus.*

Introduction

Diabetes is a metabolic -disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate, and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extracellular hyperglycemia which results in tissue damage and chronic vascular complications in both types I and II Diabetes Mellitus[1,2]

Previous studies have shown that hs-CRP is associated with insulin resistance, type 2 diabetes, and higher HbA1c levels. A recently retrospective observed the hs-CRP levels correlated with HbA1c levels. Mean HbA1c levels were

significantly higher in patients who had hs-CRP levels of 1 mg/L or more.[1] In the year 2015 Chinese study was also revealed through multivariate stepwise regression analysis that indicated that HbA1c correlated with hs-CRP. [2] A Turkish study also reported a positive correlation between serum hs-CRP and HbA1c. [3]

Chronic inflammation plays an important role in the development and progression of late complications of diabetes. C-reactive protein (CRP), an acute phase reactant, is a highly sensitive marker of inflammation. Its level rises dramatically during an inflammatory process. [4] CRP has a long half-life, affordability of estimation, and stability of its levels with no circadian variation, and therefore is one of the best markers of vascular inflammation.[5] CRP has been found to be associated with disorders like DM, cardiovascular disorders, metabolic syndrome, Rheumatoid Arthritis, renal failure, etc.[6,7,8] The serum high sensitivity CRP (hsCRP) level is higher in patients with Type 2 diabetes than in normal subjects and plays an important role in the development and progression of Type 2 DM.[9]

India is having the highest number of T2D individuals worldwide, with a prevalence of 11.6% in urban populations.[10,11] Furthermore, Asian Indians are known to be at a high risk for T2D, CVD, and metabolic syndrome. [12,13] Although elevated levels of hs-CRP have been observed in expatriate adult Indians[14] and adolescents residing in India[15], data on adult individuals residing in India are scanty. Therefore, the present study was designed to study the correlation of hs-CRP levels with HbA1c in type II subjects in MMU Mullana.

Materials and Methods

The present study was conducted at M.M. Institue of Medical Sciences and Research, Mullana. Ambala, Haryana. Fifty patients were taken from OPD or indoor wards of the department of medicine. All the patients fulfilled the inclusion/exclusion criteria into the study after obtaining written informed consent. All patients were subjected to detailed history and systemic examination. In every patient routine biochemical investigations were sent along with hsCRP and HbA_1C. The result was compiled using SPSS and appropriate statistical tests were used.

Inclusion Criteria

- Age above 18
- Type 2 diabetes mellitus

Exclusion Criteria

- Gestational diabetes
- Cardiovascular abnormalities (IHD, RHD)
- On anti-inflammatory drugs
- No history of RA arthritis
- No history of acute infections (UTI, URTI)
- No history of chronic infection like HBV, HCV
- No history of collagen vascular disease like SLE

Results

Table 1: Descriptive analysis of Age Group in study population (n=100)

Age Group	Frequency	Percentage
17-35	11	11.00%
36-50	43	43.00%
51-65	33	33.00%
66 and above	13	13.00%
Mean Age	50.97±13.4	

Descriptive analysis of Age Group in study population shows the maximum number of samples in the age group of 36-50 years, a mean age 50.97 years, a maximum age of 89 years and the lowest age of 18 years.

Figure 1: Pie chart of Age Group distribution in study population (n=100)

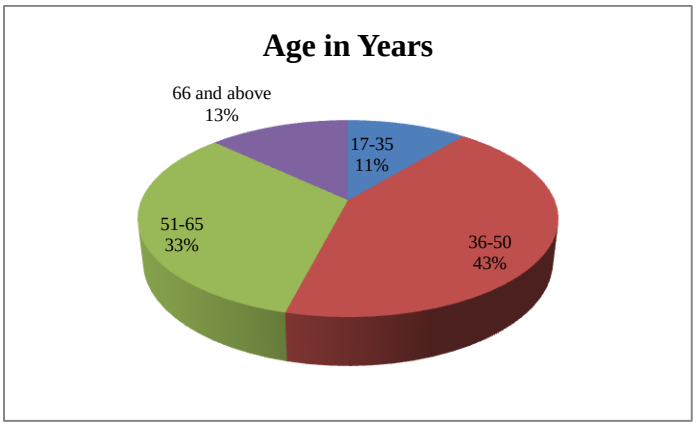


Table 2: Descriptive analysis of Gender in study population (n=100)

Gender	Frequency	Percentage (%)
Male	74	74
Female	26	26

In our study 74% are male and 26% are female that were enrolled.

Figure 2: Bar chart of Gender distribution in study population (N=100)

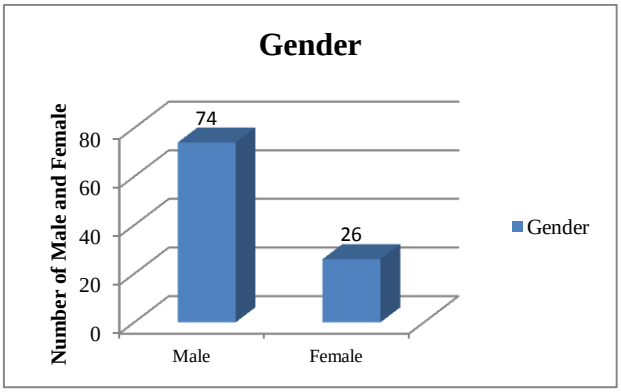


Table 3: Descriptive analysis of HBA1C category in study population (N=100)

HbA1c Levels	Frequency	Percentage
Up to 6.5	6	6.00%
6.6-7.5	13	13.00%
7.6-8.5	19	19.00%
8.6-9.5	17	17.00%
Above 9.6	45	45.00%

In our study population maximum patients had HbA1c levels more than 9.6; 45%, mean Hba1c levels was 9.86, maximum of 19.90 and a minimum level of 4.90.

Figure 3: Bar chart of HbA1c levels distribution in study population (N=100)

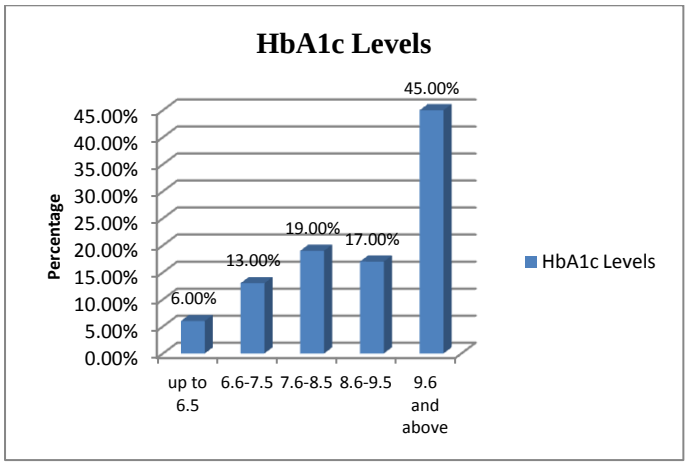


Table 4: Descriptive analysis of hs-CRP category in study population (n=100)

hs-CRP Levels	Frequency	Percentage
≥3	79	79.00%
<3	21	21.00%

In our study population, 79% had hs-CRP levels ≥3.0 and 21% had hs-CRP levels <3.0

Figure 4: Pie chart of hs-CRP distribution in study population (N=100)

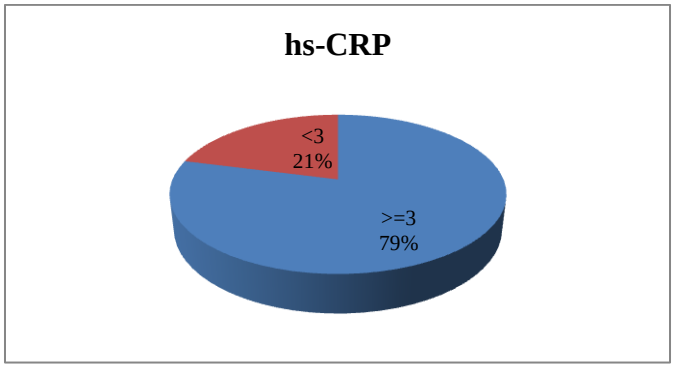


Table 5: Descriptive analysis of Duration of Diabetics Mellitus category in study population (n=100)

Duration of Diabetes Mellitus	Frequency	Percentage
Up to 5 years	59	59.00%
Up to 6-10 Years	25	27.00%
11 Years and above	16	16.00%

Maximum 59 (59%) patients had diabetic from less than 5 years

Figure 5: Pie chart of Duration of Diabetics Mellitus distribution in study population (n=100)

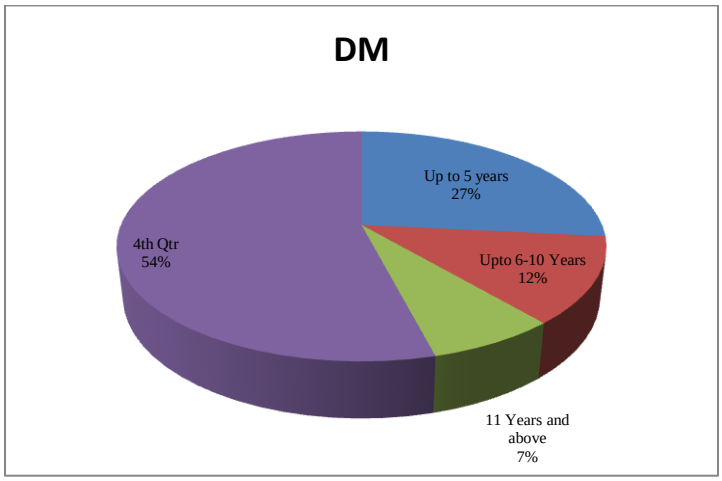


Table 6: Descriptive analysis of BMI category in study population (n=100)

BMI Category	Frequency	Percentage
<23	9	9.00%
≥23	91	91.00%

91% of the study population had a BMI ≥ 23 and 9% had a BMI < 23. Mean BMI of the study population is 25.64 with lowest BMI recorded was 22.50 and highest BMI recorded was 29.70

Figure 6: Bar chart of BMI category distribution in study population (n=100)

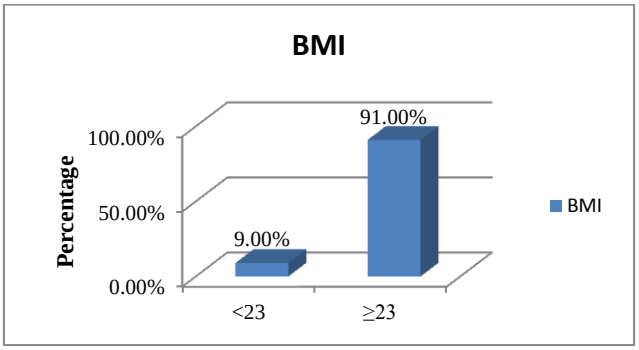


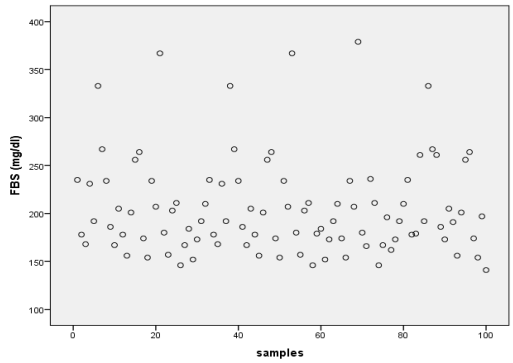
Table 7: Descriptive analysis for FBS in study population (n=100)

Parameter	Mean ± STD	Median	Minimum	Maximum	95% C.I for EXP(B)	
					Lower	Upper
FBS	205.27± 50.23	192	141.00	379.00	195.30	215.24

In our study population we achieved a mean FBS 205.27, maximum FBS recorded is 379, and minimum FBS recorded 141.

Figure 7: showing values of FBS obtained in study population (n=100)

Scattered diagram



Part- 2 Inferential analysis: Factors associated with elevated hs-CRP

Table 8: Association of HS CRP category with Age Group of study population (N=100)

Age Group	HS CRP Category		Chi-Square	P-Value
	≥3 (n=79)	<3 (n=21)		
17-35	7 (8.9%)	4 (19.0%)	3.243	0.355
36-50	33 (41.8%)	10 (47.6%)		
51-65	27 (34.2%)	6 (28.6%)		
66 and above	12 (15.2%)	1 (4.8%)		

In our study, there was no relation between hs-CRP and Age group (p>0.05)

Figure 8: association with hs-CRP with age group of study population (n=100)

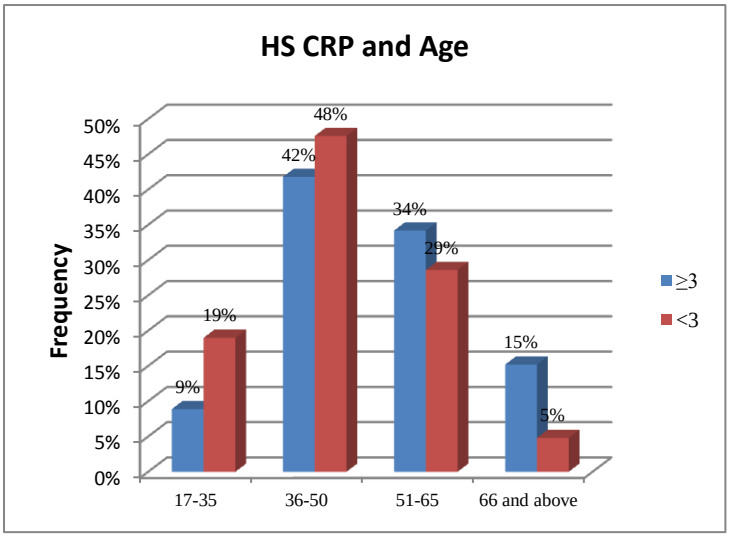


Table 9: Association of HS CRP with Gender of study population (n=100)

Gender	HS- CRP		Chi Square	P-Value
	≥3 (n=79)	<3 (n=21)		
Male	58 (73.42%)	16 (76.19%)	0.066	0.797
Female	21 (26.58%)	5 (23.80%)		

In our study, hs-CRP levels were found to be independent of Gender (p>0.05)

Figure 9: Association with hs-CRP with age group of study population

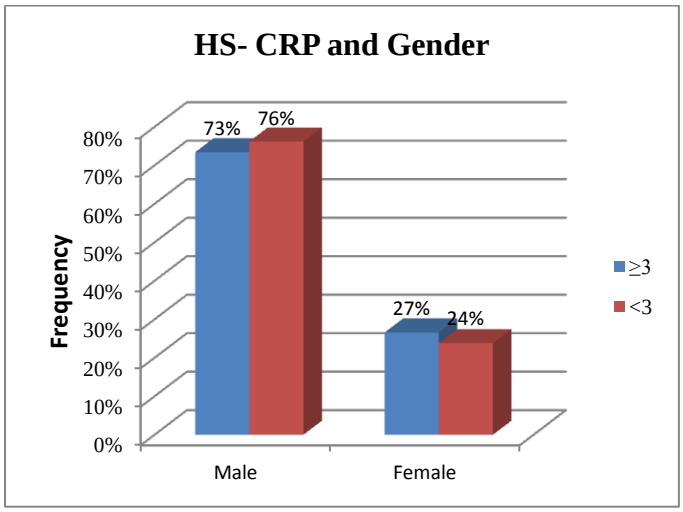


Table 10: Association of hs-CRP with Duration of Diabetics of study population (n=100)

Duration of Diabetics Mellitus	hs-CRP		Chi-Square	P-Value
	≥3(n=79)	<3(n=21)		
≤5 years	42	17	6.801	0.033
6-10 years	21	4		
≥11 years	16	0		

In our study hs-CRP levels were found to be significant with increasing duration of DM (p>0.05)

Figure 10: Association of hs-CRP with Duration of Diabetics of study population (n=100)

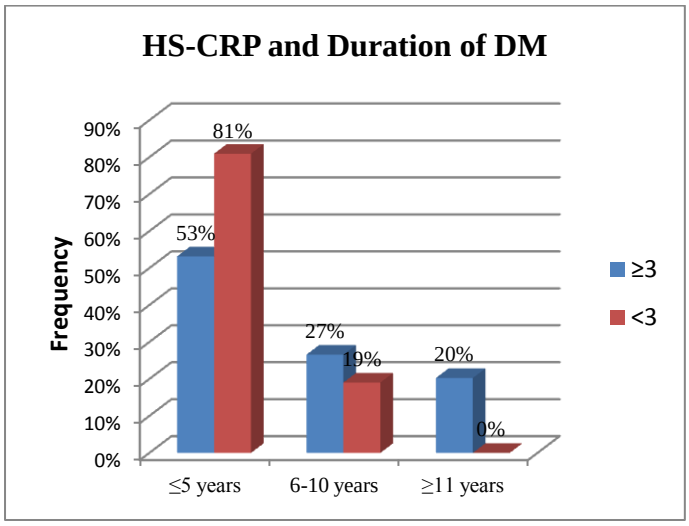
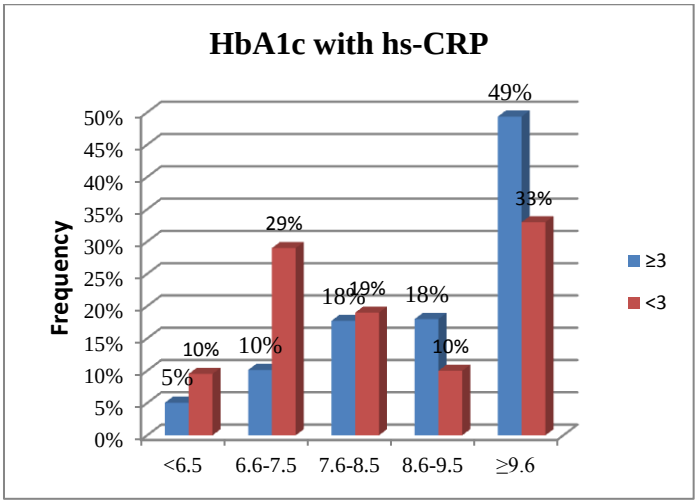


Table 11: Association of hs-CRP with HBA1C category of study population (n=100)

HbA1c	Hs_CRP		Chi-Square	P-Value
	≥3(n=79)	<3(n=21)		
<6.5	4 (5.06%)	2 (9.52%)	6.222	0.183
6.6-7.5	8 (10.12%)	6 (28.57%)		
7.6-8.5	14 (17.72%)	4 (19.04%)		
8.6-9.5	14 (17.72%)	2 (9.52%)		
≥9.6	39 (49.36%)	7 (33.33%)		

In our study hs-CRP levels were found to significant with increasing levels of HbA1c (P>0.05)

Figure 11: Association of hs-CRP with HbA1c levels of study population (n=100)



Discussion

In the present study diabetic patients were older with mean 50.97±13.4 years and the majority 74% being male as similar to study done by Amanullah S et al[16] Reported mean age of 51 years of diabetic subjects. In the prospective study done by Sasidharan A et al[17] enrolled 50 patients in the study, there were 36 (78%) males and 14 (28%) female patients. The minimum age was 34 years old and maximum age was 75 years old which is similar to the present study. 91% of the study population had a BMI ≥ 23 and 9% had a BMI < 23. Mean BMI of the diabetic population is 25.64 with lowest BMI recorded was 22.50 and highest BMI recorded was 29.70.

This was further confirmed by the study done by Ni Mhurchu et al[18]. Eric and John[19] and NHANES[20] the report indicates that most adults with diagnosed diabetes were overweight or obese, the prevalence of overweight or obesity was 85.2 % and the prevalence of obesity was 54.8%. Cosin Aguilar et al[21] from this study state that the obese patients showed the higher prevalence of diabetes.

Elevated hs-CRP levels frequently cluster with well-established risk factors of T2DM such as obesity and insulin resistance. [22] Therefore, we extensively evaluated the effect of markers of these conditions on hsCRP levels. BMI and WC were observed to be the dominant contributors of hsCRP levels here. These observations reiterate the role of obesity as a major determinant of hs-CRP levels in this population. Similar observations have been previously made by Forouhi NG et al where they found obesity as a major determinant of hs-CRP levels in healthy expatriate South Asians. [23]

In our study population, 79% had hs-CRP levels ≥3.0 and 21% had hs-CRP levels <3.0. It concludes that higher prevalence of increase of hs-CRP in subjects with Type 2 diabetes. Studies on western populations have shown low-grade systemic inflammation to be one of the mechanisms by which known risk factors such as obesity, smoking, and Hypertension promote the development of diabetes mellitus as studies conducted by Pradhan et al. [24] 2001; Pfutzner and Forst,[25]. However, there are few studies of hs-CRP in Asian Indians, a very high- risk group for diabetes as reported by Mohan et al.[1] 2003 and Mohan et al. [27]

In the present study, we evaluated the association between hs-CRP and risk factors like age, gender, duration of DM and Hba1c. We found no statistically significant correlation among them except the duration of DM., we document the association of hs-CRP levels with glycemic control in North Indian adults. The CRP levels are significantly increased in diabetics. In this study, a strong correlation is present between CRP and a host of other variables such as age, BMI, waist circumference, waist-hip ratio, systolic and diastolic blood pressure, serum triglyceride, family history of diabetes, physical inactivity, use of antihypertensive drugs, and hormonal replacement therapy. However, a strong positive correlation exists between CRP and risk of developing diabetes in women.[19]

These results are also in agreement with previous studies, Bhavita Patel[28], in their study; the lowest levels of hsCRP were found in normal patients and were lower in comparison to obese-diabetics. On univariate analysis, hs-CRP was found to be significantly increased in patients with diabetes mellitus ($p < 0.021$) and those with abnormal waist circumference ($p<0.003$).

In the recent study, Geetha Bhaktha et al[29] reported a high level of Hs-CRP in diabetic subjects when compared to normal individuals. hs-CRP failed to show any correlation with BMI, FBS, and HbA1c. Diabetes is considered as an inflammatory disease hence they observed an increase in the hs-CRP level in diabetes than in the normal. Since the vascular complication was totally absent hs-CRP failed to show any correlation with BMI, FBS, and HbA1c which is similar to the present study.

After adjustment of mean insulin among men and women, it was found that there is a concomitant increase in HbA1c level with CRP as reported by Wu T et al.[30] King et al. found a strong correlation between HbA1c levels and CRP. Besides, they also found that CRP levels were associated with HbA1c levels.[31] The difference in results in the present study from the previous literature may be due to only inclusion criteria and design of the study.

Anubha Mahajan et al[32] aimed to assess the association of hs-CRP with T2D and to determine its correlates in North Indians of Indo-European origin. They demonstrate the association of low-grade systemic inflammation, as indicated by elevated hs-CRP levels, with T2D in North Indian population which is similar to the present study.

Roopakala MS et al enrolled 50 DN patients in the age group of 50- 60 years with more than ten years of duration of diabetes were recruited for the study and 25 age-and-sex-matched healthy subjects were included in this study as controls. The hsCRP levels showed a positive correlation with HbA1c in DN. These results suggest that estimation of serum hs-CRP levels and aiming at good glycemic control help in early intervention and prevention of further complications in diabetic patients. [33]

Ajay Meshram et al stated that Anthropometric parameters found to be high in diabetic subjects compared with non-diabetic subjects. The high hs-CRP levels in diabetic subjects were also observed. The results concluded that hs-CRP has a strong association with diabetic individuals. [34]

Over the years, accumulating evidence suggests that hs-CRP may be associated with an increased risk of future cardiovascular events in otherwise healthy individuals.[35] The magnitude of this association, however, seems to be strongly affected by the presence or absence of T2D.

Conclusion

The advantages of this study include the systematic recruitment of subjects and rigorous assessment of different parameters traits. Given the marked difference in the levels of anthropometric and biochemical parameters between urban and rural set-ups, samples have been obtained from a well-defined population, representing a single ethnic group inhabiting urban locales. Nevertheless, our study is limited by its cross-sectional design, which precludes conclusions regarding the cause and effect relationships. This study strongly warrants future investigations that probe the role of genetic variants and other environmental factors that influence the elevation of hsCRP levels in this high-risk group.

Reference

1. Brownlee M and Cerami A. Biochemistry of the complications of diabetes mellitus. Annu rev. Biochem, 1981; 50:385-432.
2. Luscher TF, Creager MA, Bckman JA, Cosentino F. Diabetes and vascular disease: Pathophysiology, Clinical conse-quences, and medical therapy: Part II. Circulation, 2003; 108 (13): 1655-1661.
3. Sarinnapakorn V and Wanicagool W. Association between hs-CRP and Hba1c in overweight type 2 diabetic female patients. J Med Assoc Thai. 2013 Mar;96(3):54-8.
4. SHI CH, WANG C, BAI R, ZHANG XY, MEN LL, DU JL. Associations among glycemic excursions, glycated hemoglobin and high-sensitivity C-reactive protein in patients with poorly controlled type 2 diabetes mellitus. Experimental and Therapeutic Medicine. 2015;10(5):1937-1942.
5. Bahceci M, Tuzcu A, Ogun C, Canoruc N, Iltimur K, Aslan C.Is serum C-reactive protein concentration correlated with HbA1c and insulin resistance in Type 2 diabetic men with or without coronary heart disease? J Endocrinol Invest. 2005 Feb;28(2):145-50.
6. Dong Q, Wright JR. Expression of C-reactive protein by alveolar macrophages. J Immunol 1996;56:4815-20
7. Wang AY. Prognostic value of C-reactive protein for heart disease in dialysis patients.CurrOpinInvestig Drugs. 2005 Sep;6(9):879-86.
8. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. Adv Cardiol 2008;45:1-16.
9. Doggen CJ, Berckmans RJ, Sturk A, Cats VM, Rosendaal FR. C-reactive protein, cardiovascular risk factors and the association with myocardial infarction in men. J Intern Med 2000; 248:406-14
10. Kang ES, Kim HJ, Ahn CW. Relationship of serum high sensitivity C-reactive

protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res Clin Pract 2005;69:151-9.
11. Yan SF, Ramasamy R, Naka Y, Schmidt AM. Glycation, Inflammation, and RAGE. A Scaffold for the Macrovascular Complications of Diabetes and Beyond. Circ Res 2003;93:1159– 69.
12. Chowdhury TA, Hitman GA. Type 2 diabetes in people of South Asian origin: potential strategies for prevention. Br J Diabetes Vasc Dis, 2007;7:279–282.
13. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. Diabetes Care, 2004; 27:1047–1053.
14. Ramachandran A, Mary S, Yamuna A, Murugesan N, Snehalatha C. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care, 2008; 31:893–898.
15. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet, 2000;356:279–284.
16. Chandalia M, Cabo-Chan Jr AV, Devaraj S, Jialal I, Grundy SM, Abate N. Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. J Clin Endocrinol Metab, 2003;88:3773–3776.
17. Vikram NK, Misra A, Pandey RM, Dwivedi M, Luthra K, Dhingra V, et al. Association between subclinical inflammation & fasting insulin in urban young adult north Indian males. Indian J Med Res, 2006;124:677–682.
18. Amanullah S, Jarari A, Govindan MK, Basha MI, khatheeja S. Association of hs-CRP with Diabetic and Non-diabetic individuals. Jordan Journal of Biological Sciences.2010;3(1):7-12.
19. Sasidharan A, Krishnamurthy A, Tagore S, Nagaraj T, Santosh HN, Nigam H. C-reactive protein and glycemic control in adults with type 2 diabetes mellitus. J Med Radiol Pathol Surg 2016;2:10-13.
20. Ni Mhurchu C, Parag V, Nakamara M, Patel A, Rodgers A, Lam TH. Body Mass index and risk of diabetes mellitus in the Asia-Pacific region. Asia Pac. J. Clin. Nutr. 2006;15(2): 127-133.
21. Eric J B and John HF. The relation between blood glucose and coronary mortality over 33 years in the Whitehall study. Diabetes Care. 2006 Jan;29(1):26-31.
22. NHANES. Prevalence of overweight and Obesity among adults with diagnosed diabetes – US, 1988-1994 and 1999- 2002. JAMA, 2005; 293: 546-547.
23. Cosin AJ, Hernandiz MA, Masramon MX. Overweight and obesity in hypersensitive Spanish patients. (The coronary study. Med Clin (Barc), 2007;10:129.
24. Chambers JC, Eda S, Bassett P, Karim Y, Thompson SG, Gallimore JR, Pepys MB, Kooner JS 2001 C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. Circulation 104:145–150
25. Forouhi NG, Sattar N, McKeigue PM 2001 Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. Int J Obes Relat Metab Disord 25:1327–1331
26. Pradhan AD, Manson JE, Rifai. N, Burning JE, Ridker PM. 2001.C-reactive protein, interleukin 6 and risk development type 2 diabetes mellitus. JAMA. 286: 327-334.

27. Pfutzner A, Forst T.2006. High-sensitivity C-reactive protein as a cardiovascular risk marker in patients with diabetes mellitus. Diabetes Technol Ther 8(1):28-36.
28. Mohan V, Shanthirani CS. Deepa R. 2003. Glucose intolerance (diabetes and IGT) in the selected south Indian population with special reference to family history, obesity and lifestyle factors. The Chennai Urban Population Study (CUPS 14). J. Assoc. Physicians India. 51: 771-777.
29. Mohan V, Shanthi Rani S, Deepa R, Premalatha G and Sastry NG. 2001. Introduction Urban difference in the prevalence of metabolic syndrome in South India. The Chennai Urban Population Study (CUPS 14). Diabet . Med. 18: 280-287.
30. Patel B, Taviad D, Malapati B, Gokani R, Shaikh N, Shah R. Association of hs-CRP levels with Obesity & Metabolic syndrome in patients with Type-2 Diabetes Mellitus: a link between inflammation, adiposity & insulin resistance. Int J Biol Med Res.2015;6(3):5104-5108
31. Geetha Bhaktha, Manjula Shantaram, Shivananda Nayak, Nagendra S. Relationship of hs-CRP level in diabetic persons free from micro and macrovascular disease. International Journal of Research and Development in Pharmacy and Life Sciences 2014, Vol. 3, No.4, pp 1070-1073.
32. Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M. Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin: The Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2002;155:65-71.
33. King DE, Mainous AG 3rd, Buchanan TA, Pearson WS. C-reactive protein and glycemic control in adults with diabetes. Diabetes Care 2003;26:1535-9.
34. Anubha Mahajan, Rubina Tabassum, Sreenivas Chavali, Om Prakash Dwivedi, Mausumi Bharadwaj, Nikhil Tandon, Dwaipayan Bharadwaj. High-Sensitivity C-Reactive Protein Levels and Type 2 Diabetes in Urban North Indians. J Clin Endocrinol Metab (2009) 94 (6): 2123-2127.
35. Roopakala M S, Pawan H R, Krishnamurthy U, Wilma Delphine Silvia C R, Eshwarappa M, Prasanna Kumar K M. Evaluation of high sensitivity C-reactive protein and glycated hemoglobin levels in diabetic nephropathy. Saudi J Kidney Dis Transpl 2012;23:286-9.
36. Ajay Meshram, Udit Agrawal, Archana Dhok, Prashant Adole, Komal Meshram, Ruchir Khare. HbA1c, hs-CRP and anthropometric parameters evaluation in the patients of diabetes Mellitus of Central Rural India. International Journal of Medical Science and Public Health 2013; 2(2):291-294.
37. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith Jr SC, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association 2003 Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107:499–51