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Role of high sensitivity C reactive protein in diabetes patients and its relationship with HbA1c and lipid profile.

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Abstract

Background: Chronic diseases such as type 2 diabetes mellitus (T2DM) get complicated with the increasing duration and severity of hyperglycemia. Hyperglycemia is a pro-inflammatory condition that causes a rise in inflammatory markers in the bloodstream. High sensitivity C reactive protein (hs-CRP) levels are higher in T2DM patients than healthy people. It plays a significant role in the progression and development of the disease.

Aims and Objectives: To evaluate the role of hs-CRP in diabetes patients and its relationship to HbA1c and lipid profile in patients with T2DM.

Materials and Methods: One hundred and forty subjects were studied after dividing them into Case (n=70; T2DM patients aged >18 years) and Control (n=70; healthy individuals) for 18 months at Sri Aurobindo Medical College and Post Graduate Institute, Hospital, Indore. Pre-structured proforma was used to collect relevant data such as age, sex, diabetes duration, glycated hemoglobin (HbA1c), hs-CRP, and lipid profile. Patients' history, physical examination, blood investigations, radiological investigations, and electrocardiography were also performed.

Results: The mean age in the Case and Control groups were 55.2 and 49.23 years, respectively (P=0.682).Higher hs-CRP (>10) was reported in the majority in the case group, while the hs-CRP level in the control group was 0-5 in the majority of the individuals (p=0.001). Uncontrolled diabetes (HbA1c ≥7) was associated with a higher level of hs-CRP (>10). Majority of the patients in the Case group with hs-CRP level 0-5 has an increased level of total cholesterol (159.31 mg/dl). The lowest HDL level (32.18 mg/dl) was reported in the Case group with a hs-CRP level of >10. The highest LDL level (106.41 mg/dl) was found in the Case group associated with a hs-CRP level of 0-5. The highest TG level (151.58 mg/dl) in the Case group was with a hs-CRP level of >10.

Conclusion: There is a significant association between hs-CRP levels and HbA1c. hs-CRP serve as a marker of hyperglycemia and altered lipid profiles in people with T2DM.

Keywords: hyperglycemia, glycated hemoglobin, chronic diseases, high sensitivity C reactive protein.

Introduction

Diabetes is a chronic problem that affects 463 million people globally and is expected to affect 700 million by 2045. In India, 77 million adults live with diabetes which is expected to rise by 134 million by 2045. (IDF 2019)

Chronic problems rise with the increasing duration and severity of hyperglycemia, and they don't show up until the second decade of hyperglycemia. Hyperglycemia is a pro-inflammatory condition that causes a rise in inflammatory markers in the bloodstream. (Fauci AS 2008).

Inflammation is a protective response to tissue injury on a local level. Inflammation causes several acute phase reactants in the liver, including serum ferritin and high sensitivity C reactive protein (hs-CRP), which are thought to play a role in insulin resistance and atherosclerosis. hs-CRP levels in the blood have been a substantial predictor of cardiovascular disease risk in people with type 2 diabetes mellitus (T2DM). Moreover, high levels of hs-CRP have been linked to an increased risk of T2DM. (Gohel MG 2013)
Previous studies have revealed that hs-CRP levels in the blood are higher in diabetic patients than in healthy people. It plays a significant role in the progression and development of the disease. (Doggen CJ 2000)

Increasing evidence reveals that dyslipidemia is frequently associated with elevated values of inflammatory markers such as hs-CRP and is linked to metabolic diseases such as obesity, T2DM, and CVD; this metabolically driven inflammation is called metabolic inflammation. (Katsiki N 2017)

There have been few investigations on the connection between hs-CRP levels and glycated hemoglobin (HbA1c), a marker of hyperglycemia and lipid profiles in people with diabetes. The present research aimed to determine the amount of hs-CRP in T2DM patients and its relationship to HbA1c and lipid profile.

Materials and Methods

An observational study was performed on 140 subjects after dividing them into Case (n=70; T2DM patients aged >18 years) and Control (n=70; healthy individuals) for 18 months at Sri Aurobindo Medical College and Post Graduate Institute, Hospital, Indore.

Ethics committee approval was obtained before starting the study.

Patients with any diseases that could alter hs-CRP levels and patients with hypertension, renal failure, and pulmonary disease were excluded from the study.

Informed written consent was taken from all the patients or their relatives. A pre-structured proforma was used to collect the baseline data. Detailed clinical examination and biochemical tests were done on all the patients.

Especially designed pre-structured proforma was used to collect relevant data such as age, sex, diabetes duration, HbA1c, hs-CRP, and lipid profile. The data was obtained from patients' history, physical examination, blood investigations, radiological investigations, and electrocardiography.

Statistical analysis

All the data analysis was performed using IBM SPSS ver. 20 software. Cross tabulation and frequency distribution were performed to prepare the tables. Quantitative data were expressed as mean and standard deviation. Categorical data were expressed as numbers and percentages. Anthropometric measurements and biochemical parameters like fasting and post-prandial plasma glucose, lipid profile, LFT, KFT, and routine urine analysis were carried out using descriptive analysis. Statistical analysis was done by One Way ANOVA or Student's t-test as appropriate to compare groups for continuous variables. The Chi-square test or Fisher’s exact test – as was deemed appropriate – was used to compare proportions. P-values < 0.05 were taken as the level of significance.

Results

The mean age in the Case and Control groups was 55.2 and 49.23 years, respectively. The majority had51-60 years in the Case group (n=25), followed by 61-70 (n=20). Whereas, in control, the majority had an age between 31-40 years (n=23), followed by 51-60 years (n=16) (P=0.682).

Table 1: Baseline characteristic of the study population

Parameters	Groups		P-value
	Case	Control	
Hb	11.25	11.70	0.462
WBC	10616.86	10450.00	0.488
PLT	1.56	4.36	0.001
hs-CRP	37.62	2.55	<0.001
FBS	166.94	122.89	<0.001
PPBS	218.85	140.52	<0.001

FBS: fasting blood sugar; Hb; hemoglobin, hs-CRP: high sensitive C- reactive protein; PLT: platelets count; PPBS; post-prandial blood sugar; WBC: white blood cells,

Higher hs-CRP (>10) was reported in the majority in the case group, while the hs-CRP level in the control group was 0-5 in the majority of the individuals (p=0.001).

Table 2: Comparing hs-CRP levels with glycemic parameters

Parameters		hs-CRP			Total	P-value
		0-5	5-10	>10		
Diabetes duration (years)	<5	12	4	16	32	0.001
	5-10	2	0	24	26	
	>10	0	1	11	12	
HbA1c (%)	Control (<7)	6	1	15	22	0.001
	Uncontrolled (≥7)	8	4	36	48	

The majority of the patients in the case group had higher total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG) than the control group across the hs-CRP levels.

Majority of the patients in the Case group with hs-CRP level 0-5 has an increased level of total cholesterol (159.31 mg/dl). The lowest HDL level (32.18 mg/dl) was reported in the Case group with a hs-CRP level of >10. The highest LDL level (106.41 mg/dl) was found in the Case group associated with a hs-CRP level of 0-5. The highest TG level (151.58 mg/dl) in the Case group was with a hs-CRP level of >10.

Albumin was present in the majority (n=39) in the Case group with a hs-CRP level of >10. The majority of the control group individuals (n=44) also had albumin present, with a hs-CRP level of >10 (p=0.346).

The case group (n=32) has more patients with urinary sugar present than the control group (n=28) (p=0.032). The mean Creatinine level was higher in the case group (1.37 mg/dl) compared to the control group (1.31 mg/dl) (p=0.421).

Discussion

Low-grade systemic inflammation has been linked to the development of diabetes, and hs-CRP could be a valuable diagnostic for predicting T2DM. Some markers of inflammation, like C-reactive protein, IL-6 fibrinogen, and PA-1, have been linked to the development of diabetes in the past. There is some heterogeneity in the association between pro-inflammatory cytokines and T2DM by race and ethnic group, implying that not all systemic inflammatory markers are linked to anincreased risk of developing T2DM. However, systemic inflammation plays a crucial role in the developing and progression of atherosclerosis. In various clinical settings, C-reactive protein, a distal biomarker of inflammation, can be used to predict cardiovascular risk. Patients having T2DM are typically regarded as having a moderate-to-high cardiovascular risk.

Nonetheless, the predictive significance of CRP in people with type 2 DM is still debatable, with some research finding that it is connected to the development of cardiovascular events (CVE) while others disagree. The causes of these discrepancies are unknown. However, they could include a variety of factors such as distinct diabetic populations with varying baseline cardiovascular risks and CRP levels and different evaluated cardiovascular endpoints during varying follow-up periods. Hyperglycemia contributes to non-controlled type diabetes persons' serum CRP levels. Several studies show that CRP is a significant predictor of diabetes risk, even after controlling for BMI, smoking history, and other variables. CRP remains to be the most accurate predictor of future coronary artery disease. (Gupta R 2022, Duncan BB 2003, Negi SI 2012)

In the present study, a higher hs-CRP level (>10) was linked to a longer diabetes duration. In the major patients with diabetes for less than 5 years, lower levels of hsCRP were found. This was a statistically significant difference. As per a study by Garg SM et al., the majority of diabetes patients (59%) have had diabetes for less than 5 years.

In the present study, uncontrolled diabetes (HbA1c ≥7) was associated with a higher level of hs-CRP (>10). The majority of the cases were diabetics with uncontrolled blood sugar levels. In a study by SS R et al., the mean of glycosylated Hb with hs-CRP of 1 was 7.52+1.03, 8.15+1.11 for hs-CRP of 1-3, and 8.90 + 1.24 for hs-CRP of >3, with a p-value of 0.004. (Gupta UK 2018)

In all ranges of hs-CRP levels, the majority of the cases in the Case group had greater TC, HDL, LDL, and TG than the controls.

The presence of albumin in the maximum patients in the Case group was associated with a hs-CRP level greater than 10. Most of the control group participants had albumin, associated with a hs-CRP level of >10. The difference was not statistically significant.

Compared to the control group, the Case group had more patients with urine sugar (p=0.032). Compared to the control group, the Case group had a higher mean creatinine level; however, insignificant.

In T2DM and diabetic nephropathy patients, the quantity of serum hs-CRP was higher than in non-diabetic controls. According to Shaheer AK et al., there might be a link between the acute phase response to hs-CRP and T2DM. (Shaheer AK 2015) Increased cardiovascular risk is linked to a high amount of inflammatory plasma proteins, particularly in T2DM individuals. The vascular risk assessment in T2DM patients could benefit from measuring inflammatory markers. Insulin resistance and raised blood sugar cause inflammation by increasing oxidative stress, which may be linked to the progression of atherosclerosis in people with diabetes. (Stehouwer CD 2002, Jager A 2002)

Mahajan A et al. discovered a link between C-reactive protein (CRP) and hyperglycemia, which matches our findings. (Mahajan A 2009) Microalbuminuria is associated with higher hs-CRP, implying that inflammatory pathways are activated in cardiovascular and renal illness in T2DM patients, according to Mojahedi MJ et al.

(Mojahedi MJ 2009). Although the exact processes are unknown, the inflammatory response could be caused by microvascular or macrovascular problems associated with T2DM. Compared to non-diabetic healthy controls, the serum hs-CRP level is higher in T2DM and diabetic nephropathy.

Festa et al. found that those who developed diabetes (as determined by an OGTT) had greater baseline serum CRP levels than those who didn't. As the baseline CRP quartile increased, there was a linear linkage trend in the incidence of DM. People with hs-CRP levels of 3 mg/L (28.6 nmol/L) at baseline developed DM in the Pizarra prospective research. (A. Festa 2002)

CRP levels in middle-aged persons with DM and impaired fasting glucose (IFG) were greater when related to healthy controls, according to Aronson et al. (D. Aronson 2004). The ADOPT investigators found that hs-CRP levels in females were higher than in men with and without metabolic syndrome (MS). (S. E. Kahn 2006) This is similar to our study demonstrating that women had higher hs-CRP levels than males, regardless of whether they had diabetes. In persons with new DM, they found a link between hs-CRP and HbA1c, BMI and HOMA-IR, and the number of MS components. The incidence of DM was 4 times greater in women with hs-CRP levels in the uppermost quartile than those with hs-CRP levels in the lowermost quartile in the Women's Health Study. (A. D. Pradhan 2002)

Earlier research has linked high levels of hsCRP to obesity and insulin resistance in North Indian adolescents and South Indian adults, respectively. (Vikram NK 2006) We showed that hs-CRP levels are linked to glycemic control in North Indian adults for the first time. The link between rising hs-CRP levels and increased fasting insulin, C-peptide, and HOMA-IR suggests subclinical inflammation and insulin resistance coexist.

Over time, evidence suggests hs-CRP is linked to an increased risk of upcoming cardiovascular events in otherwise healthy people. (Pearson TA 2003) However, whether T2DM is present or not appears to have a significant impact on the degree of this connection. As seen above, the distribution of hs-CRP is notably different between T2DM and non-diabetic individuals. T2DM was seen to be a major risk factor for the occurrence of CVD in this cohort, with 36 percent of cases being classed as "high-risk," compared to only 21 percent of non-diabetics.

Conclusion

Our findings and accumulated evidence suggest that hs-CRP is linked to a raised risk of cardiovascular events in the near future in otherwise healthy people. However, having or not having T2DM appears to have a significant impact. To conclude, there is a significant association between hs-CRP levels and HbA1c. hs-CRP serve as a marker of hyperglycemia and lipid profiles in people with diabetes.

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