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Original Article

Internal Medicine Section

Association of hsCRP Levels with Microvascular Complications in Prediabetics, Newly Diagnosed and on Treatment Type 2 Diabetes Mellitus Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Low-grade chronic inflammation is recognised as the predominant cause of the pathogenesis and progression of Type 2 Diabetes Mellitus (T2DM) and its microvascular complications. High-sensitivity C-Reactive Protein (hsCRP) is a biomarker for inflammation that may indicate the underlying mechanisms of diabetes, such as insulin resistance and vascular damage.

Aim: To compare hsCRP levels across three glycaemic categories- prediabetes, newly diagnosed T2DM, and on-treatment T2DM- and to determine its correlation with glycaemic control measures Glycated Haemoglobin (HbA1c), Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS) and microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy.

Materials and Methods: The present hospital-based, cross-sectional, analytical study was conducted over 18 months (October 2023 to March 2025) at Dr DY Patil Medical College, Hospital, and Research Centre, Pimpri, Pune, Maharashtra, India. One hundred fifty participants aged ≥18 years were randomly assigned to three groups: prediabetics, newly diagnosed T2DM (≤18 months), and T2DM under treatment. Measurements included FBS, PPBS, HbA1c, and hsCRP using an immunoturbidimetric assay. Diabetic retinopathy was diagnosed via fundoscopy, nephropathy was assessed through the urine albumin-creatinine ratio, and peripheral neuropathy was screened using a 10g monofilament and sensory examination. Data were analysed using IBM Statistical Package for Social Sciences (SPSS) v20. Comparisons between groups were conducted with One-way Analysis of Variance (ANOVA) and the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results: Mean hsCRP values were significantly higher in newly diagnosed (7.87±1.26 mg/L) and on-treatment diabetics (7.26±2.30 mg/L) compared with pre-diabetics (2.72±2.80 mg/L; $p<0.001$). hsCRP exhibited a strongly positive correlation with HbA1c ($r=0.616$), FBS ($r=0.223$), and PPBS ($r=0.461$). Patients with diabetic retinopathy, nephropathy, and neuropathy had significantly elevated hsCRP levels compared to those without complications ($p<0.001$).

Conclusion: hsCRP is a valuable marker of inflammation associated with poor glucose control and the development of diabetic microvascular complications. Regular monitoring can aid in the early detection of risk, facilitating targeted anti-inflammatory therapy and strict glycaemic control.

Keywords: Glycaemic parameters, High sensitivity C reactive protein, Inflammation, Nephropathy, Neuropathy, Retinopathy

INTRODUCTION

Diabetes Mellitus (DM) is a global metabolic disorder characterised by persistent hyperglycaemia caused by impaired insulin secretion, insulin action, or both [1]. Among the different types, T2DM is the most prevalent, affecting more than 90% of all diabetic patients. It is a significant public health concern in India due to lifestyle changes, urbanisation, and genetic susceptibility, all contributing to the increasing disease burden [2]. Microvascular and macrovascular chronic diabetes complications are major factors in high morbidity and mortality worldwide [3].

Previously, the pathogenesis of T2DM was attributed to insulin resistance and beta-cell dysfunction. However, in recent years, the focus has shifted to chronic low-grade systemic inflammation as a key mediating mechanism of insulin resistance and diabetic complications [4]. Among numerous inflammatory biomarkers, hsCRP has been described as a useful and readily available marker of systemic inflammation. The hsCRP is produced in the liver in response to increases in cytokines such as Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α), both of which are elevated during conditions of insulin resistance [5].

An increase in hsCRP has also been reported to be linked to the onset of T2DM and is traditionally correlated with worsening glycaemic control. Some studies have demonstrated a positive correlation between hsCRP levels and glycaemic markers such as FBS, PPBS, and HbA1c [6,7]. In addition, hsCRP levels have been correlated with the severity and prevalence of diabetic microvascular complications such as retinopathy, nephropathy, and neuropathy. Inflammation has been identified as a critical factor in the development of diabetic complications, in addition to being a contributing factor in the development of diabetes [8].

Furthermore, prediabetes, characterised by intermediate hyperglycaemia, is now well known to be a proinflammatory state. Pre-diabetic patients exhibit elevated levels of inflammatory markers such as hsCRP, which are predictive of the onset of overt diabetes and early end-organ damage. Thus, measuring hsCRP in diabetic and pre-diabetic patients shows promise for early risk stratification and preventive therapy [9,10]. Despite the growing evidence, the use of hsCRP as an ancillary clinical marker in diabetes management is not fully exploited, particularly when resources are limited. With the aim of assessing the level of hsCRP in patients with prediabetes, newly diagnosed T2DM, and on-treatment T2DM, this present study was initiated.

Additionally, the study also aimed to investigate the correlation between glycaemic control indicators and hsCRP, as well as the prevalence of microvascular complications, to examine its potential application as a prognostic and predictive marker in clinical scenarios.

MATERIALS AND METHODS

The present hospital-based cross-sectional study was carried out in the Department of General Medicine at Dr DY Patil Medical College, Hospital, and Research Centre, Pimpri, Pune, Maharashtra, India from October 2023 to March 2025. Ethical clearance was obtained from the Institutional Ethics Committee (IEC Approval No.: IESC/PGS/2023/16).

Inclusion and Exclusion criteria: Adults aged ≥18 years were recruited and divided into three groups: those with prediabetes, newly diagnosed T2DM; diagnosed in the past 18 months), and patients under treatment for T2DM. Exclusion criteria included a diagnosis of Type 1 diabetes, acute infections, autoimmune conditions, cancer, chronic kidney disease, recent surgery, pregnancy, or current treatment with immunosuppressive or anti-inflammatory drugs. Individuals with hsCRP levels >10 mg/L were also excluded to avoid confounding due to acute inflammation.

Prediabetes, as determined by the American Diabetes Association (ADA) criteria, was defined by Fasting Plasma Glucose (FPG) levels of 100-125 mg/dL (5.6-6.9 mmol/L), a postprandial 2-hour Oral Glucose Tolerance Test (OGTT) result of 140-199 mg/dL (7.8-11.0 mmol/L), or HbA1c levels of 5.7-6.4%. T2DM was diagnosed with FPG ≥126 mg/dL (7.0 mmol/L), 2-hour OGTT plasma glucose ≥200 mg/dL (11.1 mmol/L), HbA1c ≥6.5%, or the presence of classic hyperglycaemic symptoms with a random plasma glucose ≥200 mg/dL (11.1 mmol/L) [11].

Sample size calculation: The sample size was determined using the formula for comparing three groups of means:

$$n=\frac{(Z_\alpha+Z_\beta)^2\times 2\sigma^2}{d^2}$$

Where:

- Z_α=1.96 (95% confidence)
- Z_β=0.84 (80% power)
- σ=standard deviation
- δ=expected effect size

An effect size (d) of approximately 1.4 was adopted based on previous Indian research by Mane KB and Asegaonkar S [12]. Using this value, the calculated sample size was approximately 130. To enhance statistical reliability and account for possible attrition, 150 participants were recruited for the study.

Study Procedure

Methodology and Parameters assessed: Following informed consent, demographic and clinical information were documented. Laboratory testing included FBS, PPBS, HbA1c, and hsCRP (assessed by immunoturbidimetric assay). Retinopathy was evaluated through fundoscopy, nephropathy was assessed using the urine albumin-creatinine ratio, and neuropathy was evaluated using a 10g monofilament and vibration perception tests.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and processed using IBM SPSS version 20. Descriptive statistics (mean, standard deviation, percentages) were calculated. One-way ANOVA and Chi-square tests were employed for comparisons between continuous and categorical variables, respectively. Pearson's correlation coefficient was used to investigate correlations of hsCRP with glycaemic parameters. A p-value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 150 individuals grouped into three categories: pre-diabetic (n=50), newly diagnosed T2DM (n=50), and on-treatment T2DM (n=50).

The mean age of the study population was 50.3±10.4 years, with a majority falling between 41-60 years across all groups. In all groupings by gender distribution, males outnumbered females. [Table/Fig-1] demonstrates the age and gender distribution of participants, with the majority belonging to the 41-60 years age range across all three groups.

Age group (years)	Pre-Diabetic (M/F)	Newly diagnosed T2DM (M/F)	On treatment T2DM (M/F)
18-30	2/2	2/1	1/1
31-40	4/4	5/4	3/3
41-50	9/7	8/7	7/5
51-60	7/6	8/6	9/8
>60	4/5	6/3	7/6
Total (n=50)	26/24	29/21	27/23

[Table/Fig-1]: Age and Gender wise Distribution Across Study Groups

Middle-aged individuals (41-60-year-old) exhibited the highest rates of prediabetes and T2DM, highlighting the need for age specific screening and management for this group. There was also a relatively smaller male excess.

[Table/Fig-2] demonstrates the mean glycaemic parameters across groups, showing significantly higher FBS, PPBS, and HbA1c in newly diagnosed and on-treatment diabetics compared to pre-diabetics. Significant differences were observed in glycaemic parameters and hsCRP levels across the three groups, with significantly higher values noted in diabetic groups compared to pre-diabetics (p<0.001) [Table/Fig-3]. [Table/Fig-3] demonstrates a significantly higher mean hsCRP level in newly diagnosed and on-treatment T2DM patients compared to pre-diabetics (p<0.001). A significant positive correlation was observed between hsCRP and HbA1c in all groups, with the strongest correlation occurring in the on-treatment diabetic group (p<0.05) [Table/Fig-4]. Similarly, [Table/Fig-5] demonstrates a significant positive correlation between hsCRP and PPBS levels in each group: pre-diabetics (r=0.335, p=0.017), new-onset T2DM (r=0.448, p=0.001), and on-treatment T2DM (r=0.493, p<0.001). Only the group receiving therapy showed a significant correlation of hsCRP with FBS (r=0.292, p=0.038).

Parameters	Pre-Diabetic	Newly Diagnosed T2DM	On Treatment T2DM	p-value
FBS (mg/dL)	110.2±7.3	143.5±15.2	133.7±14.9	<0.001
PPBS (mg/dL)	158.4±13.5	217.9±18.7	196.4±17.3	<0.001
HbA1c (%)	6.0±0.3	8.4±0.5	7.8±0.6	<0.001

[Table/Fig-2]: Mean Glycaemic Parameters

Group	hsCRP (mg/L)	p-value
Pre-Diabetic	2.72±2.80	<0.001
Newly Diagnosed T2DM	7.87±1.26	
On Treatment T2DM	7.26±2.30	

[Table/Fig-3]: Mean hsCRP Levels in Study Groups

Group	Correlation Coefficient (r)	p-value
Pre-Diabetic	0.391	0.005
Newly Diagnosed T2DM	0.589	<0.001
On Treatment T2DM	0.656	<0.001

[Table/Fig-4]: Correlation of hsCRP with HbA1c

[Table/Fig-6] demonstrates the distribution of microvascular complications across the study groups, with higher frequencies in

Group	Parameters	Correlation Coefficient (r)	p-value
Pre-Diabetic	FBS	0.168	0.234
Newly Diagnosed T2DM	PPBS	0.335	0.017
	FBS	0.267	0.063
On Treatment T2DM	PPBS	0.448	0.001
	FBS	0.292	0.038
	PPBS	0.493	<0.001

[Table/Fig-5]: Correlation of hsCRP with FBS and PPBS

Group	Retinopathy (n)	Nephropathy (n)	Neuropathy (n)
Pre-Diabetic	2	3	4
Newly Diagnosed T2DM	11	10	12
On Treatment T2DM	17	15	16

[Table/Fig-6]: Distribution of microvascular complications

diabetic groups. The mean hsCRP value was significantly higher in individuals with complications (P<0.001) [Table/Fig-7]. The hsCRP levels progressively increased with the number of microvascular complications (p<0.001) [Table/Fig-8]. A significant increase in hsCRP levels with increased Body Mass Index (BMI) categories was also observed in the study participants (p<0.001) [Table/Fig-9].

Complication Type	Status	Mean hsCRP (mg/L)	p-value
Retinopathy	Present	8.34±1.21	<0.001
	Absent	4.45±2.85	
Nephropathy	Present	8.12±1.45	<0.001
	Absent	4.37±2.70	
Neuropathy	Present	7.98±1.58	<0.001
	Absent	4.26±2.94	

[Table/Fig-7]: Association between microvascular complications and hsCRP levels

BMI Category	Mean hsCRP (mg/L)	p-value
<25 kg/m^2	3.56±2.14	<0.001
25-29.9 kg/m^2	6.78±2.71	
≥30 kg/m^2	8.25±1.92	

[Table/Fig-8]: Association between BMI Category and Mean hsCRP Levels

No. of Complications	Mean hsCRP (mg/L)	p-value
None	3.26±2.31	<0.001
1	6.24±2.58	
2	7.93±2.21	
3	9.17±1.36	

[Table/Fig-9]: hsCRP Levels by number of microvascular complications

DISCUSSION

This cross-sectional study assessed hsCRP levels in individuals with prediabetes, new-onset, and on-treatment T2DM, examining its correlation with glycaemic indicators and microvascular complications. The results indicate a rising trend in hsCRP from prediabetes to diabetes, confirming its role as an early indicator of inflammation and a tool for risk assessment in diabetes management.

The strongest correlation was observed between hsCRP and HbA1c (r=0.656, p<0.001) in the treated Type 2 diabetes group. Previous studies by Seo Y and Shin H in a Korean population also found a positive association between hsCRP and HbA1c, suggesting a link between inflammation and poor glycaemic control [6]. This study further revealed significant positive correlations between hsCRP and glycaemic parameters such as HbA1c, FBS, and PPBS, consistent with findings by Bhaskar S et al., in poorly controlled diabetics [7]. Additionally, a significant association was identified between elevated hsCRP levels and the presence of diabetic microvascular complications- namely, retinopathy, nephropathy, and neuropathy, supported by Zhao L et al., explanation of the inflammatory mechanisms contributing to these complications [8].

The study also confirmed elevated hsCRP levels in pre-diabetic individuals, indicating the inflammatory nature of early glucose dysregulation [9,10]. Higher hsCRP levels in new-onset and treated T2DM compared to pre-diabetics suggest worsening inflammatory processes with the progression of metabolic derangement. This aligns with the research by Pradhan AD et al., and Koziarska-Rościszewska M et al., emphasising the inflammatory basis of T2DM and the importance of hsCRP in assessing metabolic and cardiovascular risks [13,14].

Significantly higher mean hsCRP levels were observed in newly diagnosed and treated T2DM compared to pre-diabetics, suggesting early systemic inflammation in the disease course, before diabetic complications manifest. This supports existing literature indicating the role of chronic inflammation in the development of insulin resistance and hyperglycaemia. The study findings are consistent with research by Püschel GP et al., and Li H et al., that highlight the interplay between inflammation, insulin resistance, and metabolic dysregulation in T2DM onset and progression [15,16].

Notably, some pre-diabetic participants exhibited microvascular complications despite not meeting the T2DM diagnostic criteria, emphasising that prediabetes is a proinflammatory state associated with early vascular damage, thus aligning with current literature by Ghule A et al., and Tsalamandris S et al., [17,18]. This underscores the importance of early detection and intervention to prevent irreversible organ damage. The findings of the study are in congruence with Festa A et al., who indicated that hsCRP is a predictor of insulin resistance and metabolic syndrome in non-diabetic patients [19].

HsCRP poor glycaemic control, and vascular damage induced by chronic inflammation are linked in a way that warrants early intervention to minimise diabetes complications and mortality risks, as discussed by González P et al., [20]. Sharif S et al., reported similar correlations, pointing out that ongoing low-grade inflammation and vascular damage increase mortality in patients with T2DM [21].

Additionally, hsCRP levels were positively linked to BMI, highlighting the role of visceral fat in systemic inflammation. Cytokines from adipose tissue, such as IL-6 and TNF-α, contribute to metabolic issues and higher hsCRP production in obese individuals, as noted by Kawai T et al., [22].

Limitation(s)

1. **Single-Center Study:** The study was conducted in a specific population, limiting its generalisability to different demographic and ethnic groups.
2. **Cross-Sectional Design:** As the study only provides a snapshot of hsCRP levels at a single point in time, it cannot establish causal relationships between inflammation, glycemic control, and microvascular complications.
3. **Influence of Confounding Factors:** Other inflammatory conditions, obesity, infections, and lifestyle factors that might affect hsCRP levels were not fully accounted for.
4. **Lack of Longitudinal Follow-Up:** The study does not assess how hsCRP levels change over time or whether interventions to lower inflammation impact glycemic control and complications.
5. **Variability in Treatment Regimens:** Differences in medication types, dosages, and adherence among treated diabetics could influence hsCRP levels and were not standardised.

6. **Absence of Intervention Analysis:** While the study highlights associations, it does not evaluate whether targeting inflammation improves diabetes outcomes or reduces complications.

CONCLUSION(S)

The study emphasises the role of hsCRP in predicting chronic inflammation in people with prediabetes and T2DM. Increased levels of hsCRP were strongly associated with poor glycaemic control as well as microvascular complications like retinopathy, nephropathy, and neuropathy. The progressive increase of hsCRP from prediabetes to overt diabetes, and its association with the complication score, underscores its usefulness in early diagnosis and risk stratification. Long-term follow-up of hsCRP in patients with diabetes may provide the potential benefit of selecting high-risk individuals, in whom early intervention might be initiated to avoid long-term vascular complications. In conclusion, hsCRP is an important inflammatory marker related to glycaemic control, obesity, and diabetes complications.

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