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Association Between C-Reactive Protein Levels and Glycemic Control Markers in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Systemic inflammation is a key pathophysiological feature of Type 2 Diabetes Mellitus (T2DM). C-reactive protein (CRP), a sensitive marker of inflammation, has been linked to T2DM risk factors, but its direct association with glycemic control markers remains inconsistent in the literature. **Objective:** This study aimed to investigate the association between CRP status and glycemic control as measured by fasting blood sugar (FBs) and glycated hemoglobin (HbA1c) in patients with T2DM. A secondary objective was to explore the relationship between CRP and various demographic, hematological, and lifestyle characteristics. **Methods:** A cross-sectional study was conducted on 119 patients diagnosed with T2DM. Participants were categorized as either CRP-positive or CRP-negative based on laboratory analysis. Data on demographics, hematological indices, iron status, and lifestyle factors were collected. Statistical analyses were performed to compare glycemic markers and other variables between the two CRP groups. **Results:** Of the 119 participants, 36 (30.3%) were CRP-positive and 83 (69.7%) were CRP-negative. The results demonstrated no statistically significant difference in FBs or HbA1c levels between the CRP-positive and CRP-negative groups. Furthermore, there was no significant association found between CRP status and demographic data (age, sex), hematological parameters, or self-reported lifestyle factors, including exercise habits, dietary patterns, and smoking status. **Conclusion:** In this patient cohort, CRP status alone was not a reliable indicator of glycemic control. The absence of a significant association suggests that the relationship between low-grade systemic inflammation, as measured by CRP, and glucose regulation in T2DM is complex and may be influenced by other unmeasured factors

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) represents a significant and escalating global health challenge. Its prevalence is rising in parallel with global increases in obesity and sedentary lifestyles, with projections indicating a substantial burden on healthcare systems worldwide (Cho et al., 2021; IDF, 2023). Pathophysiologically, T2DM is a heterogeneous metabolic disorder defined by chronic hyperglycemia, which arises from a complex interplay of insulin resistance, progressive β -cell dysfunction, and excessive hepatic glucose production (DeFronzo et al., 2020; Zheng et al., 2022).

A key component of T2DM pathophysiology is a state of chronic, low-grade systemic inflammation. C-reactive protein (CRP), a sensitive hepatic acute-phase reactant, is frequently elevated in individuals with T2DM and serves as a key biomarker for this inflammatory state. Previous research has consistently linked elevated CRP levels with features of metabolic syndrome, including central obesity, reduced insulin sensitivity, and heightened cardiovascular risk (Altaf et al., 2021; Chen et al., 2021; Duan et al., 2023; Kim et al., 2022; Zhang & Li, 2023). However, the direct association between CRP and primary glycemic control indicators, namely fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), remains equivocal across different studies and populations. This inconsistency suggests a complex relationship that warrants further investigation (Lin et al., 2022; Zhao et al., 2021). Mechanistic evidence suggests that CRP may be more than a passive bystander, potentially contributing directly to the pathogenesis of insulin resistance by interfering with insulin signaling pathways and impairing vascular endothelial function. Elevated CRP concentrations are associated with reduced glucose uptake in skeletal muscle and the upregulation of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), which further exacerbate metabolic dysregulation (Chen et al., 2022; Lee et al., 2021). Consequently, monitoring CRP holds potential clinical utility for assessing disease severity and predicting adverse outcomes. Its established link to an increased incidence of macrovascular events, such as myocardial infarction and stroke, highlights its value as a prognostic marker in T2DM populations (Gao et al., 2023; Wang et al., 2020). Given the uncertain clinical utility of CRP as a direct marker of glycemic status, this study was designed to address this gap. The primary aim was to investigate the association between CRP levels and the key glycemic control markers as fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) in a cohort of patients with T2DM. A secondary objective was to explore the relationship between CRP and various demographic, hematological, and lifestyle characteristics.

2. METHOD

1. Materials and Methods

Study Design and Participant Recruitment

This cross-sectional study was conducted between January and April 2024. A total of 119 patients with a pre-existing diagnosis of type 2 diabetes mellitus (T2DM) were enrolled. Participants were recruited from the outpatient diabetes clinics of Al-Wahda Hospital and affiliated primary care centers in Derna. The study protocol was designed in accordance with ethical principles for medical research.

Inclusion and Exclusion Criteria

All participants were required to have a confirmed diagnosis of T2DM. Exclusion criteria were established to minimize confounding factors and included: a diagnosis of severe liver dysfunction (e.g., viral hepatitis, cirrhosis), renal impairment (defined as a blood creatinine concentration > 1.5 mg/dL), known malignancy, a history of atherosclerotic disease, or any active chronic inflammatory conditions such as rheumatoid arthritis.

Data and Sample Collection

Following an overnight fast, a 7 mL venous blood sample was collected from each participant by a trained phlebotomist. The blood was immediately aliquoted into three separate vacuum tubes for specific analyses:

2. A 3 mL plain tube with a clot activator for serum separation (used for CRP analysis).
3. A 2 mL sodium fluoride tube to inhibit glycolysis (used for plasma FBG analysis).
4. A 2 mL EDTA (ethylenediaminetetraacetic acid) tube for whole blood analysis (used for HbA1c and CBC).

In addition to blood collection, demographic, clinical history, and lifestyle data were obtained from each participant using a structured questionnaire.

Laboratory Analyses

All samples were processed and analyzed promptly after collection. Serum was used for the quantitative determination of C-reactive protein (CRP). For the primary analysis, CRP results were dichotomized into "positive" or "negative" based on the clinical reference threshold indicating inflammation. Plasma was analyzed to determine fasting blood glucose (FBG) levels. Glycated hemoglobin (HbA1c) and a complete blood count (CBC) were measured using whole blood from the EDTA tubes.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the cohort's characteristics; continuous variables were presented as mean \pm standard deviation (SD) or median and interquartile range (IQR), while categorical variables were presented as frequencies and percentages (n, %). The Chi-square test was employed to compare proportions of categorical variables between the CRP-positive and CRP-negative groups. For continuous variables, independent samples t-tests or Mann-Whitney U tests were used as appropriate based on data distribution. A two-tailed p-value of less than 0.05 was considered statistically significant.

3. ETHIC APPROVAL

Al-Jabal Akhdar Branch Committee for Bioethics (JCB) has reviewed and discussed your application to conduct the above-mentioned research in the Life Science department, School of Basic Science, Libyan Academy for Postgraduate Studies- Al-Jabal Akhdar Branch. The following submitted documents have been received, reviewed, and approved in the Al-Jabal Akhdar Branch committee for Bioethics (JCB) meeting number (8), held on Tuesday 22 /04/2025, and was given this reference number: **NBC: 004. H. 25. 12**

4. RESULT

A total of 119 patients were included in the study, of which 56(47.1%) were males and 63(52.9%) were females. The mean age of patients with T2DM was found to be 53.82 years (SD= 12.04), ranged from 16 to 82 years.

Table 1: Demographic and Clinical Characteristics of Study Participants

Mean \pm SD		Frequency	Percentage
Age	53.91 \pm 11.83		
SEX	Female	63	52.941
	Male	56	47.059
RBC	3.99 \pm 0.44 $\times 10^{12}/l$		
HGB	12.15 \pm 1.62 g/dl		
HCT	38.68 \pm 4.99 %		
MCV	90.67 \pm 10.71 fl		
MCH	30.40 \pm 10.12 pg		
MCHC	30.89 \pm 1.58 g/dl		
FBs	187.92 \pm 92.85 mg/dl		
HBA1C	Median (IQR) 7.41 % (8.50–6.71)		
CRP	Negative	83	69.748
	Positive	36	30.252

This table presents the demographic and clinical characteristics of the 119 patients with type 2 diabetes who participated in the study. The mean age of the participants was 53.91 \pm 11.83 years. The cohort consisted of 63 (52.941%) females and 56 (47.059%) males. Regarding blood parameters, the mean red blood cell count (RBC) was 3.99 \pm 0.44 $\times 10^{12}/l$, hemoglobin (HGB) was 12.15 \pm 1.62g/dl, and hematocrit (HCT) was 38.68 \pm 4.99 %. Mean corpuscular volume (MCV) was 90.67 \pm 10.71 fl, mean corpuscular hemoglobin (MCH) was 30.40 \pm 10.12 pg, and mean corpuscular hemoglobin concentration (MCHC) was 30.89 \pm 1.58g/dl. Fasting blood sugar (FBs) had a mean of 187.92 \pm 92.85mg/dl. Glycated hemoglobin (HbA1c) had a median (IQR) of 7.41 % (6.71-8.50).

C-reactive protein (CRP) levels were negative in 83 (69.748%) patients and positive in 36 (30.252%) patients.

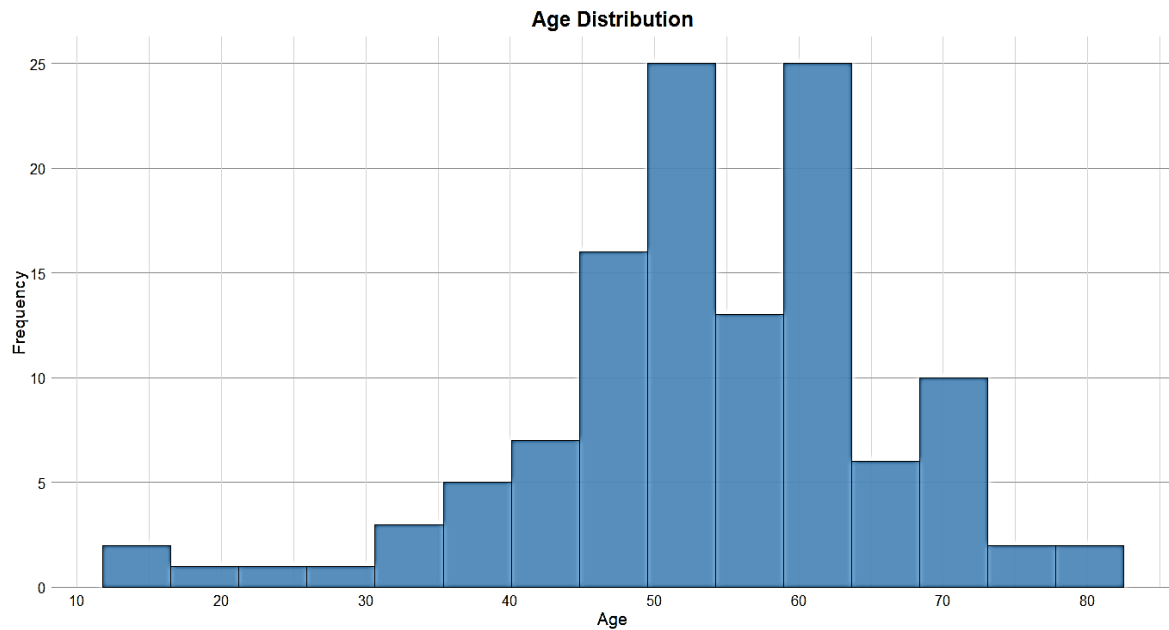


Fig. 1: Age Distribution of Study Participants

This histogram illustrates the distribution of ages among the study participants. The x-axis represents age, and the y-axis represents the frequency of participants within each age bin. The chart shows a relatively wide age range among the participants, with a notable concentration of individuals in the 45-65 age bracket. There are fewer participants at the younger (e.g., 10-30 years) and older (e.g., 70-80+ years) ends of the spectrum, with the highest frequencies observed around 50-60 years of age.

Table 2: Health and Lifestyle Characteristics of Study Participants

		Frequency	Percentage
Have you been diagnosed with type 2 diabetes?	No	3	2.521
	Yes	116	97.479
Do you have a history of iron deficiency anemia?	No	93	78.151
	Yes	26	21.849
How long have you been diagnosed with type 2 diabetes?	1–5 years	48	40.336
	Less than 1 year	12	10.084
	More than 5 years	59	49.580
Do you suffer from chronic diseases?	No	76	63.866
	Yes	43	36.134

How many iron-rich meals do you consume er week?	1 meal	15	12.605
	2 meals	8	6.723
	2-3 meals	1	0.840
	3 meals	12	10.084
	3-4 meals	9	7.563
	3-5 meals	2	1.681
	4 meals	3	2.521
	5 meals	5	4.202
	6 meals	4	3.361
	7 meals	3	2.521
	8 meals	1	0.840
	Low	2	1.681
	No	9	7.563
	Normal	1	0.840
	Rarely	1	0.840
	Daily	21	17.647
	Sometimes	22	18.487
Do you take any nutritional supplements?	No	79	66.387
	Yes	40	33.613
How much do you exercise?	3 times a week	6	5.042
	No	4	3.361
	Once or twice	15	12.605
	Rarely	94	78.992
Are you a smoker?	Former smoker	9	7.563
	No	99	83.193
	Yes	11	9.244
Do you consume alcohol?	No	117	198.319
	Yes	2	1.681
Have you experienced shortness of breath?	No	84	70.588
	Yes	35	29.412
Are you suffering from fatigue?	No	90	75.630
	Yes	29	24.370
Have you ever suffered from dizziness?	No	78	65.546
	Yes	41	34.454
Have you experienced heart palpitations?	No	82	68.908
	Yes	37	31.092
Have you suffered from unexplained weight loss?	No	110	92.437
	Yes	9	7.563
Are you undergoing any treatment for anemia?	No	115	96.639
	Yes	4	3.361
Type of diabetic treatment	Dietary regulation	69	57.983
	Insulin	39	32.773
	Tablets	11	9.244

Table 2 provides a breakdown of the health and lifestyle characteristics of the 119 study participants with type 2 diabetes. A vast majority of the participants, 116 (97.479%), were diagnosed with type 2 diabetes, while only 3 (2.521%) did not. Regarding the history of iron deficiency anemia, 93 (78.151%) reported no history, and 26 (21.849%) reported a history of it. The duration of type 2 diabetes diagnosis varied, with 48 (40.336%) diagnosed for 1-5 years, 12 (10.084%) for less than 1 year, and 59 (49.580%) for more than 5 years. Chronic diseases were reported by 43 (36.134%) participants, while 76 (63.866%) did not suffer from them. The frequency of iron-rich meal consumption varied significantly among participants. For example, 21 (17.647%) consumed iron-rich meals daily, and 22 (18.487%) sometimes, while others reported specific numbers of meals per week.

In terms of nutritional supplements, 79 (66.387%) did not take them, and 40 (33.613%) did. Exercise frequency was low, with 94 (78.992%) rarely exercising, 15 (12.605%) exercising once or twice, 6 (5.042%) exercising 3 times a week, and 4 (3.361%) not exercising. Smoking status showed that 99 (83.193%) were non-smokers, 11 (9.244%) were current smokers, and 9 (7.563%) were former smokers. Most participants, 117 (98.319%), did not consume alcohol, while 2 (1.681%) did. Concerning symptoms, 35 (29.412%) experienced shortness of breath, 29 (24.370%) suffered from fatigue, 41 (34.454%) experienced dizziness, and 37 (31.092%) had heart palpitations. Unexplained weight loss was reported by 9 (7.563%) participants. Finally, for anemia treatment, 115 (96.639%) were not undergoing treatment, and 4 (3.361%) were. The type of diabetic treatment included dietary regulation for 69 (57.983%), insulin for 39 (32.773%), and tablets for 11 (9.244%).

Table 3: Comparison of Characteristics by CRP Status

Characteristic	negative N = 83 ¹	positive N = 36 ¹	p-value ²
Sex			
Female	41 (49%)	22 (61%)	0.3
Male	42 (51%)	14 (39%)	
Age (years)	54.0 (48.0-60.0)	54.0 (49.5, 64.0)	0.6
Red Blood Cell Count (million cells/ μ L)	4.0 (3.8-4.0)	4.0 (4.0, 4.0)	0.2
Hemoglobin (g/dL)	12.0 (11.0-13.0)	12.8 (11.1, 13.2)	0.3
Hematocrit (%)	38.9 (36.0-42.0)	39.5 (35.5, 44.0)	0.4
Mean Corpuscular Volume (fL)	91.0 (88.0-96.0)	94.0 (88.0, 96.0)	0.6
Mean Corpuscular Hemoglobin (pg)	29.9 (27.0-31.0)	29.0 (28.0, 31.0)	0.8
Mean Corpuscular Hemoglobin Concentration (g/dL)	31.0 (30.0-32.0)	31.0 (30.0, 32.0)	0.7

¹ n (%); Median (Q1-Q3); Mean (SD)

Table 3 presents a comparative analysis of various demographic, clinical, medical history, and lifestyle characteristics between participants with negative CRP levels (N = 83) and those with positive CRP levels (N = 36). The p-values are provided to indicate the statistical significance of the differences observed between these two groups. For demographic and routine hematological parameters, no statistically significant differences were found between the CRP negative and CRP positive groups. Specifically, the distribution of sex (p=0.3) did not differ significantly, with 49% female in the negative group and 61% female in the positive group, and 51% male in the negative group and 39% male in the positive group. Similarly, age (median 54.0 years for both groups, p=0.6), red blood cell count (4.0 million cells/ μ L for both, p=0.2), hemoglobin (12.0 g/dL negative vs. 12.8 g/dL positive, p=0.3), hematocrit (38.9% negative vs. 39.5% positive, p=0.4),

mean corpuscular volume (91.0 fL negative vs. 94.0 fL positive, p=0.6), mean corpuscular hemoglobin (29.9 pg negative vs. 29.0 pg positive, p=0.8), and mean corpuscular hemoglobin concentration (31.0 g/dL for both, p=0.7) showed no significant differences. Furthermore, key iron-related markers such as serum iron (92.9 μ g/dL negative vs. 85.7 μ g/dL positive, p=0.3), transferrin (100.0 mg/dL negative vs. 75.0 mg/dL positive, p=0.2), total iron-binding capacity (99.0 μ g/dL negative vs. 138.5 μ g/dL positive, p=0.2), and ferritin (293.0 ng/mL negative vs. 280.0 ng/mL positive, p=0.2) were also not significantly different between the two CRP status groups.

Table 4: lifestyle and medical history by CRP Status

Characteristic	negative N = 83 ¹	positive N = 36 ¹	p-value ²
History of Iron Deficiency Anemia	17 (20%)	9 (25%)	0.8
Duration of T2DM Diagnosis			
1–5 years	31 (37%)	17 (47%)	0.4
Less than 1 year	10 (12%)	2 (6%)	
More than 5 years	42 (51%)	17 (47%)	
Chronic Diseases	32 (39%)	11 (31%)	0.5
Iron-Rich Meals per Week			
1 meal	11 (13%)	4 (11%)	0.7
2-3 meals	1 (1%)	0 (0%)	
2 meals	4 (5%)	4 (11%)	
3-4 meals	6 (7%)	3 (8%)	
3-5 meals	2 (2%)	0 (0%)	
3 meals	8 (10%)	4 (11%)	
4 meals	3 (4%)	0 (0%)	
5 meals	3 (4%)	2 (6%)	
6 meals	4 (5%)	0 (0%)	
7 meals	3 (4%)	0 (0%)	
8 meals	1 (1%)	0 (0%)	
daily	13 (16%)	8 (22%)	
Low	1 (1%)	1 (3%)	
No	7 (8%)	2 (6%)	
Normal	0 (0%)	1 (3%)	
Rarely	1 (1%)	0 (0%)	
sometimes	15 (18%)	7 (19%)	
Nutritional Supplements	24 (29%)	16 (44%)	0.2
Exercise Frequency			
3 times a week	4 (5%)	2 (6%)	0.12
No	1 (1%)	3 (8%)	
Once or twice	13 (16%)	2 (6%)	
Rarely	65 (78%)	29 (81%)	
Smoking Status			
Former smoker	7 (8%)	2 (6%)	0.5
No	67 (81%)	32 (89%)	
Yes	9 (11%)	2 (6%)	
Alcohol Consumption	2 (2%)	0 (0%)	0.9
Type of Diabetic Treatment			
Dietary regulation	48 (58%)	21 (58%)	0.6
Insulin	26 (31%)	13 (36%)	
Tablets	9 (11%)	2 (6%)	

² Pearson's Chi-squared tests; Wilcoxon rank sum test; Welch Two Sample t-test

Beyond physiological markers, lifestyle and medical history variables also demonstrated no significant association with CRP status. There was no significant difference in the history of iron deficiency anemia (20% negative vs. 25% positive, $p=0.8$), duration of type 2 diabetes diagnosis ($p=0.4$), or the presence of chronic diseases (39% negative vs. 31% positive, $p=0.5$). Similarly, self-reported iron-rich meal consumption per week ($p=0.7$), nutritional supplement use (29% negative vs. 44% positive, $p=0.2$), exercise frequency ($p=0.12$), smoking status ($p=0.5$), alcohol consumption ($p=0.9$), and the type of diabetic treatment ($p=0.6$) did not show statistically significant differences between participants with negative and positive CRP levels.

These findings suggest that CRP status in this cohort is not significantly associated with the evaluated demographic, clinical, or lifestyle factors. The data for this table were presented as n (%) for categorical variables and Median (Q1-Q3) or Mean (SD) for continuous variables. The statistical tests used for comparison included Pearson’s Chi-squared test, Wilcoxon rank sum test, and Welch Two Sample t-test.

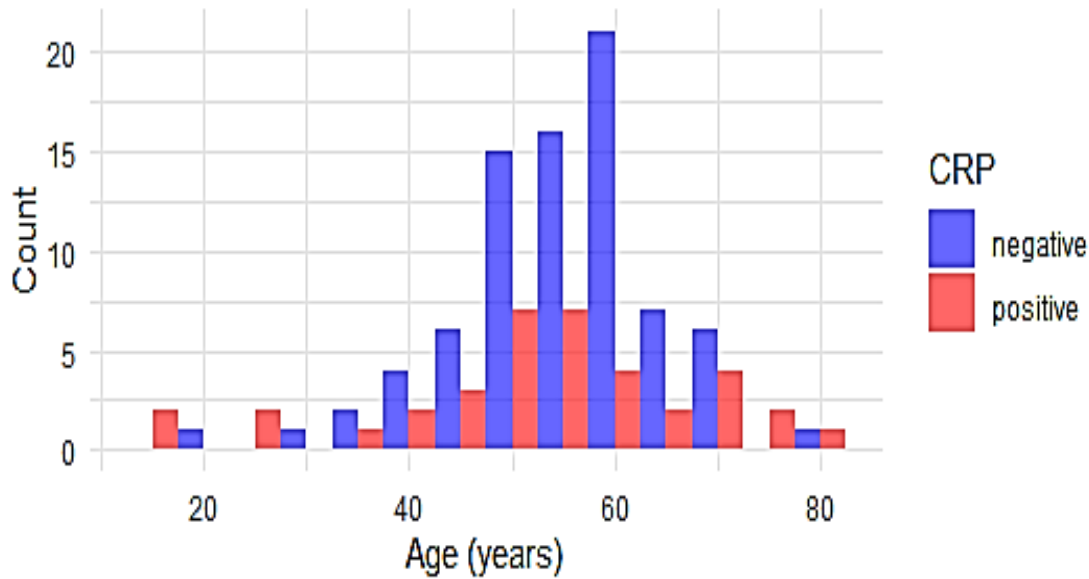


Fig. 2: Age Distribution by CRP Status

This bar chart displays the age distribution of participants, stratified by their C-reactive protein (CRP) status (negative or positive). The x-axis represents age in years, and the y-axis indicates the count of individuals. The blue bars represent participants with negative CRP, and the red bars represent those with positive CRP. The chart shows that both CRP negative and positive groups have individuals across a similar age range. While there are more CRP negative individuals overall, the distribution across age groups appears somewhat similar between the two CRP statuses, without a clear visual indication of one group being consistently older or younger than the other.

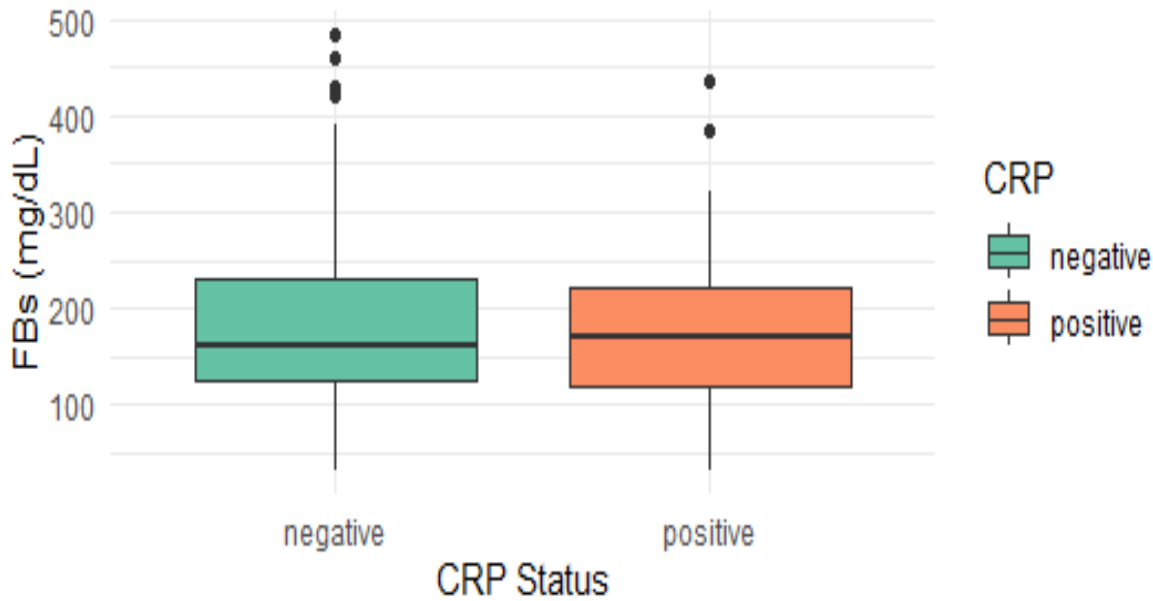


Fig. 3: Fasting Blood Sugar by CRP Status

This box plot visualizes the distribution of fasting blood sugar (FBs) levels based on CRP status (negative or positive). The x-axis indicates the CRP status, and the y-axis represents FBs in mg/dL. The green box plot shows the FBs distribution for CRP negative individuals, and the orange box plot shows it for CRP positive individuals. Both groups exhibit a wide range of FBs values, with several outliers visible as individual points above the upper whisker. The median FBs levels (indicated by the horizontal line within the box) appear to be relatively similar between the CRP negative and CRP positive groups, suggesting no substantial difference in the central tendency of fasting blood sugar based on CRP status.

5. DISCUSSION

This study aimed to evaluate the relationship between C-reactive protein (CRP), a marker of systemic inflammation, and glycemic control indicators—fasting blood sugar (FBs) and glycated hemoglobin (HbA1c)—in patients with type 2 diabetes mellitus (T2DM). The primary finding of this investigation was the absence of a statistically significant association between CRP status and either FBs or HbA1c levels. This suggests that in this study cohort, CRP, when assessed as a dichotomous variable, may not serve as a direct proxy for glycemic control.

Our results stand in contrast to several recent studies that have reported a positive association between elevated CRP levels and poor glycemic control in T2DM, underscoring the inflammatory nature of the disease (Alam et al., 2022; Chen et al., 2021; Islam et al., 2023). The discrepancy between our findings and the existing literature may be attributable to several factors. Significant inter-patient heterogeneity, including variations in anti-diabetic or anti-inflammatory therapeutic regimens, could mask a potential association. Furthermore, the presence of comorbid conditions may modulate CRP levels independently of glucose metabolism, thereby confounding the relationship between inflammation and glycemic status.

Extending beyond glycemic markers, our analysis also revealed no significant associations between CRP levels and key lifestyle or clinical history variables, including diabetes duration, physical activity, smoking status, or the use of nutritional supplements. This finding is inconsistent with a body of evidence suggesting that sedentary behavior, poor dietary habits, and smoking are positively correlated with elevated inflammatory markers in T2DM populations (Gopalakrishnan et al., 2022; Nakamura et al., 2023; Rahman et al., 2021; Gao et al., 2022; Kim et al., 2023). This divergence could stem from population-specific differences, the potential for underreporting of lifestyle behaviors in a clinical setting, or the influence of unmeasured confounding variables. Notably, the generally low frequency of physical activity reported by participants in our study may have created a "floor effect," limiting our statistical power to detect meaningful differences in CRP levels between subgroups.

Several limitations should be considered when interpreting these findings. First, the reliance on CRP as a solitary inflammatory marker may not fully capture the complexity of the inflammatory state in T2DM; a panel including other cytokines and markers of insulin resistance would provide a more comprehensive assessment. Second, the absence of data on key confounders, particularly body mass index (BMI), limits our ability to control for the well-established influence of adiposity on systemic inflammation. Finally, the modest sample size and cross-sectional design of the study preclude the establishment of causal relationships and limit the generalizability of the findings to a broader population.

5. CONCLUSION

this cross-sectional study did not identify a statistically significant association between C-reactive protein status and the primary glycemic control markers, HbA1c and fasting blood glucose, in patients with T2DM. Similarly, no link was observed between CRP and various hematological, lifestyle, or demographic factors within this cohort. While systemic inflammation remains a cornerstone of T2DM pathophysiology, our findings suggest that the clinical utility of CRP as a standalone, sensitive biomarker for monitoring glycemic control is limited. Future research should therefore employ larger, prospective cohorts and longitudinal designs to establish causality. Incorporating a broader panel of inflammatory biomarkers (e.g., cytokines) and metabolic parameters (e.g., insulin resistance indices, BMI) will be essential to fully elucidate the intricate interplay between inflammation and glycemic regulation in T2DM.

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