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Serum Complement C3 and C4 Levels, C-Reactive Protein, and Random Blood Glucose in Type 1 Diabetes Mellitus: A Case-Control Study

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Abstract: Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by pancreatic beta-cell destruction and absolute insulin deficiency. This case-control study compared serum complement C3, complement C4, C-reactive protein (CRP), and random blood glucose (RBS) between 32 patients with T1DM and 30 apparently healthy controls in Al-Najaf, Iraq. Associations among biomarkers were assessed using Spearman correlation, and age-adjusted multivariable logistic regression and receiver operating characteristic (ROC) analysis were used to evaluate associations with T1DM and discriminatory performance. RBS, CRP, and C3 were significantly higher in patients with T1DM than in controls ($P \leq 0.002$), whereas C4 did not differ significantly ($P = 0.308$). In age-adjusted regression, CRP (adjusted odds ratio [aOR] 2.952; 95% CI 1.317–6.617; $P = 0.009$) and C3 (aOR 256.36 per 1 g/L; 95% CI 2.030–32,373.878; $P = 0.025$) were associated with T1DM, although the very wide confidence interval for C3 indicates substantial imprecision. C3 and C4 were strongly positively correlated in the T1DM group ($r_s = 0.614$; $P < 0.001$), but neither complement component correlated significantly with RBS or CRP. ROC analysis showed that CRP had the highest discriminatory performance (AUC = 0.864; 95% CI 0.772–0.955), followed by C3 (AUC = 0.726; 95% CI 0.601–0.850); C4 was not significant (AUC = 0.573; $P = 0.324$). Because of the small sample, age imbalance, case-control design, and data-derived cut-offs, these findings are hypothesis-generating and require validation in larger, age-matched prospective studies.

Keywords: Type 1 diabetes mellitus; C3; C4; C-reactive protein; inflammation; complement system; ROC curve

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder caused by immune-mediated destruction of pancreatic beta cells, leading to absolute insulin deficiency and lifelong insulin therapy (Jacobsen & Schatz, 2026).

Hyperglycemia, oxidative stress, endothelial dysfunction, and low-grade inflammation are important features of the disease (Evans-Molina *et al.*, 2025). Although pancreatic autoantibodies remain central to diagnosis, growing evidence supports a role for innate immunity, adaptive immunity, inflammation, and

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metabolic pathways in T1DM pathogenesis(Evans-Molina *et al.,* 2025; Insel *et al.,* 2015) .

The complement system participates in innate immunity, antigen presentation, T-cell responses, cytokine signaling, and inflammatory processes (Ricklin *et al.,* 2018). Genetic variation in complement-related genes and alterations in complement proteins have also been implicated in islet autoimmunity and the development of type 1 diabetes (Hu *et al.,* 2025; Onengut-Gumuscu *et al.,* 2024). C3 is a central component shared by the classical, lectin, and alternative complement pathways, whereas C4 participates mainly in the classical and lectin pathways (Ricklin *et al.,* 2018). Because both proteins are largely hepatically synthesized and can behave as acute-phase reactants, their circulating concentrations may reflect both inflammatory activation and complement consumption (Ricklin *et al.,* 2018; Sarkar *et al.,* 2023).

Previous studies suggest that complement-related proteins and inflammatory markers may be altered in T1DM, but findings remain inconsistent and may vary with disease stage, metabolic status, and population characteristics (Hussein *et al.,* 2006; Rudman *et al.,* 2023; Sarkar *et al.,* 2023; Webb-Robertson *et al.,* 2024). Data from Middle Eastern populations, including Iraq, remain limited (Hussein *et al.,* 2006).

Therefore, this study aimed to compare serum C3 and C4 concentrations between patients with T1DM and apparently healthy controls in Al-Najaf, Iraq. Secondary objectives were to assess within-group correlations of C3 and C4 with CRP and RBS, and to explore the ability of these biomarkers to discriminate patients with T1DM from controls.

Materials and Methods

Study design and setting: A case-control study was performed at the Diabetes Unit, Al-Sadr Teaching Hospital, Al-Najaf, Iraq, from 23 October 2023 to 20 April 2024.

Participants: The study included 62 participants: 32 patients with type 1 diabetes mellitus (T1DM) and 30 apparently healthy controls. T1DM was diagnosed according to American Diabetes Association criteria, including typical hyperglycemic symptoms with random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), 2-hour plasma glucose ≥ 200 mg/dL during a 75-g oral glucose tolerance test, or HbA1c ≥ 6.5%, together with clinical features and specialist physician confirmation consistent with T1DM. Patients had a previous diagnosis of T1DM established by a specialist physician at the Diabetes Unit of Al-Sadr Teaching Hospital and were aged 10–50 years. Both sexes were included. Controls were apparently healthy individuals without a known history of diabetes mellitus, autoimmune disease, or chronic inflammatory condition. Absence of diabetes in controls was confirmed by random blood glucose < 140 mg/dL and absence of known diabetes diagnosis; where available, fasting glucose and/or HbA1c were also reviewed. Controls were recruited from individuals attending the hospital for routine check-ups or accompanying patients and were matched to patients as closely as feasible by sex and age. Participants were recruited by convenience sampling from individuals attending the Diabetes Unit during the study period. No a priori sample-size calculation was performed; the sample comprised the eligible participants available during the study period.

Exclusion Criteria: Participants were excluded if they had type 2 diabetes mellitus or another form of diabetes; a history of autoimmune disease other than T1DM; acute infection or inflammatory illness at the time of sampling; severe renal, hepatic, or cardiovascular disease; pregnancy; use of medications known to substantially affect immune or inflammatory markers; or refusal to provide informed consent. Disease duration, insulin regimen, and body mass index were not systematically collected and were therefore not included in the analysis.

Sample Collection: A single venous blood sample was collected from each participant during the study visit. Serum was separated from the collected blood samples and stored at −20 °C until laboratory analysis. Serum C3, C4, and CRP concentrations were measured, and random blood glucose (RBS) was assessed as an indicator of current glycemic status.

Laboratory Investigation: Venous blood samples were allowed to clot and were then centrifuged to obtain serum. Serum C3 and C4 concentrations were measured using commercially available human complement C3 and C4 enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. Serum CRP was measured using a quantitative latex immunoassay, and random blood glucose (RBS) was determined using the glucose oxidase method. Internal quality-control materials at low and high concentrations were run with each batch, and results were accepted only when control values fell within the predefined acceptable limits. All assays were performed according to the manufacturers' instructions and standard laboratory quality-control procedures.

Ethical Considerations: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the relevant institutional review committee before the study began. Written informed consent was obtained from all adult participants. For participants younger than 18 years,

written informed consent was obtained from a parent or legal guardian, and assent was obtained from the minor. The confidentiality of participants' information was maintained throughout the study, and all data were anonymized and coded.

Statistical Analysis: All statistical analyses were performed using SPSS software, version 26. Categorical variables, including sex, were expressed as frequencies and percentages and compared between groups using Pearson's chi-square test. Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of histograms, and were expressed as mean ± SD for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test, as appropriate. Because age differed significantly between the T1DM and control groups, multivariable logistic regression was performed with age included as a covariate. T1DM status was the dependent variable (1 = T1DM, 0 = control), while age, CRP, C3, and C4 were entered simultaneously as continuous variables. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. Multicollinearity was assessed using variance inflation factors (VIF); a VIF > 5 was considered indicative of potential multicollinearity. Given the small number of events relative to the number of predictors, the risk of overfitting and unstable estimates was high; therefore, the regression model was treated as exploratory, and results were interpreted cautiously. As a sensitivity analysis, age-adjusted models were also examined with CRP, C3, and C4 entered separately, and standardized coefficients were considered to facilitate comparison across predictors.

Result and Discussion

Result

Demographic Characteristics of the Study Population: The study included 62 participants, comprising 32 patients with T1DM and 30 apparently healthy controls. The sex distribution was comparable between the two groups, with females accounting for 50.0% of each group and males accounting for the remaining 50.0%. No statistically significant difference in sex distribution was observed between the groups (P = 1.000). The mean age was 26.88 ± 8.71 years in the T1DM group and 36.03 ± 2.82 years in the control group. The control group was significantly older than the T1DM group (P < 0.001).

Random Blood Glucose: Random blood glucose (RBS) levels were significantly higher in patients with T1DM than in healthy controls. The mean RBS level was 224.06 ± 39.33 mg/dL in the T1DM group compared with 107.40 ± 3.89 mg/dL in the control group (P < 0.001).

Inflammatory and Immunological Biomarkers: Serum CRP levels were significantly higher in patients with T1DM than in healthy controls. The mean CRP level was 3.77 ± 3.87 mg/dL in the T1DM group compared with 0.67 ± 0.79 mg/dL in the control group (P < 0.001). Similarly, serum C3 levels were significantly higher in patients with T1DM than in healthy controls. The mean serum C3 level was 1.50 ± 0.53 g/L in the T1DM group compared with 1.10 ± 0.25 g/L in the control group (P = 0.002).

In contrast, serum C4 levels were numerically higher in patients with T1DM than in healthy controls; however, the difference was not statistically significant. The mean C4 level was 0.39 ± 0.33 g/L in the T1DM group and 0.25 ± 0.07 g/L in the control group (P = 0.308) **(Table 1)**. Therefore, the present findings do not provide sufficient evidence of a significant difference in circulating C4 levels between patients with T1DM and healthy controls.

Table 1. Comparison of demographic, glycemic, and immunological biomarkers between the type 1 diabetes and control groups.

Parameter	Type 1 Diabetes (n=32)	Control Group (n=30)	p-value
Sex - Female	16 (50.0%)	15 (50.0%)	1.000
Sex - Male	16 (50.0%)	15 (50.0%)	1.000
Age (years)	26.88 ± 8.71	36.03 ± 2.82	< 0.001
RBS (mg/dL)	224.06 ± 39.33	107.40 ± 3.89	< 0.001
CRP (mg/dL)	3.77 ± 3.87	0.67 ± 0.79	< 0.001
C3 (g/L)	1.50 ± 0.53	1.10 ± 0.25	0.002
C4 (g/L)	0.39 ± 0.33	0.25 ± 0.07	0.308

Note. Data are presented as n (%) or mean ± SD. P values were obtained using Pearson's chi-square test for sex and the independent-samples t-test or Mann–Whitney U test for continuous variables, as appropriate. RBS, random blood glucose; CRP, C-reactive protein.

Logistic Regression: Age-adjusted multivariable logistic regression analysis showed that both CRP and C3 were significantly associated with T1DM. CRP was significantly associated with T1DM, with an adjusted odds ratio of 2.952 (95% CI: 1.317-6.617; P = 0.009). C3 was also statistically associated with T1DM (aOR = 256.36 per 1 g/L increase, 95% CI: 2.030-32,373.878; P = 0.025). Because C3 was entered per 1 g/L, a large change relative to the observed variability (SD 0.53 g/L in patients and 0.25 g/L in controls), the large point estimate largely reflects the scale of the predictor rather than a strong effect. In contrast, C4 was not significantly associated with T1DM (aOR = 0.072, 95% CI: 0.000-

25.283; P = 0.379). The extremely wide confidence interval for C3 indicates considerable uncertainty and low precision of the estimated effect size, likely related to the small sample size and the limited number of events per predictor. Accordingly, the association between C3 and T1DM should not be regarded as strong or definitive, should be interpreted cautiously, and should be confirmed in larger studies **(Table 2)**.

Table 2. Multivariable logistic regression predicting type 1 diabetes status (adjusted for age).

Predictor Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Age	0.703	0.557 - 0.887	0.003
CRP (mg/dL)	2.952	1.317 - 6.617	0.009
C3 (g/L)	256.36	2.030 - 32,373.878	0.025
C4 (g/L)	0.072	<0.001 - 25.283	0.379

Note. Dependent variable: T1DM (1) versus control (0). Age (years), CRP (mg/dL), C3 (g/L), and C4 (g/L) were entered simultaneously as continuous variables; aORs are per one-unit increase in each predictor. aOR, adjusted odds ratio; CI, confidence interval.

Correlation Analysis: Spearman's rank correlation analysis was performed to assess the relationships among RBS, CRP, C3, and C4 within the T1DM and control groups. Among patients with T1DM, a strong positive correlation was observed between serum C3 and C4 levels (rs = 0.614, P < 0.001). No statistically significant correlations were observed between C3 and RBS (rs = 0.121, P = 0.510), C3 and CRP (rs = 0.137, P = 0.455), C4 and RBS (rs = −0.076, P = 0.680), C4 and CRP (rs = 0.164, P = 0.369), or RBS and CRP (rs = 0.161, P = 0.380). Among healthy controls, significant positive correlations were observed between C3 and CRP (rs = 0.368, P = 0.046) and between C3 and C4 (rs = 0.381, P = 0.038). The remaining correlations were not statistically significant **(Table 3)**.

ROC Analysis: ROC curve analysis demonstrated that CRP had the highest discriminatory performance for distinguishing patients with T1DM from healthy controls, with an AUC of 0.864 (95% CI: 0.772-0.955; P < 0.001). At the optimal cut-off value of 1.50 mg/dL, CRP showed a sensitivity of 68.8% and a specificity of 90.0%. C3 also demonstrated statistically significant discriminatory ability, with an AUC of 0.726 (95% CI: 0.601-0.850; P = 0.002). At the optimal cut-off value of 1.35 g/L, C3 showed a sensitivity of 37.5% and a specificity of 96.7%. In contrast, C4 did not demonstrate statistically significant discriminatory ability, with an AUC of 0.573 (95% CI: 0.423-0.723; P = 0.324). For C4, although the cut-off value of 0.35 g/L yielded a specificity of 93.3%, its sensitivity was only 37.5% **(Table 4; Figure 1)**. All cut-off values were data-derived in the present sample, and these estimates should be regarded as preliminary rather than as evidence of validated diagnostic performance.

Table 3. Spearman correlation matrix across the T1DM and control groups [Spearman's rank correlation coefficient (rs), P value].

Groups	Study variables	RBS	CRP	C3	C4
T1DM (n = 32)	RBS	1.000	0.161 (P = 0.380)	0.121 (P = 0.510)	-0.076 (P = 0.680)
	CRP	0.161 (P = 0.380)	1.000	0.137 (P = 0.455)	0.164 (P = 0.369)
	C3	0.121 (P = 0.510)	0.137 (P = 0.455)	1.000	0.614* (P < 0.001)
	C4	-0.076 (P = 0.680)	0.164 (P = 0.369)	0.614* (P < 0.001)	1.000
Control (n = 30)	RBS	1.000	-0.205 (P = 0.278)	-0.359 (P = 0.052)	0.275 (P = 0.141)
	CRP	-0.205 (P = 0.278)	1.000	0.368* (P = 0.046)	0.251 (P = 0.181)
	C3	-0.359 (P = 0.052)	0.368* (P = 0.046)	1.000	0.381* (P = 0.038)
	C4	0.275 (P = 0.141)	0.251 (P = 0.181)	0.381* (P = 0.038)	1.000

Note. Values are Spearman's rank correlation coefficients (rs) with two-tailed P values in parentheses. *Statistically significant correlation (P < 0.05). Correlations were analyzed separately within each group and are considered exploratory.

Table 4. ROC curve analysis and discriminatory performance of inflammatory and complement biomarkers.

Biomarker	Area Under the Curve (AUC)	95% Confidence Interval (CI)	Optimal Cut-off Value	Sensitivity (%)	Specificity (%)	p-value
CRP	0.864 (Good)	0.772 - 0.955	≥ 1.50 mg/dL	68.8 %	90.0 %	< 0.001
C3	0.726 (Fair)	0.601 - 0.850	≥ 1.35 g/L	37.5 %	96.7 %	0.002
C4	0.573 (Poor)	0.423 - 0.723	≥ 0.35 g/L	37.5 %	93.3 %	0.324

Note. Optimal cut-off values were data-derived and were selected and evaluated in the same dataset; sensitivity and specificity may therefore be optimistic and require external validation. AUC, area under the receiver operating characteristic curve; CI, confidence interval.

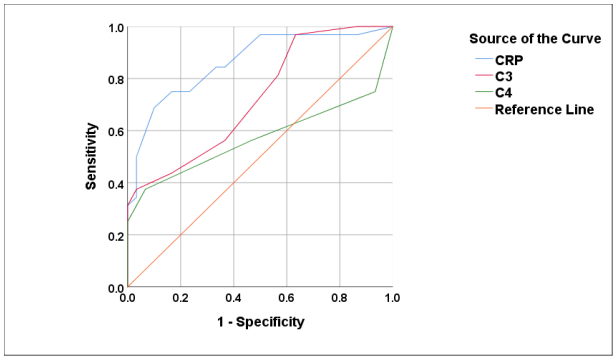

Figure 1. ROC curves evaluating the discriminatory performance of CRP, C3, and C4 biomarkers for distinguishing patients with T1DM from healthy controls.

Discussion

Main Findings and Interpretation: In the present study, RBS, CRP, and serum C3 were significantly higher in patients with T1DM than in healthy controls, whereas C4 did not differ significantly. Within the T1DM group, neither C3 nor C4 correlated significantly with CRP or RBS. These findings therefore reflect between-group differences rather than demonstrated within-group associations with inflammation or glycemic status (Rudman *et al.,* 2023; Sarkar *et al.,* 2023).

Glycemic Disturbance: The higher RBS in patients with T1DM is consistent with absolute insulin deficiency and impaired glucose homeostasis (Jacobsen & Schatz, 2026; American Diabetes Association Professional Practice Committee, 2025). However, RBS reflects short-term glycemic status and can be influenced by recent food intake, physical activity, and insulin administration (American Diabetes Association Professional Practice Committee, 2025). Future studies should include HbA1c to better assess long-term glycemic control (American Diabetes Association Professional Practice Committee, 2025).

Inflammatory Activity and CRP: Higher CRP concentrations in patients with T1DM suggest greater systemic inflammatory activity (Hassan, 2016; Pérez-Segura *et al.,* 2020; van Heck *et al.,* 2025). However, CRP is a nonspecific acute-phase marker and may be influenced by infection, adiposity, glycemic control, and other inflammatory conditions (Ali *et al.,* 2020; Van Heck *et al.,* 2025). Therefore, the present finding should be interpreted as an association with the studied cohort rather than evidence of a disease-specific inflammatory mechanism (Ali *et al.,* 2020; Van Heck *et al.,* 2025).

Complement Components C3 and C4: The higher C3 concentration in patients with T1DM may reflect complement-related alterations, but circulating concentrations do not directly measure complement activation (Ricklin *et al.,* 2018; Rudman *et al.,* 2023). Genetic and proteomic evidence also suggests that complement system proteins may contribute to islet autoimmunity and the development of T1DM (Hu *et al.,* 2025; Onengut-Gumuscu *et al.,* 2024). The nonsignificant difference in C4 suggests that the present findings do not provide sufficient evidence for a generalized increase in circulating C4 in T1DM (Hussein *et al.,* 2006; Sarkar *et al.,* 2023). The strong C3–C4 correlation in the T1DM group should be considered hypothesis-generating and may reflect shared hepatic synthesis or parallel changes in circulating complement levels (Damilano *et al.,* 2024; Ricklin *et al.,* 2018).

ROC Interpretation: CRP showed the highest discriminatory performance, followed by C3, whereas C4 was not significant. Because the cut-off values were derived and evaluated in the same small sample, these estimates are exploratory and likely optimistic (Rudman *et al.,* 2023; Sarkar *et al.,* 2023). Therefore, CRP, C3, and C4 should be considered research biomarkers rather than established diagnostic markers for T1DM (Sarkar *et al.,* 2023; Webb-Robertson *et al.,* 2024).

This study has several limitations. First, the relatively small sample size and single-center design may limit generalizability. Second, despite statistical adjustment, the T1DM and control groups differed significantly in age, which may have resulted in residual confounding. Third, RBS was used as the measure of glycemic status and does not reflect long-term glycemic control. Fourth, the cross-sectional design precludes causal or temporal inference. Fifth, clinical variables that may influence inflammatory and complement concentrations, including disease duration, insulin regimen, BMI, and HbA1c, were not available for analysis. Sixth, the regression estimates, particularly for C3, were imprecise, and ROC cut-offs were data-derived without external validation. Finally, only circulating C3 and C4 concentrations were measured, and functional complement activity was not assessed. Larger, multicenter, age-matched prospective studies incorporating HbA1c, pancreatic autoantibodies, and functional complement assays are warranted.

Conclusion

Patients with T1DM in the studied cohort had significantly higher serum CRP and C3 concentrations than healthy controls, whereas serum C4 concentrations did not differ significantly. C3 and C4 were strongly positively correlated in the T1DM group, but neither complement component correlated significantly with RBS or CRP. ROC analysis showed that CRP had the highest discriminatory performance, followed by C3, whereas C4 was not significant. These findings suggest inflammatory and complement-related alterations in T1DM, but the small sample size, age imbalance, and case-control design limit their interpretation. Therefore,

CRP, C3, and C4 should currently be considered research biomarkers rather than established diagnostic markers.

Recommendations

1. Larger multicenter studies should be conducted in different Iraqi populations to validate the present findings and improve generalizability.
2. Longitudinal studies should assess whether changes in C3, C4, and CRP are associated with disease duration, disease progression, and metabolic control.
3. Future studies should include HbA1c, pancreatic autoantibodies, and functional complement assays to better characterize the immunoinflammatory profile of T1DM.
4. Confounding factors such as age, BMI, disease duration, treatment, infection, and metabolic control should be considered in future studies.
5. CRP and C3 showed some discriminatory potential, but they should not replace established diagnostic criteria or routine clinical markers of T1DM.

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