

Assessment of Serum Complement C3 and C4 Levels in Patients with Type 2 Diabetes Mellitus in Al-Najaf Province, Iraq: A Case-Control Study

Eman Th. Nadhaif Al-Fatlawy

Department of Clinical Laboratory Sciences, College of Pharmacy, University of Al-Kufa, Iraq.

Corresponding author: imanth.nadhaif@uokufa.edu.iq

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is an abnormal long-term metabolic condition in which people have high blood-sugar levels, low-grade inflammation, and abnormal immune system activity. The complement system, namely, complement components C3 and C4, might be potentially involved in metabolic inflammation and insulin resistance. Random blood sugar (RBS) and glycemic parameters levels may also give some clues about changes in inflammation and metabolism in these patients with T2DM. **Objective:** To compare the levels of complement C3, complement C4, C-reactive protein (CRP), and RBC level between patients with T2DM and apparently healthy subjects in Al-Najaf Province, Iraq and investigate association between these biomarkers. **Methods:** A case-control study was conducted at the Diabetes Unit, Al-Sadr Teaching Hospital, Al-Najaf, Iraq, from October 2024 to April 2025. The study enrolled 35 patients with T2DM and 30 apparently healthy controls. Demographic data, including age and sex, were recorded. Serum C3, C4, CRP, and RBS levels were measured and compared between groups. Spearman's correlation analysis, multivariable logistic regression, and receiver operating characteristic (ROC) curve analysis were performed. A p-value of < 0.05 was considered statistically significant. **Results:** Patients with T2DM were significantly older than controls (54.43 ± 11.62 vs. 36.03 ± 2.82 years; $p < 0.001$), while sex distribution was comparable between groups ($p = 0.730$). RBS was markedly higher in patients with T2DM than in controls (291.31 ± 63.62 vs. 107.40 ± 3.89 mg/dL; $p < 0.001$). Similarly, T2DM patients had significantly higher serum CRP (9.07 ± 7.54 vs. 0.67 ± 0.79 mg/dL; $p < 0.001$), C3 (1.53 ± 0.57 vs. 1.10 ± 0.25 g/L; $p < 0.001$), and C4 levels (0.47 ± 0.34 vs. 0.25 ± 0.07 g/L; $p = 0.016$). Among patients with T2DM, CRP correlated positively with C3 ($r_s = 0.336$, $p = 0.048$) and C4 ($r_s = 0.564$, $p < 0.001$), while C3 was strongly correlated with C4 ($r_s = 0.653$, $p < 0.001$). In multivariable logistic regression, age (adjusted odds ratio = 1.438, 95% confidence interval: 1.073–1.926; $p = 0.015$) and CRP (adjusted odds ratio = 2.406, 95% confidence interval: 1.110–5.217; $p = 0.026$) were independently associated with T2DM. CRP demonstrated excellent discriminatory performance for T2DM, with an area under the ROC curve of 0.937 (95% confidence interval: 0.884–0.990; $p < 0.001$). **Conclusion:** Patients with T2DM had significantly elevated serum C3, C4, CRP, and RBS levels compared with healthy controls. The positive correlations of CRP with C3 and C4 support an association between complement components and systemic inflammation in T2DM. Although C3 and C4 were elevated in the patient group, they were not independently associated with T2DM after adjustment for age and CRP. CRP showed the strongest discriminatory ability among the evaluated biomarkers. Larger, age-matched prospective studies are needed to clarify the potential clinical and pathophysiological role of complement components in T2DM. **Keywords:** Type 2 diabetes mellitus; Complement C3; Complement C4; C-reactive protein; Random blood sugar; Inflammation.

Article Information

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INTRODUCTION

The growing prevalence of type 2 diabetes mellitus (T2DM) and its tremendous microvascular and macrovascular complications have made it a chronic and progressive metabolic disorder and a significant public health issue worldwide. While hyperglycemia is a hallmark of T2DM, the disease is also known to be a multifactorial condition to date characterised by insulin resistance, progressive pancreatic β -cell dysfunction, chronic low-grade inflammation, oxidative stress and dysregulated immune-metabolic interactions. These pathways help develop and progress complications of diabetes (1).

Physiopathologically, chronic low-grade inflammation is regarded as a major part of T2DM. Hyperglycemia and associated metabolic changes may have negative consequences by generating oxidative stress, and by triggering inflammatory pathways that can lead to poor insulin function, impaired endothelial function and normal glucose metabolism. As a result, the role of inflammatory biomarkers as markers of metabolic disturbances and disease-associated inflammation in T2DM has become more important (1,2).

The complement system plays a major role in innate immunity and in host defenses, inflammatory regulation and tissue homeostasis. The linkage between complement activation and metabolic disorders, such as obesity, insulin resistance and T2DM is increasingly being published. Complement component C3 has received particular attention because it may be involved in adipose-tissue inflammation and metabolic dysfunction. Elevated circulating C3 concentrations have been associated with an increased risk of incident T2DM, indicating that C3 may serve as a biomarker of metabolic disturbances and diabetes risk (3).

Complement component C4 is a major protein of the classical and lectin pathways of

the complement system and contributes to immune activation and inflammatory responses. Compared with C3, C4 has been less extensively investigated in the context of T2DM. However, alterations in serum C4 concentrations have been reported in patients with T2DM and may reflect changes in complement-related inflammatory activity associated with metabolic dysregulation (4). Further investigation of C4, together with C3, may therefore provide a more comprehensive assessment of complement-related alterations in T2DM.

C-reactive protein (CRP) is an established circulating marker of systemic inflammation. Increased CRP concentrations have been associated with low-grade inflammation and metabolic abnormalities in individuals with T2DM (2,5). Assessment of CRP alongside complement components may consequently help characterize the inflammatory profile associated with T2DM.

Random blood sugar (RBS) is a routinely used clinical measure of circulating glucose and provides an indication of the glycemic state at the time of sampling. Diagnostic interpretation of random plasma glucose should take into account the presence of hyperglycemic symptoms and established diagnostic criteria; therefore, RBS should be regarded primarily as a glycemic parameter rather than a direct measure of chronic glycemic control (6). Evaluating RBS together with CRP and complement components may nevertheless help describe the metabolic and inflammatory profile of patients with T2DM.

Despite increasing evidence linking complement-related inflammation with metabolic dysfunction, information regarding serum C3 and C4 concentrations in different populations remains limited. Data from Iraqi populations, particularly from Al-Najaf Province, are also scarce. Therefore, this study aimed to compare serum C3, C4, and CRP

levels, as well as RBS, between patients with T2DM and apparently healthy controls in Al-Najaf Province, Iraq. The study also examined the correlations among these metabolic, inflammatory, and complement-related parameters.

MATERIALS AND METHODS

Study Design and Participants: This was a case control study performed in the Diabetes Unit at Al-Sadr Teaching Hospital, Al-Najaf Province, Iraq from October 2024 to April 2025. 65 subjects were recruited: 35 affected by type 2 diabetes mellitus (T2DM) and 30 subjects who did not have any medical condition. The specialist physician in the Diabetes Unit made the diagnosis of T2DM.

Inclusion Criteria: Participants included both males and females who were subjected to consultation with a specialist doctor at the Diabetes Unit and diagnosed with T2DM. Apparently healthy men and women appearing in the control group did not have a previous diagnosis, nor had they a history of any major chronic disease including diabetes mellitus.

Exclusion Criteria: Exclusion factors were acute infections, autoimmune disorders, malignancies, severe chronic disorders and any other disorders that might affect inflammatory, metabolic or immune parameters.

Blood Collection and Laboratory Measurements: All participants had venous blood drawn under aseptic conditions, which was allowed to clot at room temperature. The serum was then separated by centrifugation of the samples. Aliquots of serum were frozen at -20°C for analysis. Complement C3 and C4 were measured in serum by using commercially available human C3 and C4 enzyme-linked immunosorbent assay (ELISA) kits respectively, according to manufacturer's instructions. Concentrations of serum C-reactive protein (CRP) were measured by quantitative latex immunoassay test and blood sugar level (random) was determined using Glucose oxidase method. The appropriate

internal quality control was applied to ensure accuracy and reliability of laboratory measurements.

RESULTS

Demographic and Clinical Characteristics: The total participants in this study were 65 (35 Type 2 Diabetes Mellitus (T2DM) + 30 healthy control). There was no significant difference in the sex distribution of the 2 groups. Females represented 54.3% of T2DM group ($n = 19$) and 50.0% of control group ($n = 15$), while males accounted for 45.7% ($n = 16$) and 50.0% ($n = 15$), respectively at $p = 0.730$.

The patients with T2DM were significantly older than healthy controls (54.43 ± 11.62) years vs (36.03 ± 2.82) years in control group ($p < 0.001$). Patients' median age was 52.0 years, while controls' was 36.0 years.

Levels of blood sugar were significantly elevated in patients with T2DM compared with control patients. The mean RBS level was (291.31 ± 63.62) mg/dL in T2DM group, compared with (107.40 ± 3.89) mg/dL in control group at $p < 0.001$.

The respective median values were 305.0 mg/dL and 108.0 mg/dL. Detailed demographic and clinical characteristics are presented in Table 1.

Inflammatory and Complement Biomarkers: Serum CRP concentrations were significantly elevated in patients with T2DM compared with healthy controls. The mean CRP concentration was (9.07 ± 7.54) mg/dL in patients and (0.67 ± 0.79) mg/dL in controls, with median values of (8.00 mg/dL and 0.45 mg/dL, respectively at $p < 0.001$).

Similarly, serum complement C3 levels were significantly higher in the T2DM group than in the control group (1.53 ± 0.57 g/L vs 1.10 ± 0.25 g/L; $p < 0.001$). The median C3 concentration was 1.50 g/L in patients and 1.10 g/L in controls.

Serum C4 was also significantly increased in T2DM patients compared with controls. The mean C4 level was (0.47 ± 0.34) g/L in patients

and (0.25 ± 0.07) g/L in controls ($p = 0.016$), while the median concentrations were 0.30 g/L and 0.20 g/L, respectively.

Table 1: Demographic, clinical, and biomarker characteristics between type 2 diabetes patients and healthy controls.

Parameters	Statistics	T2DM Patients (n=35)	Control Group (n=30)	p-value
Sex (Females/ Males)	Frequency (%)	19 (54.3%)/ 16 (45.7%)	15 (50.0%)/ 15 (50.0%)	0.730
Age (years)	Mean $\pm$ SD	54.43 $\pm$ 11.62	36.03 $\pm$ 2.82	< 0.001
	Median (IQR)	52.00 (13.00)	36.00 (4.50)	
RBS (mg/dL)	Mean $\pm$ SD	291.31 $\pm$ 63.62	107.40 $\pm$ 3.89	< 0.001
	Median (IQR)	305.00 (105.00)	108.00 (4.00)	
CRP (mg/dL)	Mean $\pm$ SD	9.07 $\pm$ 7.54	0.67 $\pm$ 0.79	< 0.001
	Median (IQR)	8.00 (13.50)	0.45 (0.60)	
C3 (g/L)	Mean $\pm$ SD	1.53 $\pm$ 0.57	1.10 $\pm$ 0.25	< 0.001
	Median (IQR)	1.50 (0.80)	1.10 (0.40)	
C4 (g/L)	Mean $\pm$ SD	0.47 $\pm$ 0.34	0.25 $\pm$ 0.07	0.016
	Median (IQR)	0.30 (0.55)	0.20 (0.10)	

Multivariable Logistic Regression

Analysis: A multivariable logistic regression model was used to evaluate the independent associations of age, CRP, C3, and C4 with T2DM status. Age was independently associated with T2DM, with an adjusted odds ratio (aOR) of 1.438 (95% CI: 1.073–1.926, $p = 0.015$). This indicates that each one-year increase in age was associated with a 43.8% increase in the odds of T2DM in the multivariable model.

CRP also remained significantly associated with T2DM after adjustment for the other variables (aOR = 2.406, 95% CI: 1.110–5.217, $p = 0.026$). In multivariable model, a

CRP increment of 1.0 mg/dL was corresponding with 2.4 fold more T2DM.

Multivariable model, however, failed to show any independent association with T2DM for either C3 or C4. C3 had an (aOR) of 24.208 (95% CI: 0.029–20269.635, $p = 0.353$), whereas C4 showed an (aOR < 0.001) (95% CI: 0.000–9.497, $p = 0.104$). Confidence intervals in this case are very wide, reflecting imprecision in estimated effects which is likely to be due to both small sample sizes and correlation between the complement biomarkers (Table 2).

Table 2: Multivariable Logistic Regression Predicting Type 2 Diabetes Status.

Predictor Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Age	1.438	1.073 – 1.926	0.015
CRP (mg/dL)	2.406	1.110 – 5.217	0.026
C3 (g/L)	24.208	0.029 – 20269.635	0.353
C4 (g/L)	< 0.001	0.000 – 9.497	0.104

Correlation Analysis: Spearman's rank-order correlation analysis was done for both T2DM and control group separately. Among patients with T2DM, CRP showed a significant positive correlation with C3 ($r_s = 0.336$, $p = 0.048$) and C4 ($r_s = 0.564$, $p < 0.001$). There was also a strong positive correlation between C3 and C4 ($r_s = 0.653$, $p < 0.001$).

No significant correlations were observed between RBS and CRP ($r_s = 0.130$, $p = 0.457$),

C3 ($r_s = -0.228$, $p = 0.188$), or C4 ($r_s = -0.180$, $p = 0.300$) among patients with T2DM.

Within healthy control group, CRP was significantly positively correlated with C3 ($r_s = 0.368$, $p = 0.046$). Moreover, C3 was positively correlated with C4 ($r_s = 0.381$, $p = 0.038$). There were no other significant correlations to be found between RBS, CRP, C3 and C4 (Table 3).

Table 3: Present Spearman's correlation coefficients among Study Grps.

Groups	Study variables	RBS/ P value	CRP/ P value	C3/ P value	C4/ P value
T2DM Patients (n = 35)	RBS	1.000	0.130 (p = 0.457)	-0.228 (p = 0.188)	-0.180 (p = 0.300)
	CRP	0.130 (p = 0.457)	1.000	0.336* (p = 0.048)	0.564* (p < 0.001)
	C3	-0.228 (p = 0.188)	0.336* (p = 0.048)	1.000	0.653* (p < 0.001)
	C4	-0.180 (p = 0.300)	0.564* (p < 0.001)	0.653* (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

ROC Curve Analysis: To assess the discriminatory power in distinguishing T2DM patients from controls, linear ROC curve analysis was employed for analyzing the

discriminatory power of these markers (CRP, C3, and C4). CRP demonstrated excellent discriminatory performance, with an AUC of (0.937) (95% CI: 0.884–0.990, $p < 0.001$).

CRP's sensitivity and specificity were 85.7% and 83.3% respectively at the threshold of ≥ 0.95 mg/dL .

C3 demonstrated fair discriminatory performance, with an AUC of (0.756) (95% CI: 0.636–0.875, $p < 0.001$). When using a cutoff ≥ 1.45 g/L, the sensitivity and specificity of C3 were 54.3% and 96.7%, respectively .

C4 showed modest discriminatory ability, with an AUC of (0.669) (95% CI: 0.535–0.802,

$p = 0.020$). With a cutoff value of ≥ 0.40 g/L, sensitivity and specificity of C4 were 45.7% and 93.3%, respectively. Over the whole panel, CRP had the best discriminatory accuracy as assessed by all available biomarkers. The ROC curves are illustrated in **Figure 1**, and the corresponding diagnostic parameters are summarized in **Table 4**.

Table 4: Receiver Operating Characteristic (ROC) Parameters for Biomarker Discrimination

Biomarkers	Area Under the Curve (AUC)	95% Confidence Interval	Optimal Cut-off Value	Sensitivity (%)	Specificity (%)	p-value
CRP	0.937	0.884 – 0.990	≥ 0.95 mg/dL	85.7%	83.3%	< 0.001
C3	0.756	0.636 – 0.875	≥ 1.45 g/L	54.3%	96.7%	< 0.001
C4	0.669	0.535 – 0.802	≥ 0.40 g/L	45.7%	93.3%	0.020

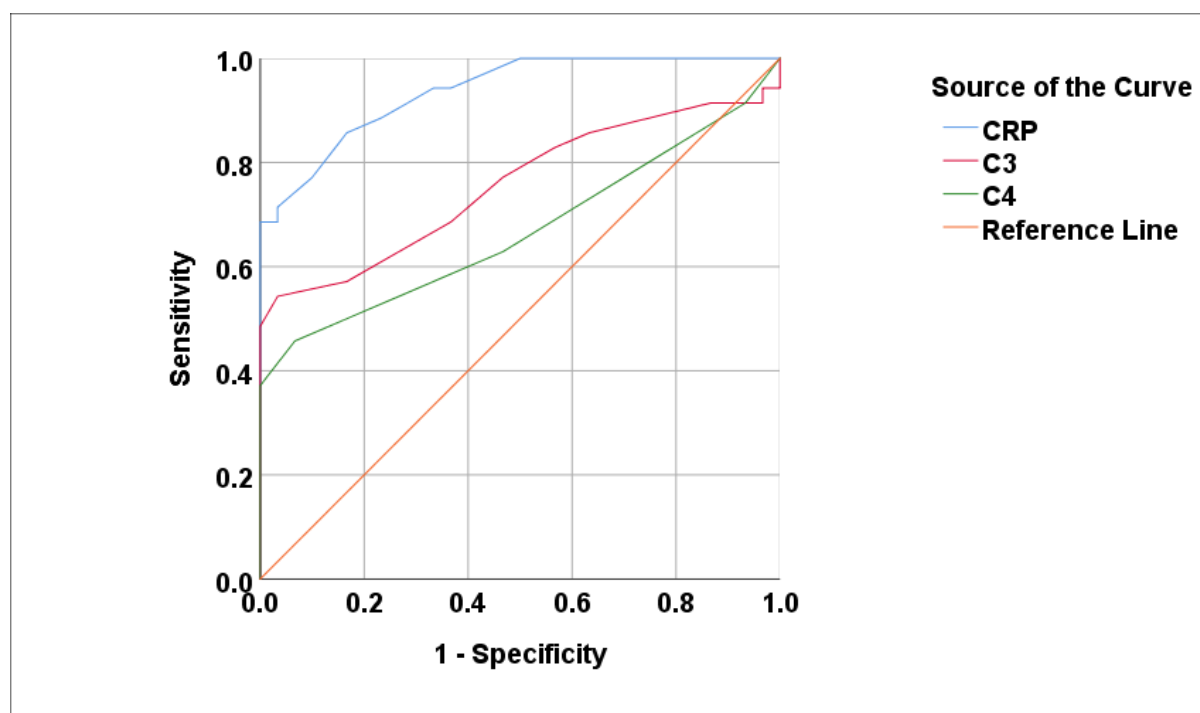


Figure 1: ROC curve analysis of predictors in type 2 diabetes patients.

DISCUSSION

The present case-control study demonstrated significantly higher serum C3 and C4 concentrations in patients with type 2 diabetes mellitus (T2DM) than in healthy controls. CRP and random blood sugar (RBS) were also significantly higher in the T2DM group. These findings indicate that T2DM in the present cohort was associated with altered circulating complement concentrations, hyperglycemia, and systemic inflammation. However, the significant age difference between the two groups should be considered when interpreting these findings.

C3 and C4 in T2DM:

The significantly higher serum C3 concentration observed in the present study is consistent with the findings of **Jiang *et al.***, who reported that higher serum C3 was associated with subsequent development of T2DM, with BMI partially mediating this association (3). The present findings are also consistent with those of Nguyen *et al.*, who reported significantly higher serum C3 concentrations in patients with T2DM than in healthy controls (4). Their study also evaluated C4; however, the difference in C4 was not statistically significant, unlike the significant increase observed in the present study (4). This difference may reflect variation in sample characteristics, metabolic status, or other unmeasured factors.

The elevation of C3 and C4 is also broadly consistent with the findings of **Wang *et al.***, who reported associations between circulating complement levels and clinical characteristics of diabetic retinopathy (7). However, this comparison is not direct because diabetic retinopathy was not assessed in the present study. Therefore, our findings support the possible involvement of complement abnormalities in diabetes but do not establish an association with diabetic retinopathy.

Complement and inflammation:

In the present study, C3 showed a significant positive correlation with CRP ($r_s = 0.336$, $p = 0.048$), while C4 demonstrated a stronger positive correlation with CRP ($r_s = 0.564$, $p < 0.001$). C3 and C4 were also strongly correlated with each other ($r_s = 0.653$, $p < 0.001$). These findings suggest that complement-related alterations may occur within the inflammatory environment associated with T2DM. **Ramanjaneya *et al.*** similarly reported associations between complement-related proteins and inflammatory and metabolic variables (8). Although their study involved gestational diabetes rather than T2DM, it provides supportive rather than direct evidence for an association between complement proteins and metabolic inflammation.

Complement and diabetic complications:

The present findings are also compatible with evidence concerning diabetic kidney disease. **Liu *et al.*** reported associations between serum complement components and kidney-function changes in patients with diabetic kidney disease (9), while **Tan *et al.*** described potential roles of complement-derived mediators in inflammatory and metabolic pathways involved in diabetic kidney injury (10). However, renal function and diabetic complications were not evaluated in the present study. Therefore, the increased C3 and C4 concentrations observed here should not be interpreted as evidence of diabetic kidney disease or functional complement activation.

CRP and glycemic status:

CRP was significantly higher in patients with T2DM and remained independently associated with T2DM after adjustment (aOR = 2.406, 95% CI: 1.110–5.217, $p = 0.026$). This finding is consistent with the inflammatory role of CRP in T2DM described by **Stanimirovic *et al.*** (11). In contrast, RBS did not correlate

significantly with CRP, C3, or C4. This may partly reflect the limitation of using a single random glucose measurement, which is affected by short-term physiological and behavioral factors. HbA1c would provide a more stable measure of long-term glycemic status.

Multivariable and ROC analyses:

Although C3 and C4 were significantly elevated in the initial comparison, neither remained independently associated with T2DM after adjustment. In contrast, age and CRP remained significant predictors. The very wide confidence interval for C3 also indicates substantial imprecision, which may be related to the small sample size and correlations among the biomarkers. Therefore, the adjusted findings should not be interpreted as evidence that C3 and C4 have no biological relevance; rather, their independent effects could not be estimated precisely in this sample.

The highest discriminatory performance was produced by the CRP with an AUC of 0.937, while for C3 it was 0.756, and C4 produced 0.669. Therefore, CRP had a better discriminatory ability than C3 and C4 among the present cohort for differentiating T2DM patients from controls. C3 and C4, which has high specificity and relatively low sensitivity, may have a supportive value or effect instead of a screening value or effect. However, suggested cutoffs should be validated in larger (in ages) population.

The evidence from Iraq is consistent with the present findings as far as possible goes. **Ahmed and Saleh** investigated C3 and C4 among patients with T2DM and healthy controls in Diyala Province, providing local evidence for alterations in complement proteins in diabetes (12). This study is particularly relevant because it involved an Iraqi T2DM population and directly assessed C3 and C4. **Saeed and Al-Aubaidi** also reported variations in C3 and C4 among Iraqi patients with type II diabetes infected with *Toxoplasma* (13). However, because *Toxoplasma* infection may itself

influence immune and complement responses, their findings should be considered supportive but not directly comparable with the present study.

Evidence from an Arab population further supports complement involvement in T2DM. **Zaghlool et al.** identified complement-related molecular signatures among T2DM subtypes in an Arab population (14). This provides supportive mechanistic evidence, although it does not directly demonstrate increased serum C3 and C4 concentrations as observed in the present study.

Furthermore, **Su et al.** reported that serum C3 was independently associated with islet β -cell function and that longitudinal changes in C3 were associated with changes in β -cell function during a 4.6-year follow-up (15). These findings are compatible with a potential metabolic role for C3; however, β -cell function and insulin resistance were not assessed in the present study.

Strengths and limitations:

The strengths of this study include the simultaneous assessment of C3, C4, CRP, and RBS; inclusion of healthy controls; correlation analysis; multivariable logistic regression; and ROC analysis. The main limitations include the relatively small sample size, single-center design, significant age imbalance between groups, and lack of data on BMI, HbA1c, diabetes duration, treatment regimen, insulin resistance, renal function, infection status, and diabetic complications. In addition, only total serum C3 and C4 were measured; therefore, functional complement activation cannot be confirmed.

Overall, the present findings are generally consistent with previous evidence showing an association between complement-related abnormalities, inflammation, and T2DM (3,4,7,8). Iraqi and Arab studies provide additional supportive evidence (12-14). However, C3 and C4 did not remain independently associated with T2DM after

adjustment, whereas CRP showed the strongest discriminatory performance.

Accordingly, C3 and C4 may be considered complement-related inflammatory biomarkers associated with T2DM rather than independent diagnostic markers of T2DM. Larger prospective studies using age-matched controls and incorporating HbA1c, BMI, renal-function assessment, diabetes duration, treatment status, diabetic complications, and specific complement activation products are needed to clarify their clinical significance.

CONCLUSION

Patients with T2DM had significantly elevated serum C3, C4, CRP, and RBS levels compared with healthy controls. The positive correlations of CRP with C3 and C4 support an association between complement components and systemic inflammation in T2DM. Although C3 and C4 were elevated in the patient group, they were not independently associated with T2DM after adjustment for age and CRP. CRP showed the strongest discriminatory ability among the evaluated biomarkers. Larger, age-matched prospective studies are needed to clarify the potential clinical and pathophysiological role of complement components in T2DM.

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