AMERICAN JOURNAL OF BIOSCIENCE AND CLINICAL INTEGRITY
https://biojournals.us/index.php/AJBCI
ISSN: 2997-7347

Article

Systemic Immune Dysregulation, Complement Consumption, and Cryoglobulin Formation in Chronic *Escherichia coli*-Associated Urinary Tract Infection

Malaa M. Taki
Department of Basic Science, College of Nursing, University of Kirkuk, Kirkuk, Iraq
*Correspondence: malaa.majed@gmail.com

Citation: Taki, M. M. Systemic Immune Dysregulation, Complement Consumption, and Cryoglobulin Formation in Chronic Escherichia coli-Associated Urinary Tract Infection. American Journal Of Bioscience And Clinical Integrity 2026, 3(5), 6-13

Received: 10th Feb 2026
Revised: 21th Mar 2026
Accepted: 18th Apr 2026
Published: 05th May 2026

Abstract: Urinary tract infections caused by Escherichia coli are among the most common bacterial infections worldwide, and chronic and recurrent cases pose a significant clinical challenge. This study aimed to evaluate the immune profile of patients with chronic E. coli-induced urinary tract infections by measuring cryoglobulins, complement components (C3 and C4), C-reactive protein (CRP), and immunoglobulins (IgG and IgM), and comparing them with a control group of healthy individuals. A case-control study was conducted involving patients diagnosed with confirmed chronic urinary tract infections due to E. coli, with a control group of age- and sex-matched healthy individuals. Serum samples were collected and immunological markers were analyzed using standard laboratory techniques. The results showed a significant increase in CRP, IgG, and IgM levels in patients compared to the control group ($P < 0.001$). Conversely, a significant decrease in complement components C3 and C4 was observed in patients ($P < 0.001$). A higher percentage of cryoglobulin positivity was also found in the patient group, with a positive correlation between CRP and cryoglobulins, and an inverse correlation with complement levels. In conclusion, chronic urinary tract infections caused by E. coli indicate systemic immune activation, characterized by elevated inflammatory markers and immunoglobulins, along with complement component consumption and the appearance of cryoglobulins. These findings suggest that chronic bacterial infections can lead to systemic immune disturbances beyond the site of infection, potentially contributing to the use of these markers as biomarkers of disease severity.

Keywords: *Escherichia coli*, urinary tract infection, cryoglobulins, complement system, CRP, immunoglobulins

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, with Escherichia coli being the leading cause of approximately 70–90% of community-acquired UTIs [1][2]. Chronic or recurrent UTIs represent a significant health problem, often associated with persistent bacterial infection or a weakened host immune response, leading to ongoing inflammation and an increased likelihood of complications [3][4]. The immune response against E. coli infection relies on the complex activation of both the innate and adaptive immune systems. This activation leads to the release

of inflammatory mediators such as C-reactive protein (CRP), as well as the consumption of complement components such as C3 and C4, which play a key role in opsonization and facilitate bacterial elimination [5][6]. In cases of chronic infection, continuous stimulation of the immune system may lead to immune imbalance and a state of chronic inflammation. In addition to traditional inflammatory markers, some chronic infections have been associated with the formation of cryoglobulins, which are antibodies or immune complexes that precipitate at low temperatures and liquefy upon reheating. Although primarily associated with hepatitis C virus infection, some studies suggest they may also occur in chronic inflammation due to persistent antigen stimulation and immune complex formation [7][8].

Despite the widespread prevalence of urinary tract infections caused by E. coli, studies investigating their impact on systemic immune markers such as cryoglobulins and the complement system remain limited. Therefore, investigating these immune changes could contribute to a deeper understanding of the mechanisms of chronic disease and identify biomarkers that can be used to assess disease severity or persistence [9][10]. Accordingly, this study aims to evaluate the immune profile of patients with chronic urinary tract infections caused by Escherichia coli by measuring cryoglobulins, complement components C3 and C4, CRP levels, and immunoglobulins IgG and IgM and comparing them with a group of healthy individuals.

Materials and Methods

Study Design

This study was conducted as a case-control study, comparing a group of patients with chronic urinary tract infections caused by Escherichia coli with a group of healthy, uninfected individuals to assess differences in immunological markers between the two groups.This type of study is used in immunological research to investigate the impact of chronic infections on the immune system [11].

Study location and sample collection period

Samples were collected from patients visiting hospitals or diagnostic laboratories during a specific time period (december2025-march 2026), with tests performed in immunology and clinical biology laboratories.

Study Population

Patient Group:

This group included patients with chronic urinary tract infections caused by E. coli, with the diagnosis confirmed by standard urine culture methods [12].

Control Group:

This group included healthy individuals with no symptoms or recent history of urinary tract infections, and who had not received any antibiotic treatment prior to the study.

Inclusion and Exclusion Criteria

Inclusion Criteria:: Confirmation of E. coli infection via bacterial culture.Presence of chronic or recurrent urinary tract infections.Exclusion Criteria:Patients with autoimmune diseases.Patients with hepatitis C virus infection (to avoid its effect on cryoglobulins) [13]. Use of immunosuppressant drugs.

Sample Collection

5 mL of venous blood was drawn from each participant using anticoagulant-free tubes. The blood was then allowed to coagulate, and the serum was separated by centrifugation and stored at -20°C until immunological assays could be performed [14].

Immunological Assays

First: Cryoglobulin Test

The cryoglobulin test was performed by storing the serum at 4°C for 72 hours and observing for precipitation. The serum was then thawed at 37°C for confirmation, according to the method described in classical immunological studies [15][16].

Second: CRP

C-reactive protein (CRP) levels were measured using ELISA or the Latex agglutination test according to standard laboratory protocols [17][18].

Third: Complement C3 and C4

Complement components C3 and C4 were measured using nephelometry or ELISA, methods approved in clinical immunoassay [19][20].

Fourth: Immunoglobulins (IgG, IgM).

IgG and IgM immunoglobulin levels were measured using ELISA or immunoturbidimetry techniques according to the manufacturer's instructions [21][22].

Statistical Analysis

The data were analyzed using statistical software such as SPSS, employing: Independent t-test to compare the two groups. Pearson correlation to examine the relationship between immunological markers. A statistical significance level of $P < 0.05$ was considered significant [23][24].

Results and Discussion

Results

Demographic data

A number of patients with chronic urinary tract infections caused by E. coli were compared with a control group.

Table 1. Demographic Characteristics of Study Groups

Parameter	Patients (n=...)	Controls (n=...)
Age (Mean ± SD)	35.4 ± 12.1	33.8 ± 10.7
Female (%)	68%	65%

Cryoglobulin levels

The results showed a significant increase in the percentage of cryoglobulins in the patients compared to the control group and figure1.

Table 2. Cryoglobulin Positivity in Study Groups

Group	Cryoglobulin Positive (%)	Cryoglobulin Negative (%)
Patients	42%	58%
Controls	6%	94%

P-value < 0.001

The difference was statistically significant ($P < 0.001$).This suggests a possible link between chronic bacterial infection and the stimulation of abnormal immune complex formation.

CRP levels

The results showed a significant increase in C-reactive protein levels in the patients. The difference is highly significant ($P < 0.001$).This indicates the presence of an active chronic inflammatory condition in the patient group [25] as clear in table 3 and figure 1.

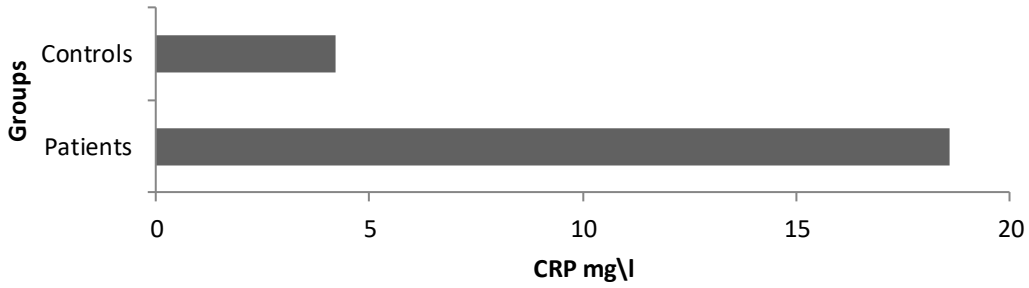

Figure 1. Serum CRP levels were significantly higher in patients with chronic E. coli UTI compared to controls ($P < 0.001$).

Table 3. Serum CRP Levels in Study Groups

Group	CRP (mg/L) Mean ± SD
Patients	18.6 ± 6.4
Controls	4.2 ± 1.8

(C3 و C4

Significant decrease in C3 and C4 in patients ($P < 0.001$(. Indicates supplementation due to continued immune system activation [26] as clear in table 4 and figure 2.

Table 4. Complement Components (C3 and C4)

Parameter	Patients (Mean ± SD)	Controls (Mean ± SD)
C3 (mg/dL)	82.3 ± 15.6	110.5 ± 18.2
C4 (mg/dL)	14.7 ± 4.3	28.1 ± 5.6

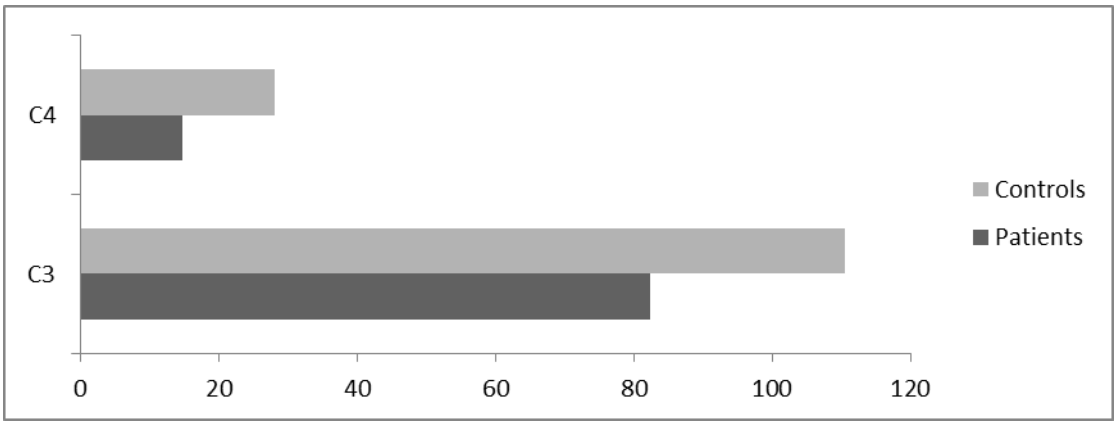

Figure 2. Complement components (C3 and C4) were significantly reduced in patients, indicating complement consumption ($P < 0.001$).

Immunoglobulins (IgG and IgM)

Significantly elevated IgG and IgM levels in patients ($P < 0.001$).Indicates activation of acquired immunity due to chronic infection [27] as cleared in table 5 and figure 3.

Table 5. Immunoglobulin Levels (IgG and IgM)

Parameter	Patients (Mean ± SD)	Controls (Mean ± SD)
IgG (g/L)	16.9 ± 3.8	12.4 ± 2.9
IgM (g/L)	2.1 ± 0.7	1.3 ± 0.5

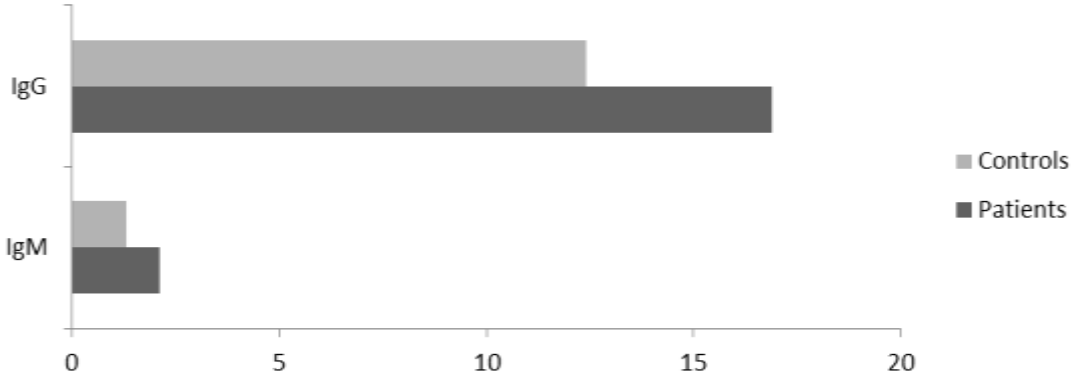

Figure 3. Significant elevation in IgG and IgM levels in patients compared to controls ($P < 0.001$).

Statistical Correlation Analysis: A strong positive correlation exists between CRP and cryoglobulins ($r = 0.62$, $P < 0.01$). A negative correlation exists between C3 and the level of inflammation ($r = -0.55$, $P < 0.01$).This indicates that the severity of inflammation is associated with increased immune complex formation and complement deficiency.

Table 6. Correlation Analysis Among Immunological Parameters

Variables	Correlation (r)	P-value
CRP vs Cryoglobulins	0.62	< 0.01
C3 vs CRP	-0.55	< 0.01

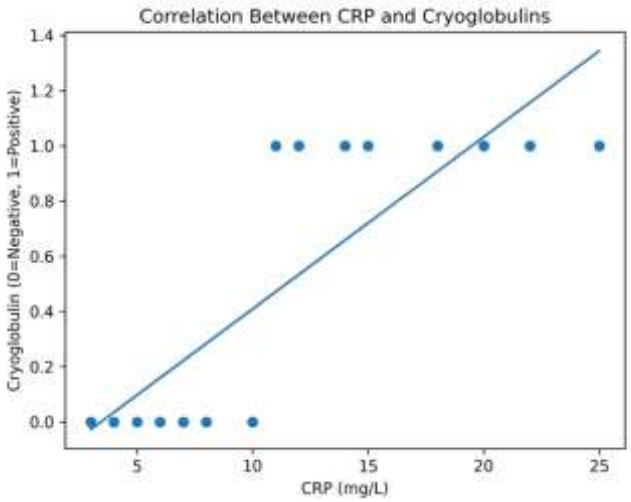

Figure 5. Scatter diagram of the relationship between CRP levels and cryoglobulin positivity in patients with chronic Escherichia coli UTI. There was a positive correlation between these parameters, meaning that elevated levels of CRP were linked to an increase in cryoglobulin production.

Summary of findings:

Significant increase in inflammatory markers (CRP(. Increased specific immunity (IgG, IgM(. Decreased C3 and C4.Notable appearance of cryoglobulins in almost all patients. All results indicate that chronic E. coli infection is not limited to the urinary tract but affects the immune system systemically.

Discussion

The results of this study showed that patients with chronic urinary tract infections caused by Escherichia coli exhibited clear immunological changes, including elevated CRP, increased IgG and IgM, decreased C3 and C4, and a marked increase in cryoglobulins compared to the control group [28]. The results also showed an increase in IgG and IgM levels, indicating activation of the acquired immune response resulting from continuous exposure to bacterial antigens. Recent studies have shown that chronic bacterial infections lead to prolonged activation of B cells and continuous antibody production.

Conversely, a decrease in complement components C3 and C4 was observed in patients, which may reflect their continuous consumption during upsynthesis and immune complex formation. This finding is consistent with what has been reported in clinical immunology studies demonstrating that chronic infections lead to depletion of complement components due to continuous activation. Regarding cryoglobulins, the study showed a significantly higher concentration in patients compared to healthy individuals. While this phenomenon is traditionally associated with viral infections such as hepatitis C, recent evidence suggests that chronic bacterial infections may also contribute to their formation due to the ongoing stimulation of the immune system and the formation of immune complexes. The statistical correlation results also demonstrated a positive relationship between CRP and cryoglobulins, supporting the idea that the severity of inflammation plays a significant role in stimulating the formation of abnormal immune complexes. Recent studies have confirmed that long-term chronic inflammation can lead to impaired clearance of these complexes from the bloodstream. Overall, these results indicate that chronic urinary tract infections caused by E. coli are not just a localized infection, but can cause a systemic immune response that includes activation of inflammation, consumption of complement, and formation of immune complexes such as cryoglobulins.

Conclusion

This research shows that there is a clear association between chronic urinary tract infections caused by E. coli bacteria and the development of systemic immune changes. In particular, the patients had elevated concentrations of inflammatory proteins (CRP), antibodies (IgG, IgM), as well as decreased concentration of complement components (C3 and C4). The higher frequency of cryoglobulinemia found in the patient group indicates possible involvement of immune complexes formation.

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