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Complement System in Psoriatic Arthritis (PsA): Investigating C3 as a Marker of Disease Activity and Treatment Response

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Abstract

Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis commonly associated with psoriasis, affecting 10% to 30% psoriasis patients. Complement component C3 has been suggested as a potential biomarker for disease activity in PsA, with elevated levels reported in moderate to severe disease that may normalize after treatment. **Objectives:** To investigate the relationship between complement C3 and disease activity in PsA. **Methods:** A prospective observational study was conducted at the Rheumatology Outpatient Clinic of Qatif Central Hospital, Saudi Arabia, involving 55 patients with active PsA. Complement activation was assessed using C3, ESR, and CRP levels before and after biological therapy. **Results:** There were no significant differences in median ESR and CRP levels before and after treatment based on gender ($p > 0.05$). Males had significantly higher baseline C3 levels compared to females ($p = 0.025$), but post-treatment C3 levels showed no significant difference ($p = 0.332$). Based on DAPSA, 46 patients (83.6%) had low disease activity, while 9 patients (16.4%) had moderate disease activity. No significant changes in C3 were observed following treatment. **Conclusions and Recommendations:** Patients with mild to moderate PsA exhibit normal C3 levels at baseline and after biological therapy, indicating that C3 behaves as a mild acute phase reactant rather than a sensitive biomarker of disease activity. Further studies are needed to assess the utility of complement components in PsA, particularly more severe disease.

Keywords

Psoriatic Arthritis, Disease Activity, Complement C3

1. Introduction

Psoriatic arthritis (PsA) is a multifaceted inflammatory disorder characterized by a combination of musculoskeletal and dermatologic manifestations [1]. PsA has a global annual incidence of 83 cases per 100,000 individuals, showing no significant gender preference, and a prevalence of 133 cases per 100,000, which demonstrates consistent variability across different regions [1].

Between 10% and 30% of people with psoriasis develop PsA. In most cases, skin manifestation appears before joint pain, but in about 15% of cases, joint pain may start first, even without prior skin lesions. PsA can be quite debilitating, affecting the entheses, as well as both small and large joints, and the spine [2]. More than half of PsA patients show progressive, erosive arthritis that causes significant functional impairment [2].

The pathogenesis of PsA is not fully understood, but the involvement of innate immunity has a significant role. The skin can release pro-inflammatory mediators like TNF, either near or away from the affected joints. Targeting and disrupting this pathological signaling might provide a promising therapeutic strategy. Similar to the skin, joints and their surrounding tissues release endogenous ligands for the innate immune system along with soluble inflammatory mediators. Recent research suggests that PsA pathogenesis is multifactorial, emphasizing the significant roles of genetic susceptibility, activation of innate immune cells, and autoimmune mechanisms [3].

The complement system is crucial for protecting the host from microbial threats, clearing debris like apoptotic cells and immune complexes, and regulating inflammation. It is continuously active at a low level but can be further activated by antibodies, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) that arise during tissue injury [4].

The complement system is a component of the innate immune defense. It identifies microbes and unwanted host molecules, enhancing phagocytosis and playing a crucial role in clearing immune complexes [2]. Complement activation leads to the formation of C3 convertase, which cleaves C3 and generates biologically active complement fragments. These fragments contribute to opsonization, chemotaxis, and cytolysis [2].

Regulating the complement system can help manage inflammatory diseases such as arthritis, but disruptions in complement regulation can also contribute to disease development. During joint inflammation, multiple products of complement activation can play a role in causing tissue damage [2] [4].

Data on the role of complement in PsA are limited in the literature. Early studies have indicated elevated plasma levels of iC3b, C4d, and Bb fragments in psoriatic patients, particularly those with erythrodermic pustular psoriasis and in those with PsA [5].

The potential role of complement activation in the development of psoriatic arthritis (PsA) is suggested by the observed reduced expression of complement regulators in these patients [5].

TNFα is a powerful proinflammatory cytokine with diverse effects and is a key driver in the inflammatory cascade. Tumor necrosis factor inhibitors (TNFi) are highly effective in treating PsA and have significantly changed its management. However, not all patients with PsA achieve a favorable response to TNFi treatment [6]. In the key clinical trials of TNFi for psoriatic arthritis (PsA), approximately 60% of patients achieved an American College of Rheumatology 20 (ACR20) response [6].

Previous research has indicated that TNFα interacts with the complement system by boosting the production of factor B and C3 in human hepatoma cell lines [5].

A biomarker is an objectively measured characteristic that reflects normal biological processes, disease processes, or responses to treatments. In PsA, biomarkers can be valuable for predicting and tracking responses to TNFi therapy. Identifying soluble biomarkers that indicate how well a patient will respond to TNFi could improve PsA management and fulfill a critical need among clinicians treating PsA [6].

To the best of our knowledge, no studies have yet reported changes in the complement system in PsA patients undergoing anti-TNF and other biological treatment. Consequently, we investigated the complement system in individuals with PsA and assessed its alterations after using biological therapy. We also evaluated the utility of ESR, CRP, and complement C3 and C4 in monitoring inflammation in these patients, and analyzed the relationship between these inflammatory markers, the Disease Activity in Psoriatic Arthritis (DAPSA) helps measure disease activity in psoriatic arthritis based on joint symptoms, CRP and pain evaluation), and the EULAR response over time.

2. Methods

2.1. Study Design

Prospective Observational study conducted at the Rheumatology Outpatient Clinic of Qatif Central Hospital, Saudi Arabia. Fifty-five patients with active PsA were recruited.

Patients were recruited from March 2023 to July 2024.

The medica-cloud-care electronic health record system was used to review medical records of each patients' hospital course. Complement activation was determined by measurement C3, ESR, CRP, before and after treatment.

Prior to enrollment, all adults aged 18 years with a diagnosis of PsA, fulfilling CASPAR criteria, active disease if there are ≥3 tender swollen joints, and inadequate response to at least one conventional DMARD. All patients were of biological naïve enrollment and started biological therapy due to inadequate response to conventional DMARDs.

Exclusion criteria included: prior exposure to any biological therapy, active infection, pregnancy or breast feeding, and history of malignancy within the last 5 years.

2.2. Data Collection and Assessment

Demographic, clinical, and laboratory data were collected. Patients were assessed at baseline, and after 6 months of therapy.

2.3. Sample Size Considerations

No formal sample size calculation was performed. The study reflects a real-world single center cohort. While the sample was adequate to detect moderate to large treatment effects, the study may have been underpowered to detect small changes in C3 levels.

2.4. Complement Activation

We assessed complement activity by measuring C3, using enzyme-linked immunosorbent assay (ELISA). Normal range was (C3 79 - 152 mg/dL).

2.5. Statistical Analysis

Data was analyzed using SPSS v26. Continuous variables were assessed for normality using Shapriro-Wilk tests and reported as median (IQR) for skewed distributions. Wilcoxon signed rank and Mann Whitney tests were used to compare pre and post treatment values. Categorical variables were analyzed using Chi-square tests. Multivariable linear regression was performed with DAPSA as a dependent variable and C3, age, gender, and BMI as independent variables. A p-value of less than 0.05 was considered significant.

3. Results

The cohort included 55 patients, predominantly female (80.0%, n = 44) compared to males (20.0%, n = 11). The mean age of participants was 42.9 years, with a standard deviation of 10.7 years, encompassing an age range from 20 to 66 years.

Regarding disease duration, the average was 6.7 years (SD: 4.2), with a median of 6.0 years.

When comparing the two genders, males had a mean age of 47.09 years (SD: 8.1), while females had a mean age of 41.93 years (SD: 11.1), with no statistically significant difference (p = 0.154). For disease duration, males had an average of 7.00 years (SD: 5.5) compared to 6.59 years (SD: 3.9) for females, also showing no significant difference (p = 0.780) are given in Table 1.

At baseline, we recorded levels of ESR, CRP, C3, and clinical parameters (DAS28, DAPSA).

We then stratified the patients based on their prior treatments, but no significant differences in complement levels were observed.

Disease severity was classified as mild to moderate in all patients according to the DAS28 and DAPSA scores.

There were no statistically significant differences in ESR (p = 0.391), CRP (p = 0.647), and C3 (p = 0.705) between pre-treatment and post-treatment values, as shown in Table 2.

Table 1. The demographic and disease characteristics of the 55 selected patients.

	Males (n = 11)	Females (n = 44)	P-value
Mean (SD) age in years	47.09 ± 8.1	41.93 ± 11.1	0.154
Mean (SD) disease duration	7.00 ± 5.5	6.59 ± 3.9	0.780

Table 2. Laboratory features PsA patients before and after treatment.

Laboratory feature	Before treatment (n = 55)	After treatment (n = 55)	P values
ESR (0 - 20 mm/h)	24.00 (0 - 128)	20.00 (1 - 120)	0.391
CRP (0 - 0.5 mg/dl)	0.33 (0 - 11.0)	0.30 (0.02 - 30.0)	0.647
C3 (mg/dl)	98.00 (35 - 170)	103.00 (10.3 - 135.0)	0.705

There were no significant differences in the ESR, CRP, and C3 before and after treatment among males and females, as shown in Table 3.

There were no statistically significant differences in ESR, CRP, and C3 levels before and after treatment for patients with low disease activity or those with moderate disease activity (2-tailed $p > 0.05$). When comparing various laboratory features between mild and moderate disease activity before and after treatment, no statistically significant differences were observed in ESR and C3 levels prior to treatment ($p = 0.187$ and $p = 0.632$, respectively). However, CRP levels were significantly higher in patients with moderate disease activity before treatment ($p = 0.020$), as shown in Table 4 and Figure 1.

Furthermore, according to the DAPSA score, 46 patients (83.6%) were classified with mild disease activity, while 9 patients (16.4%) had moderate disease activity. No patients were categorized as having severe disease activity.

There was no statistically significant difference in the proportion of patients with mild or moderate disease activity based on gender ($p = 0.855$), as shown in Table 5.

After treatment, significant increases in ESR and CRP levels were noted in patients with moderate disease activity compared to those with low disease activity ($p = 0.004$ and $p = 0.009$, respectively), as shown in Table 6.

When comparing various laboratory features between mild and moderate disease activity (DAPSA) before and after treatment, we found no statistically significant differences in ESR and C3 levels prior to treatment ($p = 0.187$ and $p = 0.632$, respectively). However, CRP levels were significantly higher in patients with moderate disease activity before treatment ($p = 0.020$).

Out of the 11 males, 10 (90.9%) had mild DAS28 scores, while 41 of the 44 females (93.2%) also had mild DAS28 scores ($p = 0.795$). All 46 patients with low disease activity exhibited mild DAS28 scores, whereas 5 of the 9 patients (55.6%) with moderate disease activity had mild DAS28 scores ($p < 0.001$).

Before treatment, patients with moderate disease activity (DAS28) had significantly higher CRP levels (p = 0.009). After treatment, those with moderate disease activity (DAS28) showed significantly elevated levels of ESR and CRP (p = 0.004 and p = 0.001, respectively), as shown in Table 7.

Both DAPSA and DAS28 primarily assess particular measures in PsA patients [7].

Low disease activity in response to treatment was associated with reductions in ESR (r = −0.395, p = 0.003) and CRP levels (r = −0.353, p = 0.008). C3 levels decreased in both low and moderate disease activity following treatment, although these changes did not reach statistical significance, as shown in Table 8.

Table 3. Comparison of laboratory features based on gender.

Laboratory feature	Male (n = 11)			Female (n = 44)		
	Before (n = 55)	After (n = 55)	p values (Males)	Before (n = 55)	After (n = 55)	p values (Females)
ESR (0 - 20 mm/h)	22.30 (0 - 95)	20.00 (1 - 120)	0.824	25.00 (3 - 128)	20.50 (3 - 96)	0.251
CRP (0 - 0.5 mg/dl)	0.56 (0 - 11.0)	0.30 (0.14 - 27.0)	0.838	0.33 (0 - 7.0)	0.31 (0.02 - 30.0)	0.684
C3 (mg/dl)	118.0 (87 - 170)	107.0 (10.3 - 135.0)	0.139	97.0 (35 - 146.0)	100.5 (73.0 - 133.0)	0.216

Table 4. Median levels of ESR, CRP, and C3 before and after treatment by gender.

Laboratory feature	Before treatment (n = 55)			After treatment (n = 55)		
	Males (n = 11)	Females (n = 44)	p values (males vs. females)	Males (n = 11)	Females (n = 44)	p values (males vs. females)
ESR (0 - 20 mm/h)	22.30 (0 - 95)	25.00 (3 - 128)	0.105	20.00 (1 - 120)	20.50 (3 - 96)	0.875
CRP (0 - 0.5 mg/dl)	0.56 (0 - 11.0)	0.33 (0 - 7.0)	0.446	0.30 (0.14 - 27.0)	0.31 (0.02 - 30.0)	0.958
C3 (mg/dl)	118.0 (87 - 170)	97.0 (35 - 146.0)	0.025	107.0 (10.3 - 135.0)	100.5 (73.0 - 133.0)	0.332

Table 5. Distribution of disease activity by gender (according to DAPSA score).

	Low disease activity	Moderate disease activity
Male	9 (81.8%)	2 (18.2%)
female	37 (84.1%)	7 (15.9%)
Total	46	9

Table 6. Laboratory characteristics based on DAPSA.

Laboratory feature	Before treatment		After treatment	
	Mild disease activity (n = 46)	Moderate disease activity (n = 9)	Mild disease activity (n = 46)	Moderate disease activity (n = 9)
ESR (0 - 20 mm/h)	22.50 (0 - 128)	26.00 (14 - 95)	18.00 (1 - 120)	37.00 (14 - 96)
	p = 0.187		p = 0.004	
CRP (0 - 0.5 mg/dl)	0.31 (0 - 11.0)	1.00 (0 - 3.30)	0.30 (0.02 - 30.0)	1.49 (0.22 - 20.0)
	p = 0.020		p = 0.009	
C3 (mg/dl)	99.00 (58 - 170)	103.0 (10.3 - 135.0)	89.00 (35 - 146)	101.0 (80.0 - 122.0)
	p = 0.632		p = 0.758	

*DAPSA (Disease Activity in Psoriatic Arthritis) scores range as follows: 0 - 4 indicates remission, 5 - 14 signifies low disease activity, 15 - 28 reflects moderate disease activity, and scores above 28 indicate high disease activity.

Table 7. DAS 28 before and after the treatment.

Laboratory feature	Mild disease activity/DAS28		Moderate disease activity/DAS28	
	Before treatment (n = 51)	After treatment (n = 51)	Before treatment (n = 4)	After treatment (n = 4)
ESR (0 - 20 mm/h)	23.0 (0 - 128)	20.0 (1 - 120)	39.50 (14 - 55)	69.50 (24 - 96)
	p = 0.001		p = 0.063	
CRP (0 - 0.5 mg/dl)	0.31 (0 - 11.0)	0.30 (0.02 - 30.0)	1.65 (0.9 - 3.3)	2.45 (1.49 - 20.0)
	p = 0.002		p = 0.125	
C3 (mg/dl)	100.0 (35 - 170)	103.0 (10.3 - 135.0)	88.0 (80 - 118)	100.0 (100 - 122.0)
	p = 0.002		p = 0.125	

*DAS28 = disease activity score in 28 joints. (remission < 2.6, mild disease activity < 3.2, moderate > 3.2 - 5.1, severe > 5.1).

Table 8. Laboratory features for DAS28.

Laboratory feature	Before treatment		After treatment	
	Low disease activity (n = 46)	Moderate disease activity (n = 9)	Low disease activity (n = 46)	Moderate disease activity (n = 9)
ESR (0 - 20 mm/h)	22.50 (0 - 128)	26.00 (14 - 95)	18.00 (1 - 120)	37.00 (14 - 96)
	p = 0.187		p = 0.004	
CRP (0 - 0.5 mg/dl)	0.31 (0 - 11.0)	1.00 (0 - 3.30)	0.30 (0.02 - 30.0)	1.49 (0.22 - 20.0)
	p = 0.020		p = 0.009	
C3 (mg/dl)	99.00 (58 - 170)	103.0 (10.3 - 135.0)	89.00 (35 - 146)	101.0 (80.0 - 122.0)
	p = 0.632		p = 0.758	

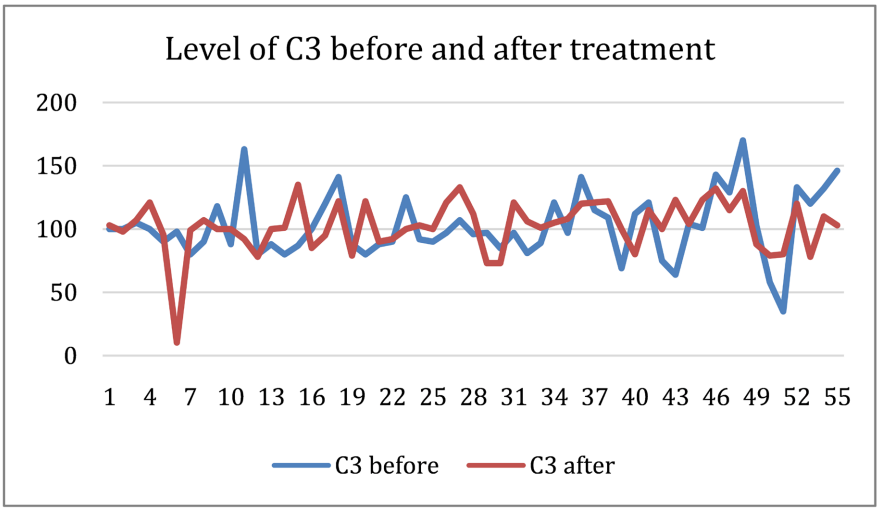

Figure 1. Level of C3 before and after treatment.

4. Discussion

In this prospective study of patients with mild-moderate PsA, baseline C3 levels were within the normal range and did not change significantly following biological therapy ($p = 0.705$). While baseline values were slightly higher than post-treatment values, these differences were not significant, suggesting that C3 reflects subtle inflammation but is not a robust biomarker of disease activity or treatment response in this population.

Complement proteins, including C3, are a part of the acute phase response and can be upregulated in chronic systemic inflammation. Prior studies indicate that PsA patients often have normal or slightly high serum complement levels, with more pronounced increases in moderate to severe disease [8]. Our findings extend this by showing that even patients with clinically mild-moderate PsA may have subtle complement activation, though these changes do not appear clinically significant.

Anti-TNF agents, which predominated in our cohort, are known to reduce systemic inflammation as reflected by CRP and ESR in large controlled trials [9]. The mechanism by which anti-TNF agents lower complement levels remains unclear. In vitro studies have shown no direct effect of these drugs in complement lysis [10], raising the possibility that C3 modulation is secondary to TNF driven systemic inflammation. In contrast, C3 level remained largely stable, supporting its role as a mild acute phase reactant rather than a sensitive marker of treatment responses. Traditional markers such as ESR and CRP remain the most reliable indicators of disease activity.

ESR, and CRP are widely used to assess PsA activity, but both are influenced by non-inflammatory markers such as sex, age, obesity, anemia, infection, pregnancy, diabetes, renal or cardiac diseases, and malignancy. Since most psoriatic patients are overweight, the interpretation of ESR and CRP can be challenging. Complement C3, by contrast, may offer a greater specificity for systemic inflam-

mation in PsA. Notably, previous studies have suggested that elevated baseline C3 levels are associated with poorer EULAR response [8], implying that C3 might serve as a negative prognostic biomarker for biological therapy outcomes.

Additionally, independent association between C3 and DAPSA after adjusting for demographic and clinical confounders strengthens the arguments that complement activation reflects PsA disease activity rather than being solely explained by age, gender, BMI, or disease chronicity.

Our finding also highlights the dynamic relationship between acute phase reactants and clinical disease indices. Changes in C3, ESR, and CRP after treatment paralleled improvements in DAS28 and DAPSA scores, underscoring the utility of these indices for capturing both clinical and serological responses. Although ESR and CRP remain useful for monitoring disease activity, their limitations in predicting treatment response underscore the need of additional biomarkers such as C3. Prior studies have shown that an elevated baseline CRP level is the strongest predictor of clinical response in PsA [8] [11] [12]. Similar results have been documented in studies of patients with RA and other spondyloarthropathies [8] [13] [14].

Recent studies in related conditions further support our findings. In a 2024 study of patient suspected axial spondylarthritis, demonstrated that circulating complement components, including lectin-pathway proteins, were associated with inflammation and indices of disease activity. These results suggest that complement activations are not unique to PsA but may represent a boarder feature of spondyloarthropathies, reinforcing the potential utility complement biomarker in disease monitoring and treatment response [15].

To our knowledge, this is only the second study that investigates the role of complement activation in PsA patients receiving biological therapy. The feasibility of routine C3 measurement given its low cost, accessibility, and standardization, support its potential as a practical biomarker in clinical practice.

Overall, C3 may provide some biological insight into systemic inflammation in PsA, however its clinical utility for monitoring disease activity or response to therapy appears limited in patients with mild to moderate disease. Future studies should examine complement activation products such as C3a, iC3b, C4 and consider patients with more severe disease to clarify the potential role of complement as a biomarker.

We believe that our findings could shed light on the mechanisms by which complement affects the pathogenesis of PsA and enhance the day-to-day management of these patients.

5. Conclusions and Recommendations

In mild to moderate PsA, total C3 levels are within the normal range and do not change significantly after biological therapy, consistent with its role as a mild acute phase reactant rather than a dynamic biomarker for disease activity.

Our study measured only total C3 due to feasibility constraints, more detailed

assessments of complement activation products were not performed. Future research should explore these pathways and their potential value alongside ESR and CRP for monitoring disease activity and predicting treatment response.

Ethical Approval

Complement System in Psoriatic Arthritis (PsA): Investigating C3 as a Marker of Disease Activity and Treatment Response.

Principal Investigator

Zahra Z Al Zahir.

Institution

QCH.

Ethics Committee Approval Number

QCH-SREC0 42/2024.

This study was conducted after the approval by the Qatif Regional Ethical and Scientific Committee (8010500). Informed consent was obtained from all participants prior to their inclusion in the study.

Participants were informed about the study's purpose, procedures, potential risks, and benefits. They were assured of their right to withdraw from the study at any time without any repercussions.

All data collected were treated with strict confidentiality, and identifying information was removed to ensure participant anonymity.

This ethical approval ensures that the rights and well-being of participants were prioritized throughout the research process.

The study was registered with "Clinical Research" (QCH-SREC0 42/2024). The protocol was approved by the Qatif Regional Ethical and Scientific Committee (8010500), and all participants provided written informed consent.

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Conflicts of Interest

No potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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