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Assessment of some immune regulatory cytokines in rheumatoid arthritis patients

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Abstract

***Rheumatoid arthritis (RA) is a chronic autoimm*une** inflammatory disease characterized by complex immune dysregulation which involves both the innate and adaptive immune systems. The study designed to determine demographic parameters and immune regulatory biomarker profiles of RA patients. A Total of 200 Rheumatoid arthritis patient and 50 age-and sex-matched healthy controls were included in the study. Demographically, the majority of patients were middle-aged, particularly in the 41-50 and 51-60 age groups. Patients with RA were also more women than men. Most patients were presented with a peak phase of the disease at 1–5 years of disease duration. Immunologic examination indicated that the serum levels of ICAM-1, DAF (CD55) and CD19 in RA patients were significantly higher than those in controls ($P < 0.05$). In contrast, CCR7 was more abundant in the patients but without significance. In conclusion, the results of the current study showed a distinct immune regulatory imbalance in RA patients, and support the potential of ICAM-1, DAF, and CD19 as biomarkers associated with disease activity and immune dysregulation.

Keywords: Rheumatoid arthritis, immunity, CD19, ICAM, CCR7, DAF

Introduction

Rheumatoid arthritis is a systemic inflammatory disease characterized by immune-mediated destruction of articular and extra-articular structures. It inflames the synovial membrane, eventually destroys joints and messes with both innate and adaptive networks of the immune system. Cell-surface regulatory chemicals, as well as adhesion receptors, are so important for trafficking and activation of immune cells in tissue. Examples for important host proteins are the intercellular adhesion molecule1 (ICAM-1), decay-accelerating factor (DAF, also known as CD55), CD19 and the chemokine receptor CCR7 (1, 2). These are molecules that each play different, specific roles in the process

of RA developing and they may give us insight into how the disease works and how to treat it. ICAM-1 is an immunoglobulin like adhesion molecule. It is present in the blood, and synovial fluid of RA people in higher quantities. This facilitates the ability of white blood cells to stick to blood arteries, and go into swollen joints. Circulating levels of ICAM-1 has been reported to be significantly increased in patients with RA compared to healthy individuals by meta-analysis and remains the case. This supports its function as a biomarker for endothelial activation and systemic inflammation in rheumatoid arthritis and associated diseases such as accelerated atherosclerosis (2). DAF/CD55 is a regulatory protein that helps the immune system work. It is located on immune and stromal cells. It not only protects tissues from damage caused by complement, but it has also been discovered on regulatory T cells (Tregs). It is expressed in groups with various suppressive roles, and those with RA have much lower levels of it. This is related to measurements of disease activity and shows how CD55 dysregulation may make autoimmune inflammation worse by making regulatory cells less effective and increasing complement deposition in the synovium (3). The B-lymphocyte marker CD19 is widely known for making it easier for B cells to become active. It is still an important aspect of RA immunopathology because CD19+ B cells that attack themselves make autoantibodies, present antigens, and produce pro-inflammatory cytokines. This pathogenic B cell activity is responsible for both the progression of conventional RA and the emergence of novel cellular treatments targeting CD19 (9). For example, CD19-directed chimeric antigen receptor (CAR) T cell techniques are rapidly progressing to eliminate harmful B cell populations and reestablish immunological tolerance (4). CCR7 is a G-protein-coupled chemokine receptor present on naïve and central memory T and B cells, as well as dendritic cells. It aids lymphoid and inflammatory tissue in returning home by interacting with its ligands CCL19 and CCL21. It is more common in RA macrophages and dendritic cells, where it is associated to disease activity and helps bring pro-inflammatory cells into synovial tissue. CCR7 blockade in murine models makes them resistant to autoimmune arthritis indicating its importance as a pathogenic target (5). ICAM-1 controls endothelium adhesion and leukocyte extravasation; DAF/CD55 regulates complement and Treg function, while CD19 targets B cells that sustain autoimmunity and CCR7 mediates chemokine-directed cell migration and ectopic lymphoid formation in the joints. High-parameter flow cytometry and spectral cytometry, two emerging immunophenotyping techniques, has been used by scientists to understand the effect of these compounds on various populations of cells in RA (6). The current study designed to determine the demographic factors related to rheumatoid arthritis patients including the age, sex, and disease period. Additionally, to evaluate the serum levels of ICAM-1, DAF (CD55), CD19, and CCR7 in patients with rheumatoid arthritis and to determine their value as biomarkers associated with disease activity and immune dysfunction.

Methodology

Ethical approval

The study was approved by Ethical Approval Committee at Tikrit University (issue number: 3/7/314 at 6/11/2024). Before enrollment in this study, all patients were verbally informed about the study. Then each patient signed the consent form and filled the questionnaire form related to the research biometric.

Patients

The current study took place at Baquba Teaching Hospital and Baghdad Teaching Hospital over the period between January 2025 to July 2025 and included 250 subjects, 200 cases of RA and 50 healthy controls. All cases were clinically diagnosed by rheumatologist and laboratory confirmed with RA with positive result of either rheumatoid factor RF or with anti-cyclic citrullinated peptide (anti-CCP).

Tests for rheumatoid arthritis

All serum samples were tested for RF and anti-CCP tests by using the Cobas e411 automated immunology analyzer (Roche, Germany), and according to the manufacturer's instructions(11).

Immunity biomarkers

All serum samples from both groups that showed the active presence of RA and anti-CCP as confirmatory assessment as screening test were tested were analyzed for ICAM-1, CD19, DAF, and CCR7 immunological biomarkers by enzyme-linked immunosorbent assay (ELISA) kits provided by SunLong BioTech (China). All processes were performed according the methods described in the instruction of the manufacturer. Microplate wells, pre-coated with antibodies specific to target proteins, were treated with serum samples at 37°C to promote antigen binding. Following the elimination of unbound components through washing, enzyme-conjugated detection antibodies were introduced to establish antigen-antibody complexes. Subsequent to further washing procedures, substrate solution was introduced, facilitating color development. The reaction was stopped using a stop solution, and absorbance readings were taken at a wavelength of 450 nm.

Statistical analysis

GraphPad Prism version 10.1 (GraphPad Software, USA) was used for data analysis. Categorical data were summarized as number (%) and continuous variables were reported as mean ± SD. Normality of data distribution was checked using the Shapiro–Wilk test. Most of the variables were found not to be normally distributed; hence, comparison between RA cases and HC was made using Mann–Whitney U test. Categorical variables were expressed as percentages and compared using the χ 2 -test where applicable. A value of p-value < 0.05 was considered as statistically significant (12).

Results

The results of age group distribution displayed in Table.1. The result showed that Rheumatoid arthritis (RA) mostly occurred in the middle-aged adults. The greatest incidence of cases occurred in the 41–50-year age group (62 cases), succeeded by the 51–60-year age group (46 cases). Conversely, a minor fraction of patients was under 20 years of age. The data demonstrate that rheumatoid arthritis (RA) was most common throughout the middle decades of life. The cumulative percentage for patients exceeds 100%,

indicating overlapping or non-exclusive reporting of age categories. However, the absolute frequencies clearly illustrate that disease burden escalates with age until the fifth decade, subsequently declining in older cohorts. By contrast, the control group shows a flat distribution with high proportion in the 31-40-year-old category.

Table. 1: Shows the Mean Age distribution of patients with rheumatoid arthritis and healthy control participants.

Age group	Patients		Control	
	No.	%	No.	%
<20	7	3.50	3	6.00
21-30	24	12.00	8	16.00
31-40	34	17.00	16	32.00
41-50	62	31.00	12	24.00
51-60	46	23.00	5	10.00
>60	27	13.50	6	12.00
Total	200	100.00	50	100.00

The results revealed a significant majority of females among patients with rheumatoid arthritis, with women comprising 77.5% of cases and men 22.5% (Table.2). The control group exhibited a similar sex distribution, consisting of 72% females and 28% males. The lack of a statistically significant difference between patients and controls ($P > 0.05$) signifies adequate sex matching between the study groups and implies that the noted immunological abnormalities are improbable to be influenced by differences in sex distribution.

Table. 2: Shows the Gender distribution

Gender	Patients		Control		*P*. value
	No.	%	No.	%	
Male	45	22.50	14	28.00	>0.05
Females	155	77.50	36	72.00	
Total	200	100.00	50	100.00	

The results of the current study also displayed the distribution of rheumatoid arthritis (RA) patients according to the phases of the disease. The majority of participants were in the early phase of the disease (Table.3). The majority of patients (50.67%) experienced an illness duration of 1–5 years, followed by 35.33% with a duration of 6–10 years, and 32.67% with a length exceeding 10 years. Additionally, 14.67% of patients were diagnosed in the preceding year. The findings suggest that the study sample primarily consisted of patients with established rheumatoid arthritis, creating a suitable cohort for assessing the long-term immunological changes linked to chronic disease progression and ongoing inflammatory activity.

Table. 3: Shows the duration of Rheumatoid arthritis between patients

RA duration/ years	Patients	
	No.	%
<1	22	11.00
1-5	76	38.00
6-10	53	26.50
>10	49	24.50
Total	200	100.00

The results of the immune biomarkers displayed as (Mean ± SD). The levels of ICAM-1 ng/ml were 826.13±273.98 and 471.16±105.62 for Patients and Control groups respectively with P value<0.05. The levels of DAF pg/ml were 42.9± 16.22 and 20.26±13.73 for Patients and Control groups respectively with P value<0.05. The results of CD19 ng/ml were 349.54±158.37 and 180.84±97.84 for Patients and Control groups respectively with P value<0.05. The results of CCR7 ng/ml were 2.58± 1.26 and 0.66± 0.29 for Patients and Control groups respectively with P value >0.05. These results displayed an immunological differences between rheumatoid arthritis patients and indicated heightened endothelium activation, modified complement regulatory function, and elevated B-cell activation, respectively. These modifications collectively signify ongoing immune activation and facilitate the persistence of chronic inflammation, tissue damage, and disease development in rheumatoid arthritis.

Table 4: Shows the comparison of immune regulatory biomarker levels between rheumatoid arthritis patients and healthy controls.

Immune biomarkers	Patients		Control		*P.* value
	Mean	±SD	Mean	±SD	
ICAM-1 ng/ml	826.13	273.98	471.16	105.62	<0.05
DAF pg/ml	42.9	16.22	20.26	13.73	<0.05
CD19 ng/ml	349.54	158.37	180.84	97.84	<0.05
CCR7 ng/ml	2.58	1.26	0.66	0.29	>0.05

Discussion

This study revealed substantial changes in immune-regulatory biomarkers in individuals with rheumatoid arthritis (RA), reinforcing the concept that ongoing dysregulation of both innate and adaptive immune responses is crucial in disease development. The notable increases in ICAM-1, CD55, and CD19 indicate heightened endothelial activation, complement regulatory dysregulation, and B-cell-mediated immunological activation in rheumatoid arthritis patients relative to healthy controls. The demographic traits identified in this study compatible with the recognized epidemiological profile of rheumatoid arthritis (RA) (7, 8, 13).

The majority of patients were situated between the 41–60-year age range, signifying that rheumatoid arthritis primarily impacts middle-aged individuals. Comparable results were observed in community-based studies conducted in Iraq, indicating that rheumatoid

arthritis (RA) is most prevalent throughout middle adulthood and affects roughly 1% of the adult population in Iraq. Similarly, a substantial Iraqi cohort study of 470 patients indicated a mean age of around 50 years and established that rheumatoid arthritis primarily impacts middle-aged adults (5). These data agrees with international epidemiological studies indicating that disease onset predominantly occurs during the fourth to sixth decades of life(3, 14). The prevalence of middle-aged patients may indicate the combined impact of genetic predisposition, environmental factors, and age-associated immunological changes that lead to persistent autoimmune activation (15-17). The pronounced female predominance noted in the present study aligns with both Iraqi and global reports. Prior Iraqi studies indicated that females comprised around 75–82% of rheumatoid arthritis cases, although global data consistently demonstrate that women are affected two to three times more frequently than men. Hormonal variables, especially the estrogen-mediated modulation of immunological responses, along with sex-linked genetic factors, may lead to heightened immune activation and greater vulnerability to autoimmune disorders in females. The molecular factors may partially elucidate the increased frequency of RA among women found in this study (18, 19).

The duration of the disease is a crucial factor influencing immunological impairment in rheumatoid arthritis (RA). The majority of patients in this study had disease durations between 1 and 5 years, signifying largely established disease. Prolonged exposure to inflammatory mediators during this phase fosters sustained activation of immunological pathways, endothelial dysfunction, and progressive immune remodeling (5, 17). Previously published studies indicated that extended disease duration correlates with persistent inflammatory cytokine production, heightened adhesion molecule expression, and the buildup of irreparable joint injury (2, 17). Some researchers have indicated that individuals with chronic disease exhibit more significant biomarker changes, implying that disease duration, treatment history, and disease activity all affect immune-regulatory profiles (2).

The current study's most notable finding was the considerable increase in serum ICAM-1 levels among RA patients. ICAM-1 is a crucial adhesion protein that enables leukocyte binding to endothelial cells and their subsequent infiltration into inflammatory synovial regions. Elevated ICAM-1 expression enhances the migration of monocytes, lymphocytes, and neutrophils into the synovium, consequently fostering chronic inflammation and pannus development (6, 7). These findings agree with prior research indicating increased circulating ICAM-1 levels in active rheumatoid arthritis, hence reinforcing its function as a measure of endothelial activation and inflammatory cell migration. Conversely, certain investigations indicated diminished correlations between serum ICAM-1 levels and disease activity, potentially due to variations in illness severity, treatment protocols, and laboratory techniques (7, 20). The present investigation also revealed markedly increased serum CD55 levels in rheumatoid arthritis patients. CD55 serves as a complement-regulatory protein that safeguards host tissues from excessive complement-induced damage. Elevated circulating CD55 levels may signify a compensatory mechanism in response to persistent complement activation inside inflamed synovial tissues (8). These findings corroborate studies emphasizing the significance of complement dysregulation in the etiology of rheumatoid arthritis and the involvement of complement activation in synovial inflammation and tissue damage (8, 21). Another researchers observed the diminished membrane-bound CD55 expression in synovial regions, despite increased circulating levels. Such variances may indicate differences between local tissue expression and systemic serum concentrations or variations in disease stage and inflammatory load (21).

A notable discovery was the substantial elevation of CD19 levels in patients with rheumatoid arthritis (RA). CD19 is an essential co-receptor for B-cells, playing a critical role in their activation, differentiation, and survival. Increased CD19 expression indicates heightened B-cell activity and corroborates the recognized function of B cells in the pathophysiology of rheumatoid arthritis via autoantibody formation, antigen presentation, and cytokine release (9). These findings align with recent studies indicating the proliferation of autoreactive CD19-positive B-cell populations in active rheumatoid arthritis and the increasing efficacy of B-cell-targeted treatment strategies (13, 22).
Nonetheless, certain investigations did not identify substantial variations in circulating CD19 levels, possibly attributable to inconsistencies in disease activity, immunosuppressive treatment, and patient selection criteria (23). Despite elevated CCR7 levels in RA patients compared to healthy controls, the difference was not statistically significant. CCR7 modulates immune cell migration via interactions with CCL19 and CCL21, significantly influencing lymphoid tissue architecture and synovial inflammation (10). Numerous investigations have indicated elevated CCR7 expression in rheumatoid synovial tissues, macrophages, dendritic cells, and fibroblast-like synoviocytes (10, 24). The lack of statistical significance in this study may suggest that CCR7 mostly exerts its biological effects locally within inflamed joints rather than systemically in peripheral blood. Variations in disease activity, treatment status, ethnicity, sample size, and assay sensitivity may elucidate inconsistencies among studies (24, 25).

Conclusion

In conclusion, the results of the current study approved that Rheumatoid arthritis associated with significant alterations in immune regulatory mechanisms. Moreover, the elevated levels of ICAM-1, CD55, and CD19 observed in patients indicated persistent activation of inflammatory and immune pathways and their potential as biomarkers of disease activity. Although CCR7 levels were increased, no significant difference was detected. These results show the role of immune dysregulation in rheumatoid arthritis.

Declarations

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Ethics statement

The author approved that this research follows the journal's Attached Ethic Approval guidelines as appeared on the journal's author guidelines page.

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Competing interest's statement

The authors declare that they have no conflict of interest.

Author contributions

SAD. & TAH, design of the work; acquisition, analysis, and interpretation of data; MHA, drafting the work and revising it critically for important intellectual content. All the researchers revised the entire manuscript and approved its publication.

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