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Original Article

Serum Interleukin-41 Levels may have a Potential Clinical Value in Patients with Rheumatoid Arthritis.

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ABSTRACT

Background: One of the immunobiological factors thought to have modulatory effects in rheumatoid arthritis (RA) is interleukin-41 (IL-41), a recently identified cytokine claimed to be up-regulated in RA patients.

The aim of the work: The objective of our research was to assess IL-41 level in the serum of patients with RA and to assess its association with the activity of the disease.

Patients and Methods: There were 51 patients with rheumatoid arthritis who participated in the study and 46 healthy controls. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) were among the indicators that were evaluated. Additionally, the Disease Activity Score (DAS28) was assessed and an enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of IL-41.

Results: Patients with RA had elevated serum IL-41 levels relative to controls (479.8 ±61.4 pg/mL vs. 260.9±39.7 pg/mL, respectively; $P < 0.001$). In the RA group, IL-41 exhibited a positive correlation with DAS28 ($r = 0.3142$, $p = 0.0045$), ESR ($r = 0.3944$, $p = 0.0034$), and CRP ($r = 0.3486$, $p = 0.0249$). Serum IL-41 levels showed no relationship with RF or anti-CCP. The diagnostic value of IL-41 for RA was estimated using the ROC curve analysis. The area under curve (AUC) was 0.745 with 71.88 % sensitivity and 68.21 % specificity, and the cut-off value for IL-41 in RA was 316.048 pg/mL ($p < 0.001$).

Conclusion: Rheumatoid arthritis and associated disease activity markers are strongly correlated with increased serum IL-41 levels in rheumatoid arthritis patients.

Keywords: Interleukin-41; Cytokines; Rheumatoid Arthritis; DAS28.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease distinguished by a significant inflammatory response impacting peripheral joints, resulting in chronic synovial hyperplasia [1].

When it comes to the pathogenesis of the disease, there are multiple factors at play, including environmental, metabolic, hormonal, genetic, and immunological variables. These factors interact with one another [1-4].

Through their pro- and anti-inflammatory properties, cytokines—glycoprotein molecules— are of critical importance in the regulation of inflammatory reactions and are involved in cellular signaling to govern immunological activities [5].

The pathophysiology of RA is associated with pro-inflammatory cytokines, including interleukin (IL)-1, IL 17A, and tumor necrosis factor (TNF)-α. It has been found that pro-inflammatory cytokines have a correlation with how active and severe the disease is [6,7].

Additionally, rheumatoid arthritis is linked to dysregulated levels of regulatory and anti-inflammatory cytokines. Imbalance between pro-inflammatory and anti-inflammatory/regulatory cytokines may influence the disease's outcome, activity, and severity [8]. Nevertheless, certain recently identified cytokines such as IL-41, are still poorly understood in RA, and their roles in the pathophysiology of the disease have yet to be fully studied.

The new immunomodulatory cytokine IL-41 is reduced in Graves' disease and inflammatory bowel disease, but it is raised in gout, rheumatoid arthritis, psoriatic arthritis and Kawasaki disease [9-15]. Rheumatoid arthritis disease activity is correlated with an increase in serum IL-41 [15]. These data point to IL-41's possible involvement in aberrant immune responses.

It is yet unknown how IL-41 contributes to the pathophysiology of rheumatoid arthritis (RA), although it is thought that aberrant IL-41 release prevents osteoblast development in RA patients, which affects how the disease progresses [14]. According to previous studies, interferon –gamma (IFN-γ) inhibits the synthesis of IL-41, whereas interleukin-4 and interleukin-17A, released by immune cells, promote macrophages to make interleukin-41. This suggests a potential function for IL-41 in Th1, Th2, and Th17 immune responses [16].

THE AIM OF THE WORK

This study aimed to investigate IL-41 concentrations in the serum of RA patients and to assess its correlation with disease activity.

PATIENTS AND METHODS

This study involved 51 rheumatoid arthritis patients who met the "2010 classification criteria" [17] and 46 healthy controls matched for age and gender, in Al-Azhar university hospitals recruited from July 2022 to April 2023 and all subjects gave their informed consent.

We excluded patients who had inflammatory or infectious diseases, chronic diseases, diabetes mellitus, pregnancy and cancer. Each participant provided anthropometric data and body mass index (BMI) was calculated by measuring height and weight. We assessed disease activity using "ESR-DAS-28, disease activity score with value <3.2 considered low, moderate 3.2: 5.1 and high > 5.1" [18,19].

Ten ml of venous blood were collected, 2 ml added to EDTA tube for CBC, 1 ml on citrate tube (4-1 v/v)) for ESR, the remaining part divided into 2 portions in 2 red plain tubes, one for routine chemical analysis (e.g. serum glucose, albumin, AST, ALT, creatinine) and other tube, centrifuged and serum well separated and stored immediately at -20º C for serology of rheumatoid arthritis and IL-41 tests.

Patients were subjected to Laboratory investigations including complete blood count (CBC) by Sysmex machine, erythrocyte sedimentation rate (ESR) Westergren method, rheumatoid factor (RF), C-reactive protein (CRP) by fluorescence immunoassay, C3, C4, anti-cyclic citrullinated protein antibody (anti-CCP) and IL-41 by ELISA. IL41 assay done after all sample reach the room temperature according to the ELISA kits instruction. The kits exclusively detect human IL41 and do not exhibit cross-reactivity with other analogous proteins. The kits exhibit a sensitivity of 39 pg/ml and a detection range from 156 to 10,000 pg/ml.

Statistical analysis: Data were analyzed using SPSS 21. variables were presented as number and percentage (for qualitative variables), mean ± SD (for quantitative variables), and intergroup differences were compared using Unpaired students' t-test (For two means) and Chi-square test (v2) (For categorical data). Spearman's rank-order correlation analysis was used to estimate the correlation coefficient (rs). IL-41's diagnostic value was determined using receiver operating characteristic (ROC) curve analysis.

RESULTS

Table (1) presents a comparison of the demographic, clinical, and laboratory data for rheumatoid arthritis patients and healthy controls. Age, sex, and BMI were not significantly different between RA patients and controls (p = 0.4705, 0.1274, and 0.4015). Subsequently, we analyzed the relations between blood IL-41 concentrations and clinical data in rheumatoid arthritis patients (RA). Serum IL-41 in the RA group did not correlate with age (r = 0.1115, p = 0.2462), BMI (r = 0.0539, p = 0.6227), or disease duration (r = 0.0116, p = 0.8893). In comparison to the controls, the RA patients had significantly elevated levels of ESR, CRP, and RF. Additionally, notable discrepancies in albumin (ALB) and platelet (PLT) count were observed between controls and RA patients.

In comparison to healthy controls, RA patients had significantly higher serum IL-41 concentrations 479.8 ±61.4 pg/mL vs. 260.9±39.7 pg/mL, respectively; P < 0.001). Upon analyzing the associations between serum IL-41 levels and clinical inflammatory indices as well as disease activity in rheumatoid arthritis patients, we observed that IL-41 exhibited a negative correlation with platelet count (PLT) (r = -+0.3258, p = 0.0411) and a positive correlation with DAS28 (r = 0.3142, p = 0.0045), ESR (r = 0.3944, p = 0.0034), and CRP (r = 0.3486, p = 0.0249). IL-41, on the other hand, does not exhibit any relationships with RF or anti-CCP.

Serum levels of complement C3 and C4 were evaluated in patients with rheumatoid arthritis; however, no correlation was found with serum

IL-41 levels, C3 (r = -0.0827, P = 0.0512), C4 (r = -0.0672, P = 0.6794). The diagnostic value of IL-41 for RA was estimated using the ROC curve analysis. The area under curve (AUC) was 0.745 with 71.88 % sensitivity and 68.21 % specificity, and the cut-off value for IL-41 in RA was 316.048 pg/mL (p < 0.001).

Table (1): Characteristic of the participants

Parameter	Patients N=51	Control N=46	P-value
F:m	42:9	37:8	0.1274
Age (y)	54.06 ± 10.18	52.28 ± 16.92	0.4705
BMI (kg/m2)	23.46 ± 4.634	23.67 ± 3.178	0.4015
Disease duration; year	8.2 ± 6.0	NA	
DAS28	3.89 ± 7.91	NA	
ESR (mm/h)	40.72±18.56	8.96± 4.57	<0.0001
CRP (mg/mL)	15.90±21.4	1.85± 3.98	<0.0001
PLT (109/L)	219.51 ± 70.46	229.02 ± 50.11	0.0346
ALB (g/L)	44.93 ± 7.16	48.68 ± 6.94	<0.0001
RF (IU/mL)	91.40± 54.05	3.7± 85.20	<0.0001
IL41 pg/mL	479.8 ±61.4	260.9±38.7	< 0.001
Anti-CCP antibody (IU/mL)	238.7±27.54	-	-
C3 (g/L)	1.24 ± 2.14	-	-
C4 (g/L)	0.22 ± 1.06	-	-

Values expressed as *n* (%) or mean ± standard deviation. Anti-CCP=anti–cyclic citrullinated, BMI= body mass index, CRP=C-reactive protein, DAS=disease activity score, ESR=erythrocyte sedimentation rate, PLT=platelet count, RF=rheumatoid factor.

DISCUSSION

Rheumatoid arthritis is a chronic, systemic autoimmune disorder distinguished by synovial tissue growth, pannus development, cartilage degradation, and systemic consequences [20]. The pathophysiology of rheumatoid arthritis (RA) is influenced by both genetic and environmental factors with immune pathways preceding the onset of joint inflammation by several years. The interaction of these factors leads to the modification of self-antigens, resulting in the immune system's inability to recognize certain protein structures, which in turn produces autoantibodies that attack self-tissues [21].

IL-41 represents a new immunomodulatory cytokine that is prominently expressed in macrophages and barrier tissues, including skin and mucosa. Additionally, it has been shown that IL-41 expression in macrophages is increased by TNFα, IL-4, IL-12, and IL-17A but it is decreased by IFN- and TGF-β (16). Although the exact role of IL-41 is yet unknown, it has been hypothesized that IL-41 regulates inflammatory responses since IL-41 knockout mice exhibited disrupted synthesis of cytokines and the emergence of inflammatory lesions.[16] According to further research, IL-41 is an anti-inflammatory cytokine that is crucial for regulating inflammatory responses in a number of autoimmune and inflammatory disorders [22].

Two recent studies have examined IL-41 levels in the serum of rheumatoid arthritis patients (RA). The initial study conducted by Zhang et al. examined serum IL-41 concentrations in a cohort comprising 159 rheumatoid arthritis patients, 28 osteoarthritis patients, and 50 healthy controls. The results indicated that rheumatoid arthritis patients exhibited elevated levels of IL-41 compared to those with osteoarthritis and healthy controls, with no substantial differences were noticed between healthy control group and osteoarthritis patients. Furthermore, IL-41 levels correlated positively with DAS28 and C-reactive protein levels, but no relation was found with ACCP antibodies [23]. In the second study, Gong et al. investigated IL-41 in 46 RA patients. Serum IL-41 levels were significantly higher in rheumatoid arthritis (RA) patients than in healthy controls and a positive correlation were identified between IL-41, DAS28, and ESR [24]. These findings align with our results, as we observed elevated levels of serum IL-41 in RA patients relative to healthy controls. Additionally, analysis of IL-4 and inflammatory indices revealed a positive correlation between IL-41 and DAS28, ESR and CRP. These results imply that IL-41 could function as a potential marker for assessing disease activity in RA. Integrating our findings with those of prior studies, we propose IL-41 may provide protective function in rheumatoid arthritis patients, with its levels potentially elevated alongside the upregulation of inflammatory cytokines.

Conversely, inflammatory and autoimmune disorders like inflammatory bowel disease and Graves' disease have been associated with lower serum IL-41 levels [25,26]. Furthermore, an inverse relationship was identified between serum IL-41 and CRP levels in individuals with coronary artery disease.[27] Nevertheless, a meta-analysis of nine studies revealed no significant differences in circulating IL-41 levels among patients with type 2 diabetes [28]. The contradictory findings suggest that IL-41 exhibits tissue and organ specificity, necessitating separate discussions of the mechanisms and cells involved in IL-41 secretion across various diseases.

In **conclusion**, rheumatoid arthritis and associated disease activity markers are strongly correlated with increased serum IL-41 levels in rheumatoid arthritis patients. Consequently, IL-41's potential use as a biomarker for RA diagnosis is therefore validated. To fully comprehend and clarify the importance of IL-40 in RA, further research is required.

Conflicts of interest: We confirm that there is no conflict of interest.

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