



Comparative Analysis of IL-17 and Resistin Levels in Rheumatoid Arthritis Patients with and without Treatment

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KEYWORDS	ABSTRACT
Etanercept; Interleukin-17a; Resistin; Rheumatoid arthritis; Rituximab.	Numerous inflamed cells in the joints of people with rheumatoid arthritis (RA) release a variety of inflammatory substances. Resistin and IL-17A levels in patients undergoing and not receiving treatment have been examined in this study. 120 RA patients were studied and divided into four groups [Group I (30 patients without treatment), group II (thirty patients receiving methotrexate), while, group III (thirty patients receiving etanercept), and Group IV (30 patients received Rituximab)]. The control consisted of 25 individuals. Blood samples were collected to measure serum levels of IL-17A and resistin by ELISA. Group I's serum levels of IL-17A were considerably greater than those of the controls, as well as those of groups III and IV. Group I also showed a large increase in resistin when compared to controls and group III, but neither group I nor groups II and IV showed any significant changes. Resistin and IL-17 showed a strong positive association. These results show that resistin and IL-17A may be associated with the pathophysiology of RA.

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1. INTRODUCTION

Inflammatory cytokines are continuously produced in RA, a chronic illness [1]. Cytokines are made when T-cells and macrophages become active and enter the synovium [2-4]. Additionally, B-cells invade the synovium and develop into plasma cells, which create rheumatoid factor (RF) and polyclonal immunoglobulin. These effector chemicals are linked to cumulative impacts, cartilage and bone degradation, and inflammation and proliferation of synovial tissue [5]. Th17 cells generate the multifaceted inflammatory cytokine IL-17. The pathophysiology of RA may be significantly influenced by IL-17. By triggering a range of inflammatory substances, such as cytokines, chemokines, and other mediators of cartilage and bone damage in synovial fibroblasts, monocytes, macrophages, and chondrocytes, it can increase inflammation [6, 7]. The finding that IL-17 is essential for the progression of RA and a successful treatment target in a number of animal models of RA lends credence to the probable significance of IL-17 in RA [8]. Resistin may play a role in the pathophysiology of RA, according to various studies. It was earlier noted that patients with RA have higher amounts of this adipokine in their joint fluid than patients without inflammatory rheumatic diseases [9]. Through the Nuclear Factor kappa B pathway, resistin has been demonstrated to both promote and be

stimulated by various cytokines, such as TNF- α or IL-6, in peripheral blood mononuclear cells. This suggests that resistin can boost its own activity through a process known as positive feedback [10, 11]. A function for this adipokine in the pathophysiology of RA is suggested by the association between elevated serum resistin in RA patients and both CRP and disease activity score-28 (DAS-28) [12]. Even though treatments with conventional disease-modifying antirheumatic drugs and biologic substances aimed at specific molecules and cellular disease agents have enhanced consequences. However, substantial disease activity remains among numerous patients. We looked into the possible role of IL-17A and resistin in the pathophysiology of RA and assessed the impact of biologic agent therapy on IL-17A and resistin in comparison to DMARDs in RA patients.

2. MATERIAL AND METHODS

2.1 Subjects

The design of this study was case-control. Each participant gave their informed consent, and the College of Medicine/Al-Nahrain University ethical board approved the study's procedure (2011). This study involved 120 RA patients. They were between the ages of 20 and 70. A specialized rheumatologist's medical exam verified each patient's assessment, which was then validated by lab and imaging tests. Following a medical assessment of the illness's activity using the DAS, the patients were categorized into four groups (strong disease severity, moderate illness activity, minimal illness activity, and remission) based on the American College of Rheumatism ACR criteria [3,14].

Four distinct categories of patients were created: Thirty patients in Group I had been diagnosed as RA patients prior to medication, whilst thirty patients in Group II underwent therapy with DMARDs, such as methotrexate. Thirty patients in Group III were given etanercept. Lastly, 30 patients in Group IV were given rituximab. Patients were receiving treatment at the Baghdad Teaching Hospital's rheumatology and rehabilitation outpatient clinic in Baghdad's Medical City. Twenty-five volunteers who appeared to be in good health and with ages and genders equaled those of the patients in the study were recruited as the group acting as a control. They ranged in age from 20 to 63 years, and none of them received therapy or reported any other systemic or chronic illnesses. Sample collection was for the period from December 2011 to June 2012. Two mls of venous blood were drawn from patients and healthy controls. Blood samples were collected in a plain plastic tube for serum separation.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria included the following; Rheumatoid arthritis patients fulfilling the 2010 ACR/EULAR criteria and age of the patients above 18. The exclusion criteria used in this study included the following; Infectious diseases, the presence of malignancy, cardiovascular complications, other autoimmune disorders or inflammation, Juvenile RA patients, smoking, pregnancy, and alcoholism.

2.3 Measurement of biomarkers

The concentrations of serum IL-17 and resistin were determined using a commercially available ELISA kit and according to the guidelines present in the leaflet, Ray Bio/ USA.

2.4 Sample size calculation

It was calculated using the online tool EPITOOLS (https://epitools.ausvet.com.au/case_controls) at a 95% confidence interval and a 5% error margin. The total sample size would be 145 (120 RA and 25 healthy controls).

2.5 Analytical statistics

SPSS13 (the statistical software for social sciences) was utilized to help with analyzing the data. The chi-square analysis was initially used to determine the range of frequencies for the variables of choice. The t-test for independent samples was applied to determine the statistical importance of a difference in the mean of a quantitative, normally distributed variable between two groups. On the other hand, the median describes non-normally distributed variables, and the use of non-parametric tests of significance was recommended. The Mann-Whitney U test was implemented

to determine the statistical significance of the difference in median between two groups. A P value of less than 0.05 was regarded as statistically important.

3. RESULTS

The age, sex, CRP, and RF results of the 145 subjects enrolled in this study are illustrated in Table-1.

Table 1. The age, sex, CRP, and RF results in the studied groups.

Age	controls	cases	<i>P-value</i>
Range	20-63	20-70	0.159 ^{NS}
Mean ± SE	42.80±2.54	46.55±1.09	
Sex			
Female	20 (80%)	100 (83.3%)	0.655 ^{NS}
Male	5 (20%)	20 (16.7)	
CRP			
Negative	23 (92%)	52 (43.3%)	0.001 [*]
Positive	2 (8%)	68 (56.7%)	
RF			
Negative	23 (92%)	64 (53.3%)	0.001 [*]
Positive	2 (8%)	56 (46.7%)	

The current findings showed a significant difference in the mean DAS among RA study groups, P<0.001. However, all groups under treatment (group II, group III, and group IV) were statistically different in their mean DAS than that in group I (without treatment), P<0.001, as observed in Table 2.

Table 2. Mean Values of DAS among RA study groups.

DAS	Mean± SE	P Value			
		ANOVA	With Group I	With Group II	With Group III
Group I	5.05±0.18	0.001	---	---	---
Group II	4.16±0.23		0.011	---	---
Group III	3.79±0.30		0.001	0.278	---
Group IV	3.89±0.25		0.001	0.421	0.778

However, concerning the activity of the disease, 40% of group I RA patients were with high disease activity, and this percentage was higher than that in other study groups II, III and IV (30.0%, 16.6% and 20.0% respectively), while the percentage of patients with low and moderate disease activity showed little variation among the four groups of patients. Conversely, the percentage of patients with remission was significantly higher in group III (treated with Etanercept), 30.0%, than in other groups I, II and IV (0.0%, 6.6% and 23.3%, respectively), Table 3.

Table 3. Frequency of DAS among RA study groups.

	Group I*		Group II		Group III		Group IV	
DAS 28	No	%	No	%	No	%	No	%
Remission	0	0	2	6.6	9	30	7	23
Low + Moderate disease activity	18	60.0	19	63.4	16	53.4	17	57
High disease activity	12	40.0	9	30.0	5	16.6	6	20.0
Total	30	100.0	30	100.0	30	100.0	30	100.0

* Group I has zero value in the mild and remission disease activity groups; Group I: No treatment group; Group II: Methotrexate treated group; Group III: Etanercept-treated group; Group IV: Rituximab-treated group; DAS28: Disease Activity Score 28.

Furthermore, group I of patients had a substantially greater concentration of IL-17 versus those in the control group ($P=0.001$). Furthermore, the level of IL-17 was not substantially different between patients in group I and those in group II RA who received medication with MTX ($p>0.05$). In contrast, patients in group III who received etanercept had considerably lower levels of IL-17 than individuals in group I. However, compared to group I patients, those receiving Rituximab had a considerably lower median concentration of IL-17 (Table 4). Furthermore, depending on the disease severity outcome, there were notable variations in the median levels of IL-17 across all patient groups (Table 5).

Table 4. Serum levels of IL-17A (pm/ml) in studied groups.

IL-17 level	Control	Group I	Group II	Group III	Group IV
Median	195	1132.5	1275	339.5	413.5

Healthy control vs. Group I ($p= .001$). Group I vs. Group II ($p=0.388$). Group I vs. Group III ($p =0.001$). Group I vs. Group IV ($p = 0.007$). Group II vs. Group III ($p=0.009$). Group II vs. Group IV ($p=0.048$). Group III vs. Group IV ($p=0.935$).

Table-5. Median level of IL-17 in RA groups according to disease activity score.

	DAS				p value
	Remission	Low	Moderate	High	
Group I					
Median	.	.	427.00	2459.50	≤ 0.001
Group II					
Median	696.00	562.50	1275.00	2425.00	0.004
Group III					
Median	300.00	258.00	489.00	3852.50	0.006
Group IV					
Median	215.00	335.00	693.00	4503.00	0.002

Table (6) revealed a considerable rise in serum resistin level among group I RA in comparison to control ($P < 0.001$). On the other hand, there was no significant difference between patients treated with MTX and patients without treatment ($p = 0.235$). In addition, there was a significant difference in the level of resistin in group III of patients in comparison with group I. Patients in group IV showed no statistically significant differences in serum resistin in comparison to group I. However, based on the disease activity score, there were notable variations in the resistin concentrations across all patient groups (Table 7).

Table 6. Serum resistin (pm/ml) qualitative data comparing RA and control groups.

Resistin level	Healthy control	Group I	Group II	Group III	Group IV
Median	267	527	393	327.5	462

Healthy control vs. Group I ($p = 0.001$). Group I vs. Group II ($p = 0.235$). Group I vs. Group III ($p = 0.016$). Group I vs. Group IV ($p = 0.236$). Group II vs. Group III ($p = 0.181$). Group II vs. Group IV ($p = 0.595$). Group III vs. Group IV ($p = 0.206$).

Table 7. Descriptive statistics of Resistin in RA groups according to DAS.

	DAS				p value
	Remission	Low	Moderate	High	
Group I					
Median	.	.	475.00	687.50	0.020
Group II					
Median	195.00	331.50	380.50	688.00	0.003
Group III					
Median	240.00	305.00	340.00	670.00	0.008
Group IV					
Median	182.00	314.00	577.50	846.50	0.002

CRP, RF, IL-17, Resistin, and DAS were all strongly correlated in this study. IL-17 was shown to have a consistently substantial positive association with both Resistin and DAS ($P < 0.00$). Additionally, DAS was found to have a strong link with both Resistin and CRP ($P < 0.000$), Table 8.

Table 8. The relationship between numerous variables among cases with RA.

		CRP	Rheumatoid factor	Serum level of IL-17	Serum level of Resistin	DAS
CRP	R	1.000	0.346	0.424	0.277	0.467
	P	.	0.000	0.000	0.002	0.000
RF	R	0.346	1.000	0.199	0.230	0.303
	P	0.000	.	0.029	0.012	0.001
Serum level of IL-17	R	0.424	0.199	1.000	0.671	0.764
	P	0.000	0.029	.	0.000	0.000
Serum level of Resistin	R	0.277	0.230	0.671	1.000	0.686
	P	0.002	0.012	0.000	.	0.000
DAS	R	0.467	0.303	0.764	0.686	1.000
	P	0.000	0.001	0.000	0.000	.

r= correlation coefficient; **. Correlation significant at the 0.01 level (2-tailed).

4. DISCUSSION

Disease-modifying antirheumatic meds with biologic properties that concentrate on particular immune system parts have influenced the manner in which RA is handled over the past 10 years. Maintaining a high standard of life and preventing further illness progression are two aspects of effective therapy; rituximab and etanercept are examples of biologic medicines that can be used alone or in conjunction with nonbiologic medications like methotrexate, according to the latest instructions issued by the American College of Rheumatology [15]. This study reported that treated groups (Methotrexate, Etanercept, and Rituximab) have lower DAS than those of the non-treatment group. Furthermore, patients treated with MTX showed two patients in remission, while Etanercept and Rituximab showed 9 and 7 patients in remission, respectively. Previous results clarify that treatment with biological therapy is more effective and a good number of RA patients reach remission [16-19]. C-reactive protein is frequently used as a laboratory measure reflecting disease activity. In the present research, RA patients' CRP concentrations were considerably higher than those of the control group. In a similar vein, Shrivastava and colleagues (2015) noted elevated CRP in RA that was suggestive of ongoing inflammation [20]. A previous study investigated the relationship between acute phase reactant quantities and DAS in RA and discovered that serum CRP is the most helpful biochemical marker for assessing disease progression in RA patients among the different tests [21]. According to the findings, 46.7% of RA patients tested positive for RF. There is no straightforward rationale for the processes that cause the percentage of RF-positive patients to decline. Plasma cells and other synovium-infiltrating lymphocytes have been shown to diminish with effective treatment [22]. It is possible to hypothesize that a decrease in inflamed lymphoplasmacytic infiltration in rheumatoid synovium will result in a decrease in RF formation since RF-forming cells are present in inflamed rheumatoid synovium and the local environment may favor synovial RF generation [23–25]. However, the present findings indicated that group I RA patients' levels of IL-17 were considerably greater than those of the control. Additionally, the elevated levels of IL-17 in RA were linked with CRP, RF, and DAS. According to other research, IL-17A is a crucial cytokine and possible target for therapy since it is extensively generated in inflammatory joints and supports inflammation. According to this research, IL-17A not only stimulates the inflammatory reaction but also amplifies TNF α 's action, which leads to more RA joint damage [26, 27]. Farag and colleagues reported that RA patients showed significantly higher mean serum IL-17A levels than controls [28]. Further, Shahrara and associates

mentioned that IL-17 stimulates monocyte movement through p38MAPK regulation and attachment to IL-17 ligands A and C produced on monocytes [29]. Patients treated with MTX didn't show statistical difference in serum level IL-17 when compared with no-treatment group, in addition, MTX treated group had lower ration of RA patients with remission state 2 (6,6 %). The outcomes indicate that a different protocol should be used for enhancing the disease status control process. On the other hand, as juxtaposed with the group receiving no treatment, patients receiving biologic therapy had substantial reduced blood IL-17A values. This find coincides with the studies of van de Veerdonk *et al.*, which determined that rituximab attenuated the local Th17 responsiveness in patients with arthritis, and that this decline was linked to significantly lower IL-17, as well as diminished inflammation and improved clinical outcomes [30]. However, Th17-specific CCR6 protein declines during biologic intervention, which could hinder these putative autoimmune cells from moving to the synovium, according to Aerts and colleagues [31]. Another interesting finding in the present study that reduction in serum level of IL-17 is associated with higher rate of remission registered upon treatment with previously mentioned biological therapies 9 (30%) and 7 (23.3%) respectively. This finding also supported by the result of correlation coefficient in current study revealing that there is strong positive correlation between serum IL-17A and each of DAS-28 and CRP in RA patients. This study supports that IL-17A implicated in pathology of RA disease. This statement argued by other research (32). A various stem of lymphocyte subpopulation likely to be making this biomarker in varying amounts in both bloodstreams and synovial tissues [32, 33]. IL-17's contribution to RA could be clarified in a variety of ways, such as imitating the joint setting and encouraging matrix turnover and cartilage degradation, particularly when additional cytokines are present [26] or stimulating osteoclasts increasing of bone erosions or completion of pro-inflammatory network IL-1 β and TNF- α , which causes joint swelling and disease by destroying the synovium matrix and breaking down cartilage collagen [33]. Additionally, the current investigation revealed that RA patients' sera had noticeably higher resistin concentrations versus healthy subjects. Furthermore, serum resistin levels showed a significant correlation with inflammatory markers as CRP, RF and with DAS. This positive correlation between resistin and inflammatory markers in RA patients in this study provided extra assistance to the hypothesis that higher resistin concentration found in RA have been involved in this disease [34-36]. An increased level of this adipokine is also reported by other studies both in patients' sera and joint fluid than controls [37, 38]. Inversely current data differ from those presented in other studies by Bokarewa *et al.* and Otero *et al.* in which serum resistin levels were not significantly different between RA patients and controls. The reason for this discrepancy could be due to differential characteristic of the investigated RA patients [8] On the other hand, Senolt and colleagues illustrated that When this adipokine gets introduced into the joints of mice, it causes an illness similar to osteoarthritis, with leukocyte infiltration of synovial tissues, Synovial barrier hypertrophy and pannus growth [34]. Another finding observed in this study was that individuals receiving-MTX have no statistically significant difference concerning serum level of Resistin from that of no treatment group together with high DAS-28 in MTX treated group. individuals receiving-biologic therapy (Etanercept and Rituximab) had lower concentration of resistin accompanied by higher rate of remission in both groups (30% and 23.3% respectively). Previous study has demonstrated that anti-TNF-alpha drug causes a fast decrease in resistin amounts in those with RA and have verified the correlation between laboratory markers of inflammation, specifically CRP and resistin levels [39]. The present study demonstrated a strong positive correlation between IL-17A and resistin levels in RA patients, suggesting a potential interaction between pro-inflammatory cytokines and adipokines in disease pathogenesis. A plausible mechanistic explanation for this relationship involves activation of the NF- κ B signaling pathway, a key regulator of inflammatory gene expression. Both IL-17A and resistin have been shown to independently activate NF- κ B, leading to increased production of pro-inflammatory mediators such as TNF- α and IL-6, which amplify synovial inflammation and joint damage. Our study has some limitations in terms of lack of of control for confounding variables such as; disease duration, treatment duration and drug dosage, as they may significantly influence biomarkers levels.

5. CONCLUSION

Our findings indicate IL-17A and resistin may be associated with the pathophysiology of RA. likewise, the association between resistin and IL-17 supplied further proof that the elevated resistin levels in patients might be connected to disease.

Conflict of interest

As stated by the author, there are no relationships of interest.

Consent for publications

All authors have to write this sentence that they read and approved the final manuscript for publication.

Availability of data and material

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Each author agreed to be accountable for all elements of this work and participated to data evaluation, designing, and editing of the final version.

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التحليل المقارن لمستويات الرزستين والانتروكين-١٧ في مرضى التهاب المفاصل الروماتويدي مع المعالجين وغير المعالجين

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الخلاصة	الكلمات المفتاحية
تُفرز العديد من الخلايا الملتهبة في مرضى التهاب المفاصل الروماتويدي مجموعة متنوعة من المواد الالتهابية. وقد فحصت هذه الدراسة مستويات الريزستين و إنترلوكين-17 لدى المرضى الذين يتلقون العلاج والذين لا يتلقونه. أجريت دراسة على 120 مريضاً مصاباً بالتهاب المفاصل الروماتويدي، وقُسموا إلى أربع مجموعات: المجموعة الأولى (30 مريضاً بدون علاج)، والمجموعة الثانية (30 مريضاً يتلقون الميثوتريكسات)، والمجموعة الثالثة (30 مريضاً يتلقون الإيتانيرسيبت)، والمجموعة الرابعة (30 مريضاً يتلقون الريتوكسيماب). وتألفت المجموعة الضابطة من 25 فرداً. جُمعت عينات دم لقياس مستويات النترلوكين و الرزستين في المصل باستخدام تقنية الاليزا. كانت المستويات الانترلوكين اعلى بكثير في مصل المجموعة الأولى أعلى بكثير من مستوياتها في المجموعة الضابطة، وكذلك في المجموعتين الثالثة والرابعة. كما أظهرت المجموعة الأولى ارتفاعاً ملحوظاً في مستوى الريزستين مقارنةً بالمجموعة الضابطة والمجموعة الثالثة، بينما لم تُظهر أي من المجموعتين الثانية والرابعة أي تغييرات ذات دلالة احصائية. و اظهر الريزستين و الانترلوكين-١٧ ارتباطاً ايجابياً قويًا تشير هذه النتائج الى ان الانترلوكين و الرزستين. قد يكونان مرتبطين بالآلية المرضية لالتهاب المفاصل الروماتويدي.	إيتانيرسيبت؛ إنترلوكين-17؛ ريزستين؛ التهاب المفاصل الروماتويدي؛ ريتوكسيماب.

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