RESEARCH ARTICLE

Evaluation of serum resistin levels in Iraqi rheumatoid arthritis patients under biological treatment and their correlated clinical disease activity index

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Abstract

Objective: The current study aimed to evaluate RA patients' serum resistin levels and to observe the relationship between disease activity and resistin.

Methods: A case-control study was conducted on (100) RA Iraqi patients during treatment with bDMARDs. The first group of 50 patients received etanercept, and the second group of 50 patients were on Rituximab (RTX). The control group comprised of 50 healthy individuals. ELISA was used to evaluate serum Resistin in and anti-CRP. Inflammatory markers ESR, and CRP with biochemical tests were conducted. In addition to estimating Clinical Disease Activity score I(CDAI) by the physicians; at Baghdad Teaching Hospital.

Results: Levels of Resistin of RA treated with RTX were significantly higher (16.30 ± 7.38ng/ml) than in RA treated with ETN (10.61 ± 5.85ng/ml) compared to the control group. (6.95 ± 1.70 ng/ml). The resistin level showed a positive correlation with Anti-CCP abs which was considered to have a high positive correlation ($p < 0.01$) in ETN group. While this correlation was lower than the RTX group, the, correlation between resistin, and ESR was the highest in RTX group whilst no such correlation was observed in the ETN group. There was a positive correlation with CDAI of RA subgroups (moderate activity ($p < 0.05$), and high activity ($p < 0.001$). The logistic regression of resistin was associated with biological treatment, odds ratio was (OR=1.138, p-value= 0.014, 95% CI.1.025-1.257) during ETN, and RTX independent of CRP.

Conclusion: There is an association between serum RSN and anti CRP as a result of disease activity independent of CRP. resist in levels can be used to determine disease activity to avoid disease progression and erosion.

Keywords: Protein, Antibodies, Etanercept, Rituximab, Disease, Physicians **DOI: https://doi.org/10.47391/JPMA.IQ-23**

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by synovial membrane inflammation and hyperplasia ("swelling"), cartilage with bone destruction ("deformity"), autoantibody production - autoimmune disease, and systemic features such as pulmonary, skeletal, cardiovascular, and psychological complications. Women are three times more susceptible than men, and the disease is more common between the ages of 40 and 50 years.[1] RA is etiologically linked to a variety of environmental risk factors, such as infections, smoking, periodontitis, hormonal and dietary factors, inactivity, and obesity.[2] Rheumatoid factors (RFs), anti-citrullinated protein antibodies (ACPA), and pro-inflammatory cytokines are among the physiologically significant proteins that B-cells secrete to support RA. As a result of the pathogenicity of RA, the management of RA patients will involve a course of therapy designed to reduce inflammation and stop the irreversible effects of uncontrolled RA.; Biological disease-modifying anti-

rheumatic drugs bDMARDs as anti-B-cells; Rituximab (RTX) or tumour necrosis factor (TNF) inhibitors like etanercept (ETN) are types of therapies used for this disorder. As a homodimer of a 12.5 kDa cysteine-rich protein, it travels through the bloodstream. Mononuclear cells are the main source of production of resistin., and by triggering immune cell activation, it has been linked to an inflammatory response.[3] In humans, circulating monocytes and macrophages are the main producers of resistin. In RA, synovial stromal cells of the joints and macrophages, B cells, which are invasive immune cells, were discovered to express resistin.[4] Resistin, a smaller amount of which is also produced by adipocytes, is involved in a number of metabolic processes, including insulin resistance. Along with other elements of the metabolic syndrome, high levels of circulating resistin. are associated with being overweight.[5] It has been observed in inflammatory regions and may be mediated by Interlukein-6, and Tumour Necrosis Factor-α.[6] Resistin's role in the inflammatory response is widely acknowledged. In response to the expression of resistin., human leukocyte Toll-like receptor 4 (TLR4), to which resistin binds, controls the production of a number of pro-inflammatory cytokines and interleukin (IL)-1, including IL-12 and IL-6.[7] Resistin is present in the blood plasma or serum, synovial fluid (SF), and synovial

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tissue of RA patients. Synovial stromal cells, like SF, and infiltrating immune cells, like B cells, and macrophages express resistin in RA- impacted joints. Resistin levels have been identified as higher in the synovial fluid and subliming layers when comparing RA patients to Osteoarthritis patients.[8] Of the analysed leucocyte subsets, monocytes have the most resistin gene (*RSN*) transcripts. In RA patients who responded to treatment, TNF-a inhibitor significantly reduced the number of inflammatory cytokines that monocytes were exposed to. Inflammatory cytokines TNF-a, IL-1, and IL-6 upregulate RSN gene expression in human peripheral blood mononuclear cells PBMCs and in human monocytes exposed to endotoxin.[9] The current study aimed to evaluate RA patients' serum resistin levels and to observe how resistin and RA disease activity are related**.**

Patients and Methods

This prospective case-control study was carried out at four main medical facilities in Baghdad; Rheumatology Consultation Clinic in Baghdad Teaching Hospital and Patients Lobby for Biological Treatment, National Centre for Teaching Laboratories, and haematological and oncological centre during the period from December 2021 to May 2022. Included were 100 patients (84 Female and 16 Male); The criteria for diagnosing RA was adopted according to American College of Rheumatology - European League Against Rheumatism (ACR- EULAR) (2010).[10] One hundred RA patients were divided into two groups who were treated with the disease-modifying anti-rheumatic drugs as biological DMARDs 50 patients treated with Etanercept, and 50 patients treated with Rituximab. Additionally, 50 healthy individuals formed the control group who matched with the patient's group in age and gender. All the information about each individual who had active RA including data about their age, height, and weight. Body Mass Index (BMI) were recorded. BMI was calculated using the equation [weight (kg) / height (m²)].[12] The family history, duration of disease, treatment of any type of bDMARDs (ETN, RTX, sDMARDs (MTX) or steroid treatment) were also recorded.[11,12] The Clinical Disease Activity was estimated for each RA patient by a rheumatologist (CDAI). The Iraqi ministry of health's ethical committee assisted in the laboratory analyses (no. 45823).

All blood samples were collected from RA patients and control individuals during treatment with ETN and RTX. Serum resistin and anti-cyclic citrullinated peptide antibody concentrations (anti-ccpAbs) were estimated using ELISA kit (My BioSource –USA). Other tests were done in medical laboratories by auto-analyser including biochemical tests (SGOT, and SGPT). Additionally, the sample size was calculated by equation 1,for a finite population.[13]

$$n = \frac{N\,P\,(1-P)}{(N-1)\left(\frac{d}{Z_{1-\alpha/2}}\right)^2 + P(1-P)} \qquad (1)$$

Statistical analyses: Using IBM SPSS version 28.0, the data's normality, homogeneity, and normal distribution, as well as its mean ± SE of the mean, were examined.[14] The comparison between the three groups was presented by the ANOVA table (Duncan test). Through the use of an independent T-test and an ANOVA table, the probability was also observed. The probability was calculated using Pearson's chi-square test on non-parametric data. A qualitative parameter (CRP) was documented using the Spearman coefficient. The relationship between the investigated parameters was ascertained using Pearson's correlation. In addition, estimated Multivariable ordinal logistic regression analysis was used to calculate adjusted odds ratios (OR), and corresponding 95% confidence intervals (CIs) for the risk of RA in non-response to biological treatments (ETN, RTX).

Results

Table 1 shows the demographic features and clinical variables of RA patients treated with (ETN) and (RTX), compared to the control group. The ESR level was significantly higher in the ETN group than in RTX group whereas SGOT level was higher in the latter and control group with the RTX group being more than the controls. SGPT was statistically higher in RTX and control group (28.16±7.83, 26.42±11.28 U/L, respectively) than in ETN (2.40±10.55 U/L).

An autoantibody (Anti-CCP) level was statistically higher in the two groups of RA than in the control group. Levels of RSN in a group of RA treated with (RTX) were significantly more (16.30±7.38) than in a group treated with (ETN)(10.61±5.85) compared to the control groups (6.95±1.70). The duration of the disease was non-significant between group1 and group2 of RA patients (8.40±6.37, 8.34±4.27 years respectively). The Gender frequency was for males in the three groups (10.0, 22.0, and 34.0, respectively); the gender frequency regarding females of ETN, RTX and control group (90.0, 78.0, and 66.0, respectively) were higher than male (10.0, 22.0, and 34.0, respectively). While the family history positivity for the two groups of RA patients [Yes, (28.0), (18.0)] were lower than those who had a higher frequency for two groups of RA patients [No, (72.0), (82.0)]. Finally, CRP was positive [60.0, and 30.0, respectively) for ETN and RTX groups of RA, and negative   in   the   control   subjects.

Demographic characteristics and clinical variables of RA patients treated with (ETN) and (RTX): Table 1 lists the characteristics of the study's healthy controls and patients. The two groups of RA patients under (ETN), and (RTX) treatment did not differ significantly amongst themselves. Whereas they were significantly older in age compared to the control group, (46.12±12.49, 46.04±14.88, 39.12±12.98 years, respectively). The results of (<25 BMI >25) revealed non-significant difference in the three groups of the current study.

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The relationship between RA characters in the two groups and resistin: The correlation coefficients showed a positive correlation among circulating RSN levels and characters of RA patients treated with ETN and RTX. The resistin level showed a positive correlation with anti-ccp abs (0.271**) which considered statistically lower correlation but, this correlation was higher than of RTX group (0.487**). While no correlations were found with the other characteristics of RA under ETN treatment. So, the finding of the current study in the RTX group showed an age-related, significant positive correlation with RSN (0.244*). In addition, a weak significant correlation of ESR, and anti-ccp abs with RSN (0.310**,0.487**) was observed which represented the highest correlation with RSN in comparison with (ETN group). The gender, BMI, duration of disease, and CRP did not correlate with the serum level of RSN, observed in Table 2.

The relation of RSN level and CDAI of the two groups of RA patients: The active groups of RA patients were sub-classified as low CDAI, moderate CDAI, and high CDAI.[15] The results of the three subgroups of CDAI as a comparison between the two RA patient groups (Etanercept and Rituximab) (Table 3). The level of RSN had a non-significant elevation in RTX of RA (19.94±7.95 ng/ml) in the Low active disease according to CDAI (14.73±8.85ng/ml) of the ETN group. The finding of RSN levels in a moderate activity of the two groups of RA during the same treatment were significantly higher in ETN group than RXN (15.86±7.85 ng/ml, 9.80±4.31 ng/ml, respectively). While the finding of serum RSN in the high activity was highly significant (*p*<0.001); (13.97±5.39 ng/ml in RTX group *vs* [9.87±5.88 ng/ml in ETN group].

Table-1: Demographic characteristics and clinical variables of RA patients that treated with (ETN) and (RTX), and control

Demographic parameters mean ± SD		RA patients with ETN	RA patients with RTX	Control
Mean Age (Years)		46.12 ± 12.49A	46.04±14.88 A	39.12±12.98 B
BMI (Kg/m2)	>25	32.69 ± 5.44 A	31.65±4.44 A	30.79±3.96 A
	<25	21.55 ± 1.92 A	22.57±1.58 A	21.40±3.16 A
ESR (mm/hr)		41.14±23.72 A	29.26±15.24B	16.36±6.44C
S. GOT(u/l)		19.78±11.07B	25.24±8.27 A	20.50±9.43 B
S. GPT(u/l)		22.40±10.55 B	28.16±7.83 A	26.42±11.28A
Anti-CCP Ab (u/ml)		0.34±0.07 A	0.33±0.05B	0.24±0.01C
Resistin (ng/ml)		10.61±5.85 B	16.30±7.38 A	6.95±1.70 C
Duration of disease (Years)		8.40±6.37A	8.34±4.27 A	-
Gender frequency (%)	Males	5 (10.0)	11 (22.0)	17 (34.0)
	Females	45 (90.0)	39 (78.0)	33 (66.0)
Family history	Yes	14 (28.0)	9 (18.0)	0 (0.0)
	No	36 (72.0)	41 (82.0)	50 (100.0)
CRP %	Positive	30 (60.0)	15 (30.0)	0 (0.0)
	Negative	20 (40.0)	35 (70.0)	50 (100.0)

S.GOT: Serum glutamic oxaloacetic transaminase, S.GPT: Serum glutamic pyruvic transaminase, u/ml: unit per millilitre, Pg/ml: picogram per millilitre, ng/ml: nanogram per millilitre. The letters in the comparisons above referred to ANOVA table (Duncan test) between the three group: A Significant differences vs control (p<0.05), B Significant differences vs RA patients with ETN, C Significant differences vs RA patients with RTX. the similar letters referred to a non- significant difference

Table-2: A correlation between Resistin and clinical parameters of ETN and RTX groups of RA.

Parameters of groups (n=100)		ETN group(n=50) Resistin(ng/ml)	RTX group(n=50) Resistin(ng/ml)
Mean Age (Years)	R	0.001	0.244*
Gender	R	0.133	0.148
BMI (kg/m2)	R	-0.138	0.006
Duration of disease(years)	R	0.218	0.056
ESR (mm/hr)	R	0.192	0.310**
Anti-ccp(u/ml)	R	0.271**	0.487**
CRP (+ , -)	rs	0.128	0.153

**Correlation was significant at the 0.01 level (2-tailed). *. Correlation was significant at the 0.05 level (2-tailed). r : pearson coefficient correlation. rs : sperman coefficient correlation

Table-3: The comparison between CDAI groups continued on 2 types of biological treatment With RSN .

CDAI groups	Resistin (ng/ml)		p-value
	ETN group (n=50)	RTX group (n=50)	
Low Activity	14.73 ± 8.85	19.94 ± 7.95	>0.05
Moderate Activity	9.80 ± 4.31	15.86 ± 7.85	<0.05
High activity	9.87 ± 5.88	13.97 ± 5.39	<0.001

CDAI: clinical disease activity index, ng/ml: nanogram per millilitre

Table-4: The logistic regression for adipokines and biological treatment

	Adipokine	p-value	OR	95% CI
Step 1a	Resistin level (ng/ml)	0.014	1.138	1.025-1.257

OR: odd ratio, 95% CI: confidence interval 95%, a. variable entered on step 1

Estimated logistic regression for RSN and biological treatment: Variables entered on step 1; RSN had a significant association with bDMARDs (ETN, RTX), p-value= 0.014, OR=1.138, CI 95% (1.025 – 1.257), (Table 4.)

Discussion

Higher resistin levels have been reported in the fluid and subliming layers of the synovium in RA patients compared to Osteoarthritis patients.[8] Presuming that elevated levels of synovial resistin correlate with RA disease activity and joint damage, along with the potential pathological impact of these levels in RA,[16] the junction where the intra-articular leukocyte count and IL-6 levels indicate the severity of the inflammation.[17] Contrarily, Other studies found no connection between level of inflammation based on CRP levels and synovial fluid resistin.[18] Some researchers have found verifiable positive correlations between serum resistin levels and both CDAI and inflammatory status according to ESR, and CRP in RA patients.[19] Some studies alleged that resistin in chronic inflammatory states like RA, could compete with lipopolysaccharide for binding to (Toll-like receptor-4) and may serve as a pro-inflammatory cytokine in human monocytes. According to subsequent research, resistin serum levels are positively correlated with CRP levels in RA, indicating that these hormones serve as pro-inflammatory cytokines in this condition.[20] The present study on the two groups comparing the ETN and RTX treatments for rheumatoid patients did not have a follow-up over an extended period as only the characteristics of the disease during treatment were studied. In general, in the serum of RA patients, RSN was elevated related to the treatment given in the two groups of RA and the socio-demographic status, compared to the control group. These outcomes agree with Nagaev *et.al*. and Fatel *etal(6,7)* , and the RSN level in ETN was lower than RTX because resistin expression with PBMCs is upregulated by pro-inflammatory cytokines such as TNF-α.[21] Therefore, a decrease in the level of RSN was observed in treated patients with ETN. The duration of disease, represented with [> 8 years] with the

two groups of RA agrees with some American populations with RA.[22] Resistin did not correlate with inflammaory markers as ESR, and CRP or duration of disease with a group of ETN and these findings agree with a study in Saudi Arabia[23] but had a positive correlation with anti-ccp abs. This finding disagrees with the study in China.[24] The results of this current study revealed that CRP did not correlate with resistin. This could be due to the observation being made during the period of treatment. This is in agreement with the results of a study by Chihara et.al[25.] No correlation of RSN with age was seen in this study, according to Pearson correlation values.[26] The clinical activity of RA is an important factor for evaluating the patient's response to bDMARDs. No significant correlations was found with CDAI of RA patients in (low activity) with the two groups on the different treatment. These results could be due to the efficacy of the ETN and RTX at this stage. These outcomes were in agreement with the results of Vasileiadis et.al.[27] In moderate and high disease activity; resistin showed a significant difference in moderate activity and a highly significant difference in high activity stage of disease. The results were in agreement with those of Rivera-Bahena et.al.[28] But there was a disagreement with the findings of with those of Hammad MH et.al on the Saudi population.[23] These findings indicate that resistin acts as a pro-inflammatory adipokine; in the two groups of patients (ETN, RTX). The duration of disease (> 8 years) under treatment might cause resistance to biological treatment. A multivariable logistic regression analyses was performed for the RSN with a biological treatment with Resistin produced by monocytes and macrophages but not adipose tissue.[26] A noteworthy finding was: Test for Disease Activity in Vectra, the RA diagnostic test, that assesses several vital biomarkers in tandem, including vascular cell adhesion molecule-1 (VCAM-1), IL-6, matrix metalloproteinases (MMP-1, MMP-3), TNF-R1, Leptin, Resistin, Serum amyloid A (SAA), and CRP, produced more precise outcomes when determining how well RA patients are responding to treatment for their disease.[29] Two significant pathogenic alterations can be seen in RA patients' synovial membrane. Both Synoviocyte types, fibroblast-like Synoviocytes (FLSs) and macrophage-like Synoviocytes (MLSs), which are significant cytokine and protease producers, are increased and activated in the case of the first. Numerous pro-inflammatory cytokines, including IL-1, IL-6, and tumour necrosis factor (TNF), are produced by MLSs. In addition, IL-6, FLSs also produce significant amounts of (MMPs). The second is the invasion of the synovial subliming by adaptive immune cells. As a result, the distinctive "pannus" formation forms at cartilage-bone interfaces. Mast cells, FLSs, dendritic or plasma cells, and macrophages make up the pannus, which mediates

damage with erosion formation in later disease.[30] In RA patients in a Netherlands study, resistin had a positive correlation with TNF- and IL6.[31] Hasseli's study concluded that Proinflammatory cytokines like (TNF- α), (IL-6), growth factors, and the upregulation of various adhesion molecules are secreted when adipokines are present. Adipokines in RA, such as adiponectin, visfatin, and resistin, have an impact on both RASFs and (Endothelial cells) ECs;[32] with these studies, resistin had a pathogenic role in RA and current findings had a strong correlation of RSN with inflammatory markers of RA (ESR, Anti –CCP abs) in the groups of RA patients, in addition to a longitudinal duration of disease and the correlation with disease activity (moderate, high activity), independent of CRP. All the above mentioned prompted us to create the logistic regression for RSN with biological treatment for the two groups of RA patients. The current findings showed resistin to be a risk factor for RA, nonresponding to bDMARDs with a proportion of (OR=1.135) at the long duration of disease (>8 years), susceptible to causing bone erosions.

Conclusion

An association was found between serum RSN and anti ccp as a result of disease activity independent of CRP. Resistin levels can be used to determine disease activity to avoid disease progression and erosion. These findings encourage future longitudinal studies to evaluate RSN expression in RA patients, as well as follow-up on RA patients' radiographic changes.

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