International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 09, 2020
ISSN: 1475-7192

The role of B cell receptor clone test and Adiponectin as a predictors of rheumatoid arthritis

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Abstract:

Rheumatoid arthritis (RA) means chronic inflammatory sickness with systemic characteristics involving joints, leading to erosive synovitis, degradation of cartilage, and destruction of joints. The aim of this study was for assessment of serum levels of B Cell Receptor (BCR) clones and Adiponectin (ADP) in RA and the correlation between them in biological, chemotherapy, biological, and chemotherapeutic treatment strategies. Seventy eight individuals have included in this study, 60 patients (51 females and 9 males) with 18 control (13 female and 5 male). Patients with RA were diagnosed by a consultant rheumatologist according to ACR / EULAR criteria in 2010. They were divided into three groups; patients had biological treatment (bio.), chemotherapy (chem.), and biological and chemotherapy. Evaluation of the RA activity using Disease Activity Score 28 (DAS28) was done. Enzyme-linked immunosorbent assay (ELISA) was used to detect B Cell Receptor and Adiponectin. BCR clones, ADP were assessed. The results showed a highly significant increase (p= 0.0001) in the serum level of BCR observed in both biological group and biological and chemotherapy groups as compared to control. The ADP serum level had a highly significant increase (p= 0.002) in the biological group as compared with the control group. There was a significant Negative correlation between ADP with BCR level (P-Value=0.039) in patients who had biological treatment.

In conclusion, In patients who had biological treatment, there was a significant increase in serum BCR levels and ADP levels.

KEY WORDS: *BCR, ADP, rheumatoid arthritis, biological treatment, chemotherapy treatment.*

I. Introduction:

As Rheumatoid arthritis is a chronic inflammatory immunological dysfunction with systemic characteristics involving joints and several other tissues leading to erosive synovitis, there is an accumulation of the chronic inflammatory cells including T and B cells, monocytes and macrophages, which appear as a result of the cell-mediated immune response in the patients with RA (1). A lot of biochemical markers are involved either

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directly or indirectly in the etiology and pathogenesis of Rheumatoid arthritis, among these parameters; dominant B Cell Receptor Clones (BCR clones) and Adiponectin (ADP), (2).

Dominant BCR clones have an important role in the pathogenesis of the disease as they appear in synovial tissue and disappear from peripheral blood with the progress of RA. In the disease's early stage, the existence of a high quantity of dominant BCR clonal signatures in blood predicts the onset of RA. Thus, the detection of BCR clones in peripheral blood or the synovium is predictive for the developmental stage of the disease (3).

In Rheumatoid Arthritis, methotrexate causes cells to release adenosine, which blocks other chemicals that promote inflammation, and it is thought that this is how methotrexate reduces inflammation in Rheumatoid Arthritis (4).

Biologic disease-modifying antirheumatic drugs (DMARDs) are drugs that were made using biotechnology for the treatment of RA. These drugs were genetically engineered to work as natural proteins in the immune system of RA patients (1).

In his study, serum levels of BCR clones as well as the other biochemical parameters have been assessed for evaluation of their influence on patients with RA and the correlation between those parameters in biological, chemotherapy, or biological and chemotherapeutic treatment strategies.

About 1% of the worlds' population is affected by rheumatoid arthritis, when determined by either the presence of rheumatoid factor (RF) in serum or erosive changes in patient's radiographs with a similar clinical presentation (5). As of 2015, around 24.5 million people are affected by RA. Rheumatoid arthritis is more common in females than in males by 2.5 times, and it is mostly observed in the old ages (6).

RA resulted in 38 thousand mortalities in 2013, from 28 thousand deaths in 1990. (9). In 1800, RA was firstly described clearly by Dr. Landré-Beauvais of Paris

(7)

Adiponectin

Adiponectin (ADP) is a cytokine secreted exclusively by adipocytes that are involved in the glucose and lipids metabolism regulation, and it also exhibits anti-inflammatory properties. Its plasma levels were found to be elevated in inflammatory diseases such as RA. A group of small proteins that mediate the leukocyte migration into inflammatory sites is called Chemokines (i.e. chemo-attractant cytokine). This group has consisted of almost fifty molecules divided into four subgroups following the number and arranging of cysteine residues (8).

II. Materials and Methods

Subjects included in the study were drawn from patients who were attending the rheumatology consultation clinic or admitted to Baghdad Teaching Hospital. The study population included seventy-eight individuals. Sixty of them had rheumatoid arthritis and eighteen control samples with no signs and symptoms of any systemic disease. The age average was ranged (30-60) years and had normal weight and length following

Body Mass Index (BMI) where the normal values are (18.5 -25) because increase and decrease in weight may be a risk factor of rheumatoid arthritis**.** DAS28 was calculated by using a calculator version by A. den Broeder, M. Zandbelt, and M. Flendrie. Published thresholds describe absolute DAS28 scores which represent remission [<2.6], mild [≤3.2], moderate [> 3.2 and < 5.1] or severe [>5.1] activity of the disease, whereas 4.1 is pondered as the finest threshold for determination of active RA (170).

The sample was divided into four groups according to the given treatment:-

1. Chemotherapy and biological treatmentgroup: Thirty-five patients diagnosed to have rheumatoid arthritis. The treatment that was taken by these patients includes both Chemotherapy and biological treatment**.**

2. Biological treatmentgroup: Twenty patients were on biological treatmentonly**.**

Which includes a solutionfor injectionin a pre-filled pen (Enbrel).

3. Chemotherapy treatment group: Five patients were on Chemotherapy treatmentonly**.**

4. Healthy control group: - Eighteen healthy control subjects with no signs and symptoms of any systemic diseases.

The collection of blood samples was done at a fixed daily time (8-11) Am. About 6 ml of venous blood samples were separated from the antecubital vein of each one, using one-use syringes. Within Gel tubes, the collection of the whole blood was done. Sera were obtained by centrifugation at 3000 rpm for 10 minutes then the supernatant sera were separated and transferred immediately into Eppendorf tubes and frozen at (- 20 ˚C) for subsequent analysis.

Statistical analysis

Data analysis was performed using the SPSS statistical program (Version(23); SPSS Inc., Chicago, IL). Analysis of variance (ANOVA) was used to determine whether there are any statistically significant differences between the means. Data were presented as mean ± Stander Deviation. Pearson's correlation (r- coefficient) was used between BCR, ADP, and disease activity. The result considered statistically significant when p-value ≤0.05.

III. Results and Discussion

B cell receptor (BCR) levels distributed among biochemotherapy, biological, chemotherapy patients and control groups

Table (1-A) illustrated the statistical analysis of BCR levels among different groups for patients of Rheumatoid Arthritis and the control group. The mean ± Stander Deviation (SD) value increased in BCR level in chemotherapy group 1.082 ± 0.365 ng/mL, chemotherapy and biological group 1.023 ± 0.325 ng/mL, and biological group 1.074 ± 0.349 ng/mL was detected in comparison with control group 0.627 ± 0.232 ng/mL.

These results showed a significant increase in the serum level of BCR (P<0.05) was observed in the chemotherapy patient group compared to the control group. A highly significant increase (p= 0.0001) in the

serum level of BCR was observed in both biological group compared to the control group and Biological and chemotherapy group compared to control group (Table 1- B)

Table 1. A: Statistical analysis of B cell receptor (BCR) levels distributed among biochemotherapy, biolodical, chemotherapy patients and control groups by ANOVA.

Parameter	Group	Mean	SD	P value
BCR (ng/mL)	**Control**	0.627	0.232	0.0001*
	Biochem.	1.023	0.325	
	Bio.	1.074	0.349	
	Chem.	1.082	0.365	

* Significant at P ≤ 0.05, SD: Stander deviation ,BCR: B Cell Receptor

Table 1. B: Multiple comparison significant (T-test) for BCR between thedifferent groups.

Groups	BCR ng/mL
	P-value
Biochem & control	0.0001*
Bio & control	0.0001*
Chem & control	0.006*
Biochem & Bio	0.565
Biochem & Chem	0.699
Bio & Chem	0.962

* Significant at P ≤ 0.05 ,BCR: B Cell Receptor

In the present study, the BCR levels increased significantly in the group of patients who treated with chemotherapy, chemotherapy, and biological group, and biological group in comparison with the control group.

On the other hand, BCR levels had a highly significant increase in both biological groups and biological and chemotherapy groupsas compared withthe control group.

A previous study byTak et al. (10), found that the clones which were detected in their study were pathogenic B cells as they were not detected in healthy controls nor in individuals at risk who didn't develop RA after follow-up, in addition, their dominance suggested the activity.

In another studyby Bucalaet al. (11), the BCR heavy chain repertoire has been measured in the peripheral blood at the mRNA level. The group of patients who had at least five dominant BCR clones in peripheral blood was probable to reveal the short-term onset of RA in 36 months. Additionally, it was found that patients with more BCR clones were at higher risk of the pending onset of arthritis. From the results, they suggested that a simple blood test might be capable of predicting patients at risk for developing RA in the next three years.

Adiponectin (ADP) levels distributed among biochemotherapy, biological, chemotherapy patients, and control groups:

The statistical analysis of Adiponectin (ADP) levels was illustrated in Table (2.A) among different groups for patients of RA and control group. The mean ± SD value increased in ADP level in both chemotherapy and biological group 11.355 ± 0.247 ng/mL, the biological group11.355 ± 0.456 ng/mL followed by the chemotherapy group 11.200 ± 0.094 ng/mL in comparison with control group 11.026 ± 0.291 ng/mL. These results showed a significant increase in the serum level of ADP ($P<0.05$) was observed in the biological and chemotherapy patient group compared to the biological group. Also, the serum level of ADP had a highly significant increase ($p= 0.002$) in the biological group compared to the control group (Table 2-.B).

Table (2-A): Statistical analysis of Adiponectin (ADP) levels distributed among biochemotherapy, biological, chemotherapy patients and control groups by ANOVA.

Parameter	Group	Mean	SD	P value
ADP (ng/mL)	**Control**	11.026	0.291	0.019*
	Biochem.	11.355	0.247	
	Bio.	11.355	0.456	

	Chem.	11.200	0.094

* Significant at P ≤ 0.05, SD: Stander deviation, ADP:Adiponectin

Table (2-B): Multiple comparisons significant (T-test) for ADP between thedifferent groups.

Groups	**ADP ng/mL** **P-value**
Biochem & control	0.209
Bio & control	0.002*
Chem & control	0.286
Biochem & Bio	0.021*
Biochem & Chem	0.715
Bio & Chem	0.334

* Significant at P ≤ 0.05, ADP:Adiponectin

The results showed a significant increase in the serum level of ADP (P<0.05) in biological and chemotherapy patient groups compared to the biological group. Also, the serum level of ADP had a highly significant increase (p= 0.002) in the biological group compared to the control group.

These results agreed with the results of (12) who performed a recent meta-analysis and it was reported that circulating adiponectin levels were significantly higher in RA patients in comparison with controls.On the other hand, previous studies have revealed that treatment of RA with anti-TNF-α treatment led to an increase in the levels of adiponectin (13).

Veluriet al. (14) showed different results; where serum adiponectin levels were significantly lower in patients with RA compared to controls. Also, there was no relation was found between adiponectin and the disease activity or BMI.Similarly,El-Hiniet al. (15) reported lower adiponectin levels in RA patients in comparison with healthy controls.

Reasons for the different results between studies for the levels of adiponectin include varying disease duration, disease activity, the origin of the study population,and sample size (12).

The correlation between B cell receptor level and other parameters in the patient's group who had biological treatment

The results showed that there was a significant Negative correlation between Adiponectin with B cell receptor level (P-Value=0.039) and it had the least value the person's correlation coefficient (-0.464), While DAS28 had non-significant positive correlation (P-Value=0.196, r=0.302). (Table 3).

Table (3): The correlation between B cell receptor level and other parameters in Bio patients.

B cell receptor Vs. Parameters	Bio.	
	R	P-Value
Adiponectin	-0.464	0.039*
DAS28	0.302	0.196

*Significant at the level ($p \leq 0.05$), Bio: biological treatment. **r:** Pearson's Correlation Coefficient

The results of the current study showed that there was a significant Negative correlation between Adiponectin with B cell receptor level followed by DAS28, meaning that high level ofAdiponectin, as well as B cell receptor level, is Negatively correlated to RA which was assessed by the DAS28 that in turn showed a Negative correlation with them. In some studies, it was found that patients with RA had consistently higher serum and synovial fluid Adiponectin levels than the control group (16).

The correlation between B cell receptor level and other parameters in the patient's group who had chemotherapy

The results showed that Adiponectin had a non-significant positive correlation with B cell receptor level (P-Value=0.306) with the person's correlation coefficient of (0.579). DAS28 had the least non-significant Negative correlation with B cell receptor level as they had the highest (P-Values = 0.894), with a person's correlation coefficient of (-0.083) (Table 4).

Table (4): The correlation between B cell receptor level and other parameters in chemotherapy patients.

B cell receptor Vs. Parameters	Chemotherapy	
	R	P-Value

Adiponectin	0.579	0.306
DAS28	-0.083	0.894

r: Pearson's Correlation Coefficient

The correlation between B cell receptor level and other parameters in the patients group who had biochemical treatment.

Table (5) showed that DAS28 which had a (P-Value=0.160) and a Negative person's correlation coefficient of (-0.243). While Adiponectin had the highest (PValue=0.475) which also indicated that it had the least non-significant positive correlation with B cell receptor level (0.130)

Table (5): The correlation between B cell receptor level and other parameters in Biochemical patients.

B cell receptor Vs. Parameters	**Biochemical**	
	R	**P-Value**
Adiponectin	0.130	0.475
DAS28	-0.243	0.160

r: Pearson's Correlation Coefficient

Limitation of the study

The limitations of this study are small sample size and the total sample 78, which was divided into 60 RA patients and 18 healthy controls. Also, there is not enough time for other measurements related to rheumatoid arthritis.

IV. Conclusion :

-In this study, it was concluded that:

1. In patients who had biological and chemotherapy treatment, there was a significant increase in serum BCR levels

2. In patients who had biological treatment, there was a significant increase in serum BCR levelsand ADP levels

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