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Physiological and Immunological Disturbance in Rheumatoid Arthritis Patients

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Abstract:

Rheumatoid arthritis (RA) is a systematic autoimmune disorder with chronic inflammation changes of unknown etiology. Various synovial inflammatory and proliferative alterations may contribute to the cartilaginous tissues and invasive bony tissues, leading to destructive joints and malformed bones. This disease is mostly due to infective microorganisms or genetic susceptibility causing immune system disturbances through triggering both T-cells and B-cells. Furthermore, different immune cells may secret cytokines, which are responsible for some RA pathogenesis activity. From ninety individuals, serum sample was collected; thirty of them were normal and sixty cases were patients with RA attended a privet medical clinic at Tikrit city from May 2019 to November 2019. Age, in both patients and control groups, ranged between (18-50) years, they had assay of Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Tumor necrosis factor (TNF)-α, Leptin, Adiponectin, and C-reactive protein. The present study shows that (IL-1, Leptin, and CRP) levels were higher in Rheumatoid Arthritis patients than control, while (IL-6, IL-10, TNFα, and ADP) levels were lower; therefore, cytokines can play an essential role in RA pathogenesis. The current study may bring attention to adiponectin and leptin for their roles in the pathogenesis of RA. Special consideration was devoted to those proteins, which act on cells associated with RA, also for possible usage of these protein levels as potential biomarkers for the disease activity and therapeutic response.

Keywords: Adiponectin (ADP), C-reactive protein (CRP), Cytokines, Leptin, Rheumatoid Arthritis (RA), Tumor Necrosis Factor-Alpha (TNF-α).

Introduction:

Rheumatoid Arthritis (RA) is regarded as a chronic inflammatory autoimmune disorder affecting females more than males with predominant observation in old people; its prevalence ranges between (0.5 - 1) % from the total community population with regional varieties (1).

RA initially affects the synovial joint linings leading to progressive disabilities and social burdens. Oedema, erythema, arthralgia with movement range limitations are the cardinal clinical joint features with symmetrical involvement. Early RA diagnosis may be regarded as the key index for the improvement of the most expected fate of the disease including less destructive joints, few progressive radiological findings, absent functional disabilities with Disease Modifying Anti-Rheumatic Drugs (DMARD) free-remission; in addition to cost-efficiency in the first twelve weeks after the appearance of early clinical symptoms which are considered as an optimal therapeutic window (2,3).

Although, early diagnosis is still a challenge since it mainly depends upon the clinical data collected from the patient's history with physical examinations; in association with specific blood tests and radiological images. The Poor healthcare system in some countries causes delayed diagnosis of RA (4).

RA has two major subtypes regarding the anti-citrullinated protein antibodies (ACPAs) presence or absence. Peptidylarginine-deaminase (PAD) is a calcium-dependent enzyme that catalyzes citrullination and alters the positive-charged arginine into neutral citrulline due to a specific post-translational modification process. ACPAs were found in about 67% of RA patients

which is regarded as an important diagnostic finding for the appearance of early arthritis that indicates the disease progression likelihood to RA (5,6).

IL-1 is a pro-inflammatory cytokine with immune activities. IL-1RI and IL-1RII are two specific receptors identified for IL-1. IL-RII is located at the cell surfaces acting as a decoy receptor, which binds and inhibits IL-1. On contrary, in serum the IL-1 receptors may bind IL-1 leading to regulate cytokine bioavailability (7,8). Different cell types like B-cells, T-cells, fibroblasts, monocytes, synovial and endothelial cells produce IL-6 (9).

Leptin is regarded as a superfamily member of type I cytokine; with a long-helix structure that resembles interleukin IL-2 and IL-6 (10). It may play a role to regulate the metabolic processes as well as controlling the immune homeostasis, which eventually causes diverse actions onto the innate immune system. In addition, leptin may serve as a pro-inflammatory cytokine of the immune responses in some diseases like psoriasis, multiple sclerosis (MS), RA, and systemic lupus erythematosus (SLE) (11-13).

Adiponectin is considered as a collagen-like protein, which has the same structure as complement factor C1q. It is mostly produced by adipocytes and exists in various molecular isoforms and with high levels in the blood. The principal functions of adiponectin include increasing the fatty acid oxidation with the glucose uptake in the muscle while decreasing the glucose synthesis in the liver (14).

Materials and Methods:

Venous blood of about (5-10) ml was taken from Rheumatoid Arthritis patients and control subjects; it was allowed to clot inside a plain tube. After doing centrifugation for 30 minutes at 3000 rpm, the serum was aspirated, then subdivided into aliquots within plastic tubes and kept at (−20 °C) till the time of estimation.

From ninety individuals, serum sample was collected; thirty of them were normal and sixty cases were patients with Rheumatoid Arthritis who attended to a private medical clinic in Tikrit city from May 2019 to November 2019. Patients and control groups were between (18-50) years. All the control persons were non-diabetics and non-smokers with neither a familial history of diabetes nor a personal history of hypertensive, thyroid, or renal diseases.

Immunological assays including IL-1, IL-6, IL-10, CRP, TNFα, Leptin, and Adiponectin, estimated by using Enzyme Linked Immunosorbent Assay (ELISA) Sunlong Biotech Company kits with the sandwich method (15).

Statistical analysis was done by using SPSS, 2001 statistical program, and a comparison was made between various groups, which were evaluated by t-test. The level of statistical significance was calculated at ($P<0.05$).

Results:

The results of the current study illustrated that the mean±SD of interleukins levels were (IL-1= 57.72±11.85, IL-6= 6.35±1.28 and IL-10= 36.9±15.84) pg/ml respectively in the RA patients group with highly significant difference ($P\leq0.01$) when compared with normal subjects (IL-1= 34.5±8.5, IL-6= 15.80±10.32 and IL-10= 110.5±40.5) pg/ml respectively.

Serum TNF-α in the RA patients group was (143.57±27.38) pg/ml with a significant decrease ($P\leq0.05$) when compared with normal subjects (358±212.13) pg/ml.

Leptin level was (253.75±158.7) ng/ml in RA patients group with no significant increase ($P>0.05$) when compared with normal subjects (160±28.49) ng/ml.

ADP level in the RA patients group was (1.6±0.18) ng/ml with a highly significant decrease ($P\leq0.01$) when compared with normal subjects (5.2±2.57) ng/ml.

CRP level was (10. 2±5.5) mg/l in the RA patients group with a highly significant increase ($P\leq0.01$) when compared with normal subjects (4.2±0.86) mg/l.

All the above results are shown in Table 1, Figs. 1 and 2.

Table 1. Serum Levels of all studied parameters in Rheumatoid Arthritis patients and control groups.

Parameters	Rheumatoid Arthritis patients	P value	Control
Number of subjects	60	-	30
Age (year)	(18-50)	-	(18-50)
IL-1 pg/ml	57.72±11.85	*P≤0.01	34.5±8.5
IL-6 pg/ml	6.35±1.28	*P≤0.01	15.80±10.32
IL-10 pg/ml	36.9±15.84	*P≤0.01	110.5±40.5
TNF-α pg/ml	143.57±27.38	**P≤0.05	358±212.13
Leptin ng/ml	253.75±158.7	***P>0.05	160±28.49
ADP ng/ml	1.6±0.18	*P≤0.01	5.2±2.57
CRP mg/l	10. 2±5.5	*P≤0.01	4.2±0.86

*P≤0.01 = statistically highly significant
**P≤0.05 = statistically significant
***P>0.05 = not statistically significant

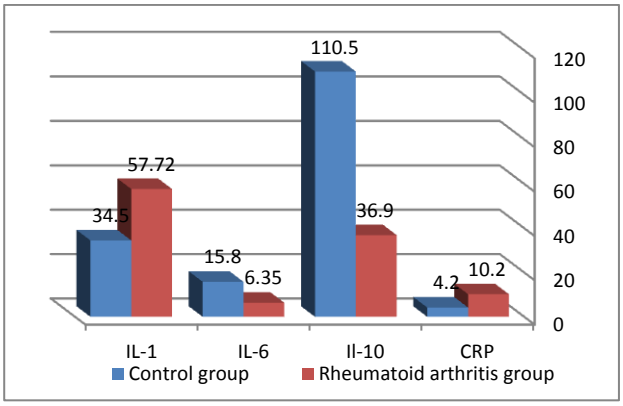

Figure 1. IL-1, IL-6, IL-10 and CRP levels in Rheumatoid Arthritis patients and control.

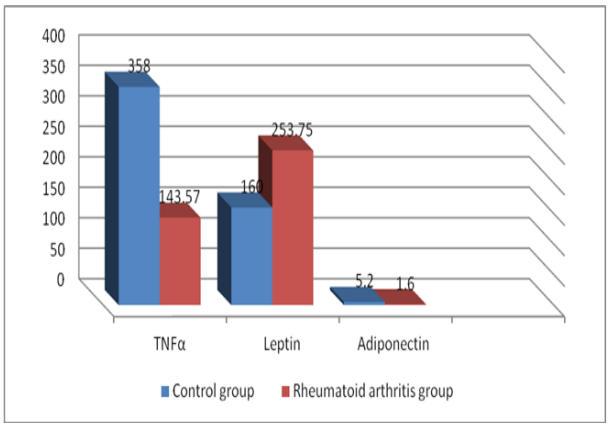

Figure 2. TNFα, Leptin and Adiponectin levels in Rheumatoid Arthritis patients and control.

Discussion:

This study revealed that IL-1, Leptin, and CRP levels increased with a highly significant difference (P≤0.01) in the RA patients group rather than control; while the IL-6, IL-10, TNFα, and ADP serum levels decreased with highly significant difference (P≤0.01).

Significant elevation in leptin serum levels of RA patients was obvious in some studies (16,17); in contrast, others have found decreased levels (18-20). However, leptin established a complicated relationship since it serves as a principal link factor between food intake and active bone metabolism as reported by Sandell (21) study.

Targonska-Stepniak et al (22) study carried out on RA in the erosive phase revealed a clear increment of leptin serum levels, which may indicate the down-regulation activity during the erosion of the joints. This finding was in agreement with the findings of the current study.

As leptin triggers the production for IL-1 receptor antagonists; therefore, RA patients treated with anakinra (IL-1 receptor antagonist) showed excellent toleration leading to protect the joint from the destruction and erosion mentioned by the Planck study (23). On the other hand, leptin may trigger the production of CRP with a specific physiological role as reported by Ali et al (24). In RA patients, a weak association of CRP with leptin was reported through various studies (25-27); contrary to the current study findings, which showed that there is an increase in the levels of them in RA patients.

The present study revealed a decreased level of adiponectin in RA patients, which may be explained due to a potential activity of this cytokine in control of the inflammatory changes. This might occur through many mechanisms including inhibiting the macrophage cells' transformation into foam cells which were reported in a study done by Yang et al (28); or stimulation of IL-10 production as it well-defined cytokine of anti-inflammatory characteristics discovered by Conti et al (29) study. In addition, the reduction in TNF-α formation demonstrated by Greenblatt et al (30), or even induction of tolerance as an action for Toll-like receptor (TLR) ligands that reported by Turner et al (31), and promotion of the anti-inflammatory M2 macrophage cells polarization that proved by Li et al (32) study. Finally, alteration in ceramide metabolism with the promotion of sphingosine-1-phosphate synthesis may explain the adiponectin anti-inflammatory activity in some cases studied by Hollet al (33).

Also, this study suggested the importance of the estimation of adiponectin serum levels and synovial fluid levels during the erosive phase of RA; this could explain its association with significant radiographical destructive injury as mentioned by Chan et al (34). While it showed high levels in comparison with osteoarthritis (OA) and even the healthy individuals as reviewed by Pontes et al (35) and Srivastavaand et al (36) studies respectively.

Although, Disease Activity Score 28 (DAS28), Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR), revealed a positive relationship with high adiponectin levels through a report done by Bankó et al (37). However, the current study findings demonstrated that the baseline adiponectin serum level might expect the progressive radiographical changes of RA for several next years; with independency of increased anti-cyclic citrullinated peptide (ACCP) antibodies with body mass index (BMI).

On the other hand, the low level of TNF-α in RA of the present study might give an explanation to those RA patients treated with the most common biological agents like anti-TNF drugs (infliximab or etanercept) who also showed an increment in adiponectin serum level as described by Li et al (38). While, the current finding disagreed with a high TNF-α level in the inflammatory

disorders of skeletal system, which might lead to conclude this cytokine influences the regional destructive bone processes that proved by Mendes et al (39), although a new proof indicates that TNF-α antagonist agent can facilitate blood vessels stiffness in RA which reported by Mercer et al (40).

This study clarified a low level of IL-6 in the RA patients group compared to control, which could explain the disease pathogenesis. As a result of the pannus formation that may be stimulated by IL-6 through increasing vascular endothelial growth factor expression (VEGF-E) and increasing resorption of bones from osteoclastogenesis, in combination with oxidative stress within the leukocytes which mentioned by Gruol (41).

Conclusion:

TNF-α, ADP, and Interleukins decreased markedly (except IL-1), but leptin and CRP increased among RA patients. RA is an autoimmune disorder; therefore, treatment with anti-inflammatory drugs may decrease or inhibit some interleukins or cytokines.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in Tikrit University.

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الاضطرابات الفسيولوجية والمناعية لدى مرضى إلتهاب المفاصل الرثوي

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الخلاصة:

إلتهاب المفاصل الرثوي هو أحد امراض المناعة الذاتية اذ يصيب أجهزة الجسم نتيجة قصور المناعة الذاتية لأسباب غير معروفة. يمكن أن يساهم التهاب الغشاء الزليلي وانتشاره في غضروف الأنسجة بتدمير المفاصل وتشوه العظام. عادة ما يعتبر هذا الاضطراب ناتجًا عن عدوى ببعض مسببات الأمراض أو الجينات القابلة للتأثر والتي تسبب خللًا في الجهاز المناعي. هذا المرض قد يرتبط أيضًا بالاستجابات المناعية للخلايا التائية والأجسام المضادة التي تنتجها الخلايا البائية. بالإضافة إلى ذلك قد تلعب الحركيات الخلوية المفرزة من قبل الخلايا المناعية المختلفة أدوارًا مهمة في التسبب في التهاب المفاصل الرثوي. تم جمع عينات مصل الدم من 90 فرداً ، 30 منهم كانوا من الاسوياء و 60 حالة تمثل مجموعة مرضى التهاب المفاصل الرثوي المراجعين الى مختبرات طبية خاصة في مدينة تكريت للفترة من شهر مايس 2019 إلى تشرين الثاني 2019. تم إجراء فحص لكل من الحركيات الخلوية 1 و 6 و 10 وعامل نخر الورم - ألفا واللبتين وأديبونكتين وبروتين سي التفاعلي لمجموعة السيطرة والمرضى والذين كانت أعمارهم بين 18-50 عاماً. أظهرت هذه الدراسة أن مستويات (الحركيات الخلوية 1 واللبتين و وبروتين سي التفاعلي) قد زادت في مرضى التهاب المفاصل الرثوي أكثر من مجموعة السيطرة بينما انخفضت مستويات (الحركيات الخلوية 6 و 10 و وعامل نخر الورم - ألفا وأديبونكتين) ، لذلك قد تلعب تلك الحركيات الخلوية دورًا مهمًا في التسبب بإمراضية التهاب المفاصل الرثوي. كذلك ركزت هذه الدراسة على دور الأديبونيكتين واللبتين في التسبب بأمراضية التهاب المفاصل الرثوي من خلال تأثيرها على الخلايا التي تشترك في حدوث المرض، وعلى إمكانية استخدام مستويات هذه البروتينات كمؤشرات حيوية محتملة لنشاط المرض و استجابة المرضى للعلاج.

الكلمات المفتاحية: أديبونكتين، بروتين سي التفاعلي، الحركيات الخلوية، لبتين، إلتهاب المفاصل الرثوي، عامل نخر الورم - ألفا.