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A Comparison of Anti-Citrullniated Peptide Antibody, Lactate Dehydrogenase, Zinc and Copper in Sera of Patients with Rheumatoid Arthritis and Healthy Control: A Cross Sectional Study

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Abstract

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disease associated with synovial tissue proliferation, cartilage destruction and pannus formation. The study aimed to determine the link among each anticyvlic anti-citrullinated peptide antibody (ACPA), lactate dehydrogenase (LDH), zinc (Zn), and copper (Cu) levels in rheumatoid arthritis (RA) patients and healthy control. Across sectional study was carried out at the Baghdad Teaching Hospital in Baghdad Iraq, and involved 110 patients (95 females and 15 men), who were matched for age and sex with 40 healthy controls (28 females and 12 males). Patients with RA were diagnosed by a specialist rheumatologist utilizing ACR/EULAR criteria in 2010. According to the type of disease-modifying anti-rheumatic drug therapy used—biologic (bDMARDs), conventional (cDMARDs), and combined (DMARDs)—patients in this study were split into three subgroups. Zn, Cu, and LDH were quantified using a spectrophotometer (AAS), whilst serum ACPA was assessed using an enzyme-linked immunosorbent assay (ELISA). The results showed that there was a significant rise in all subgroups of ACPAs ($p<0.001$), Zn ($p<0.001$), and Cu ($p<0.001$) when compared to the healthy control, but no significant differences across subgroups. LDH levels increased significantly in the chemotherapy and bio-chemotherapy subgroups as compared to healthy controls, but LDH levels decreased significantly in the biology subgroup when compared to the chemotherapy and bio-chemotherapy subgroups. Changing therapy types has no effect on raising levels of ACPA, Zn, and Cu, however, it has an effect on LDH levels. The Biology subgroup showed no significant difference among RA patients subgroup and healthy control.

Keywords: Anti-Citrullinated Peptide Antibodies, Autoimmunity, Copper, Lactate dehydrogenase, Rheumatoid Arthritis (RA), Synovitis, Zinc.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that can damage the tissue lining the joints the skin, eyes, and other organ in some cases. The severity of the disease varies from patient to patient. The risk factors include gender, genetics, age, and exposure to the environment (air pollutants, cigarette smoking, and occupational exposure). The onset of this disease is usually between the ages of 35 and 60 years, with periods of remission , exacerbation [1,2].The global prevalence of RA was estimated in a recent meta-analysis as 0.46%, while the prevalence rate is 1% in iraq[3,4].Autoantibodies are one of the distinguishing features of rheumatoid arthritis (RA). A lot of research has been done on anti-citrullinated protein antibodies (ACPAs) [5]. Autoantibodies targeting acetylated proteins, such as anti-acetylated

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peptide antibody (AAPA) [6], and others have more recently been added to existing autoantibody systems that recognize post-translationally changed proteins [7].ACPAs, which are autoantibodies that attack citrullinated peptides, were identified as highly specific markers present in RA patients and first described in 1964 [8]. In the inflammatory process, citrullinated proteins play an important role in stimulating the production of antibodies. ACPA is produced by B plasma cells, and Fibrin is the major citrullinated protein in RA joints [9]. The lactate dehydrogenase (LDH) enzyme is present in almost all tissues and it's required in the final step of anaerobic glycolysis. It is released during tissue injury and inflammation [10]. Inflammation in RA and RA-like disorders is not restricted to joints and affects many organs of the body, so it is worth studying an inflammatory marker such as S.LDH, which is involved in multi-system inflammation [11]. Trace elements that include Zn, Cu, and other have been identified as one of these components, and their homeostasis is critical to controlling several parts of the inflammatory and immunological systems. Zn has been shown to play a role in maturation, cell cycle progression and differentiation [12]. It may have a role in arthritis because it is crucial for the innate and adaptive immune systems, as well as bone development, regeneration and controlling a number of inflammatory response components [13]. Cu may also influence the oxidant defense system by functioning as a catalytic cofactor and coordinating with Se and Zn, which are also responsible for adequate cartilage mineralization and the production of elastin and collagen structures, according to research [14]. In addition, tissue regeneration, bone formation, ATP production, and hemoglobin synthesis furthermore, it is a crucial component of the central nervous system's development [15]. Abnormal trace elements concentrations are associated with the regulate of gene expression inflammatory response, bone metabolism and regulate of transcriptional like cyclooxygenase-2, matrix metalloprotease 2 and inducible nitric oxide synthase , which are potentially associated with RA [16]. Hence, the objective of this study was investigate the role of ACPA, Zinc ,Copper and LDH in Rheumatoid arthritis patients and identify a predictor for treatment response, which in turn can guide early treatment decisions among middle-aged and older of Iraqi patients.

Materials and Methods

Five milliliters of blood were withdrawn from 110 RA patients (95 females and 15 males) with a range age of 36–65 years, and 40 healthy controls (28 females and 12 males) matched in age and sex to the patients. Furthermore, the samples were placed in the gel tubes. After that, they were spun in a centrifuge at 3000 rpm for 10 minutes, then separated and transfered to 0.5 ml Eppendorf tubes, which were subsequently frozen at -20 °C for further analysis. The study was conducted in Baghdad Teaching Hospital/Medical City between September 15, 2022, and March 25, 2023. Diagnosis, treatment, and follow-up of all patients were performed in this clinic and young individuals, or individuals with a history of disability, psychological and mental diseases, malignant tumors, autoimmune diseases were excluded from the study. The patients were divided into three subgroups : (1) biological treatment subgroup (consisted of thirty-eight patients on the bDMARDs treatment), (2) conventional cDMARD subgroup (thirty -eight patients received MTX) and (3) combined DMARD subgroup (thirty –four patients had received biology and chemotherapy). The human ACPAs were determined by using Sandwich ELISA (Biorad, Germany) from the SunLong Biotech kit (China). LDH levels were determined using a commercial kit (BIOLAB) that was measured by a spectrophotometer (BIOLAB instrument). The conversion of NADH to NAD+ results in a decrease in absorbance. LDH activity in the specimen is directly proportional to the wavelength of 340 nm. Whereas the determination of Zn utilized the direct colorimetric test without deproteinizing the sample by using a commercial kit (LTA, Italy), and copper concentrations were determined using a commercial kit (LTA, Italy), which was measured by a spectrophotometer (CECELL 3000).

Ethical Considerations

Ethical approval was obtained from the University of Technology ethical committee for this study. In addition, Verbal consent was obtained from all participants prior to their involvement.

Statistical Analysis

The data was analyzed using SPSS-V26, with parametric data provided as means ± standard error.

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Age, gender, and differences between patients and control were compared using independent samples T test. Serum ACPAs, LDH, Zn, and Cu levels were compared between RA patients and healthy control.

Results

In this study, 110 RA patients (95 female and 15 % male,) were compared to 40 healthy controls. Patients ranged in age from 50 to 59 years old on average. Female gender outnumbered male gender (5:1) as shown in Table 1

Table 1. Showed demographic characteristics of patients.

Characteristics	Patients n=110
	Mean (min-max)
Age (years)	51 (36-75)
Male	15 (13.7%)
Female	95 (86.36%)
	Treatment
Biology	38 (34.5%)
Chemotherapy	38 (34.5%)
Biochemotherapy	34 (30.9%)

The mean ± SE of ACPA in healthy control and RA patients were 19.98 ± 3.29ng/mL and51.05 ± 5.613ng/mL respectively, as showed in Table. 2

Table 2. Levels of ACPA in sera of healthy control and RA patients.

Parameter	Healthy control Mean ±SE	Patients Mean ±SE	P-value
ACPAs (ng/mL)	19.98±3.29	51.05±5.613	0.0001**

Statistical analysis of ACPAs levels distributed among RA patients' subgroup and healthy control groups by ANOVA. The mean±SE of ACPA in biology 57.11±4.56 ng/mL more than chemotherapy and biochemotherpy (49.76±5.48, 46.27±3.18) ng/mL respectively when compared with healthy controls (19.98±3.29) ng/mL, as shown in Table 3

Table 3. Serum Human ACPAs Levels in RA subgroup Patients and apparently healthy control.

ACPAs (ng/mL)			
Healthy control Mean ± SE	**Biology Mean ±SE**	**Chemotherapy Mean ±SE**	**Biochemotherapy Mean ±SE**
19.98 ±3.29	57.11± 4.56	49.76± 5.48	46.27± 3.18

Table.4 reveals that there were highly significant variations in ACPA levels through RA subgroup patients (biology, chemotherapy, and biochemotherpy) as compared to healthy control (P ≤ 0.0001). Multiple comparison showed there was no significant difference between subgroups with each other.

Table 4. Multiple comparisons of ACPA levels between patients' subgroups and healthy control.

Parameters	Group treatments	*p*-value
ACPAs (ng/mL)	HC vs. Biology	0.0001**
	HC vs. Chemotherapy	0.0001**
	HC vs. Bio-chemotherapy	0.0001**
	Biology vs. Chemotherapy	0.2
	Biology vs. Biochemotherapy	0.2
	Chemotherapy vs. Biochemotherapy	0.4

** Highly Significant at P ≤ 0.001
ACPAs: anticitrulinated peptide Antibodies, HC: healthy control, P-value: probability value, ng/mL: Nanograms per milliliter

Results in the current study demonstrated that the levels of LDH in RA subgroup biology are [106.0 ±7.87IU/L, chemotherpy137.8 ±11.65IU/L, biochemotherpy 154.5 ±3.82IU/L and healthy control 100.5 ± 12.71] as shown in Table 5

Table 5. Serum Human LDH Levels in Patients and healthy.

LDH (IU/L)			
Healthy control Mean ± SE	**Biology Mean ±SE**	**Chemotherapy Mean ±SE**	**Biochemotherapy Mean ± SE**
100.5±12 .71	106.0±7. 87	137.8±11.65	154.5±3.82

LDH: lactate dehydrogenase, IU/International units

Results in Table 6 showed a significant increase in the serum levels of LDH in chemotherapy and biochemotherpy subgroup patients of RA compared to healthy controls, while there was no significant difference between biology subgroupas compared to healthy control (p = 0.96). Whereas multiple comparisons of subgroups with each other showed a significant decrease in biology subgroup as compared to the chemotherapy subgroup and biochemotherapy subgroup. Moreover, there is no significant difference between the chemotherapy subgroup compared to biochemotherapy subgroup.

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Table 6. Multiple Comparisons for LDH in studied Group treatments.

Parameters	Group treatments	p-value
LDH (IU/L)	HC vs. Biology	0.96
	HC vs. Chemotherapy	0.02*
	HC vs. Bio-chemotherapy	0.0004**
	Biology vs. Chemotherapy	0.08*
	Biology vs. Biochemotherapy	0.002**
	Chemotherapy vs. Biochemotherapy	0.59

* Significant at P ≤ 0.05
** Highly Significant at P ≤ 0.01
LDH:Lactate dehydrogenase ,HC: healthy control , IU/international units per Liter

Results demonstrated that the levels of Zinc in RA subgroup [biology 103.4 ± 6.22 µg/dl, chemotherapy110.4 ± 7.04 µg/dl and biochemotherpy 109.1 ± 7.78 µg/dl] higher than zinc level in the HC group 82.35 ± 7.74 by AONVA as investigate in Table 7

Table 7. Serum Human Zinc Levels in Patients and healthy.

Zinc (µg/dL)			
Healthy control Mean ± SE	**Biology Mean ±SE**	**Chemotherapy Mean ±SE**	**Biochemotherapy Mean ± SE**
82.35 ± 7.74	103.4 ± 6.22	110.4 ± 7.04	109.1 ± 7.78

Microgram per deciliter (µg/dl), healthy control (HC)

Results showed a significant increase in level of zinc in biology subgroup and a highly significant increase of chemotherapy and biochemotherpy as compared to healthy control. Multiple comparisons revealed that were no significant difference between subgroup with each other are revealed in Table 8

Table 8. Multiple Comparisons for Zinc in RA patients' subgroup and healthy control

Parameters	Group treatments	p-value
Zinc (µg/dl)	HC vs. Biology	0.011*
	HC vs. Chemotherapy	0.001**
	HC vs. Bio-chemotherapy	0.005**
	Biology vs. Chemotherapy	0.45
	Biology vs. Biochemotherapy	0.56
	Chemotherapy vs. Biochemotherapy	0.12

* Significant at P ≤ 0.05
** Highly Significant at P ≤ 0.01
Microgram per deciliter (µg/dl), healthy control (HC)

The results demonstrated that the levels of Cu in RA subgroup were [biology 251.5 ± 7.14 µg/dl, chemotherpy 251.0 ± 10.75 µg/dl and biochemotherpy 265.6 ± 8.57 µg/dl] higher than Cu level in the healthy control group 93.84 ± 3.19 µg/dl as shown in Table 9

Table 9. Serum Human Cu Levels in Patients and apparently healthy control.

Copper (µg/dL)			
Healthy control Mean ± SE	**Biology Mean ±SE**	**Chemotherapy Mean ±SE**	**Biochemotherapy Mean ± SE**
93.84 ± 3.19	251.5 ± 7.14	251.0 ± 10.75	265.6 ± 8.57

Copper: (Cu), microgram per deciliter (µg/dl), healthy control (HC)

Results revealed that there was a highly significant increase in levels of Cu through all RA subgroup patients as compared to healthy control (P ≤ 0.0001). Multiple comparison showed there was no significant difference between subgroups with each other's as showed in Table 10

Table 10 . Multiple Comparisons for Copper in RA patients' subgroup and healthy control

Parameters	Group treatments	p-value
Copper (µg/dl)	HC vs. Biology	0.0001**
	HC vs. Chemotherapy	0.0001**
	HC vs. Bio-chemotherapy	0.0001**
	Biology vs. Chemotherapy	0.98
	Biology vs. Biochemotherapy	0.76
	Chemotherapy vs. Biochemotherapy	0.73

** Highly Significant at P ≤ 0.01
Copper: (Cu), microgram per deciliter (µg/dl), healthy control (HC)

In RA, Pearson's correlation was utilized to examine the possible correlation between ACPA and (LDH, Zn and Cu). Results showed a significant positive correlation between ACPA and LDH (R = 0.624, P = 0.001) in the biology subgroup, whereas no significant correlation between ACPA with other parameters in different subgroups of RA patients as shown in Table 11

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Table 11. The Correlation between ACPAs (ng/ml) and other Parameters in in studied Group treatments

	ACPAs (ng/ml)					
Parameters	**Biology**		**Chemotherapy**		**Biochemotherapy**	
	R	P-value	R	P-value	R	P-value
Cu	-0.116	0.18	0.102	0.65	-0.125	0.57
Zn	-0.294	0.60	0.060	0.79	-0.004	0.98
LDH	0.623**	0.0019**	-0.013	0.95	0.041	0.85

** Highly Significant at P ≤ 0.01
Copper: (Cu), Zinc (Zn), Lactate dehydrogenase (LDH)

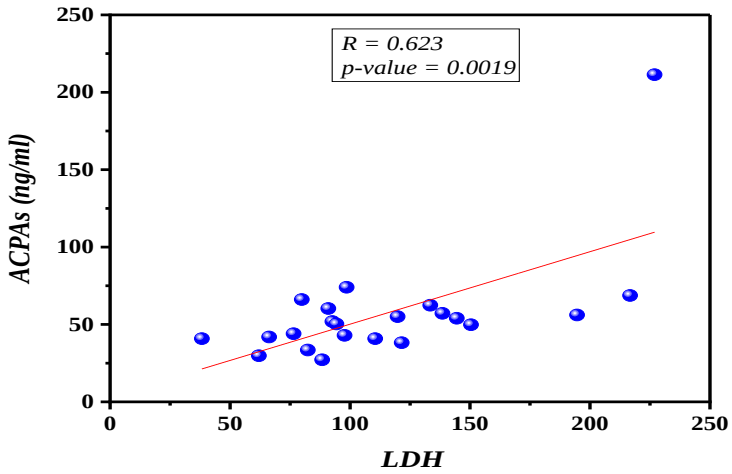

Figure 1. Plot displays ACPA-LDH correlation in RA biology subgroup

Discussion

Results of the current study demonstrated a highly significant increase in levels of ACPA in RA patients. A great percentage of RA patients produce ACPA as a result of early RA's lack of tolerance and the increase of the anti-citrullinated antibody response, which is significantly associated with the development of arthritis [17, 18]. Additional studies have found that anticitrullinated peptide antibodies are linked to Human Leukocyte Antigen – DR isotype (HLA-DR) shared epitope status [19]. The current study's findings are consistent with data from other research studies conducted throughout the world which show that the primary target of ACPA in the pre-clinical phase of RA is osteoclast precursor and osteoclast cells located in bone marrow. Furthermore, ACPA can cause bone destruction by inducing proinflammatory cytokines such as (IL-1, IL-12), which spread to the joint and cause inflammation of the synovial[20]. Moreover, the study found that is no significant difference in patients receiving only chemotherapy or biological treatment, or combined biological with chemotherapy treatment. This is consistent with previous research reported that individual reach RA diagnosis; the ACPA repertoire remains relatively stable over time with small changes in ACPA levels and only occasional seroconversion[21]. The main reason is that ACPA-positive B cells undergo multiple cycles of germinal center reaction, thus accumulating cell mutations and carrying out homotypic transformation. The citrulline-specific immune response can produce long-lived plasma cells and a stable titer of ACPAs[22]. In addition, the ACPA reactivity level significantly decline in beginning use of DMARD treatment (during the first three month), and then remains stable[23]. Furthermore, the ACPA subtypes differ depending on the different antigens and antibody isotypes. Targeted therapy can only target some of them, which is a limitation of targeted biology therapy[24]. In addition, the lack of consciousness about rheumatic disease among Iraqis, a lack of training among Iraqi health care professionals, and it ought to be added that patients have very limited access to biology treatment, which is provided only by the national Ministry of Health[25]. Niitsue *et al.* [26] reported that elevated LDH levels were roughly 97% of RA patients that treated by MTX. In normal inflammation, CD8+ T

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lymphocytes (CD8) can release proinflammatory cytokines such as (IL-1, IL-12) and cellular breakdown mediators. In RA, CD8 activity is dependent on LDH activity, and B cell activation is similarly impacted by LDH activity, the FX11 inhibitor (Lactate Dehydrogenase Inhibitor) and LDHA inhibitor, GSK2837808A, have been shown to reduce the inflammatory potential of CD8+ and B lymphocytes by inhibiting LDH [27].The data of the present study revealed an increase in the level of zinc in RA due to the fact that zinc is a necessary element and dietary supplement that has been shown to lower the incidence in rheumatoid arthritis sufferers, so zinc is required for the down regulation of inflammatory responses. In addition, zinc supplements in combination with MTX prevent damage of intestinal and protect enterocyte cell proliferation during RA treatment[28]. Moreover, Serum Cu and Zn levels increase in RA patients due to antagonistic relationship between copper and zinc, with overdoses reducing copper absorption [29], for these reasons mentioned above, patients are provided with zinc during treatment. Nonetheless, our findings were consistent with other studies by Dhiaj ***et al.,*** [30]. The results in our study demonstrated that the levels of Cu in the RA subgroup increase compared to healthy controls because, during rheumatoid arthritis inflammation, biomarkers cytokines such as interleukin-1 (IL-1) regulate the secretion of ceruloplasmin in liver cells, content of copper in the blood increases as ceruloplasmin is transported from the liver cell to the serum [31,32]. In addition, the results showed a significant positive correlation between ACPA and LDH in biology subgroup, indicating that the fact that sodium lactate can cause CD4+ T helper cells to change into the Th17 subset and that ACPA-producing B cells play a role in the inflammatory process of RA suggests that lactic acid (LA) may indirectly contribute to the proinflammatory process of ACPA production [27.] In addition , the biology drug mechanism that genetically engineered monoclonal antibodies and receptor constructs were specifically designed to target extracellular mediators of inflammation with high specificity and do not have the capability of crossing the plasma membrane of a cell[33]. Moreover, monocarboxylate transporter(MCTs) are important transporters that are crucial for the intracellular production and transmembrane transport of LA. The transfer of LA into or out of cells by MCT1 depends on the metabolic status of cells[34] These findings are consistent with a recent study by Cunningham ***et al.,*** **which** found that patients with ACPA-positive RA have a larger clinical therapeutic impact than patients with ACPA-negative RA [35,36]. The study had limitations, including limited sample size for direct comparison of RA subgroup, single-center open-labeled design without double-blinding, potential information bias from physicians. Larger, longer-term studies with objective outcome measures are needed to confirm findings.

Conclusion

Most RA patients produce ACPA, and treatment doesn't affect ACPA levels. LDH levels increase with severity of RA. Zinc and copper are essential trace elements for metabolism and immune function. Zinc supports healthy cartilage growth and immune response, while copper ions increase joint inflammation. DMARD or b DMARD therapy choice depends on patient's comorbidities and contraindications.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration’s approval.
- No animal studies are present in the manuscript.

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- No potentially identified images or data are present in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Technology.

Authors' Contributions

M. H. M participated in specifying the title of the research and also diagnosed patients according to disease-specific criteria of this study. A. M. participated in specifying the title of the research and studying the variation of parameters and their relationship with disease. F. Q. collected specimens, prepared the samples to work, determined levels of all parameters using many approaches in many devices, and conducted a statistical study for research.

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ارتباط الأجسام المضادة للببتيد المضاد للسيترولينات والانزيم المزيل للفوسفات القاعدي المرضى المصابين بألتهاب المفاصل الرثوي

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الخلاصة

المفاصل الروماتويدي (RA) هو مرض مناعي ذاتي جهازي مزمن يرتبط بتكاثر الأنسجة الزليلية وتكوين السبل. كان الغرض من هذه الدراسة هو تحديد العلاقة بين هذه العوامل ومستويات الأجسام المضادة للببتيد المضاد للسيترولين(ACPA) ، والانزيم النازع لهيدروجين اللاكتات (LDH) ، والزنك (Zn) ، والنحاس (Cu) في مرضى التهاب المفاصل الروماتويدي .(RA) أجريت الدراسة في مستشفى بغداد التعليمي في بغداد، العراق، وشارك فيها 110 مريضاً (95 أنثى و15 رجلاً)، الذين تمت مطابقتهم من حيث العمر والجنس مع 40 من الاشخاص الاصحاء(28 أنثى و12 ذكراً). تم تشخيص المرضى الذين يعانون من التهاب المفاصل الروماتويدي من قبل مجوعة اطباء الروماتيزم المتخصص باستخدام معايير ACR/EULAR في عام 2010. وفقًا لنوع العلاج المضاد للروماتيزم المُعدل للمرض المستخدم - البيولوجي(bDMARDs) ، التقليدي(cDMARDs) ، والمختلط - (DMARDs) .تم تقسيم المرضى في هذه الدراسة إلى ثلاث مجموعات فرعية. تم قياس كمية الزنك والنحاس و LDHباستخدام مقياس الطيف الضوئي(AAS) ، في حين تم تقييم مصل ACPA باستخدام مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA) أظهرت النتائج وجود ارتفاع ملحوظ في جميع المجموعات الفرعية لـ ACPAs ($p<0.001$)، الزنك($p<0.001$) ، والنحاس ($p<0.001$) بالمقارنة مع مجموعة الاشخاص الاصحاء ، ولكن لا توجد فروق ذات دلالة إحصائية بين المجموعات الفرعية. زادت مستويات LDH بشكل ملحوظ في المجموعات الفرعية للعلاج الكيميائي والعلاج الكيميائي الحيوي بالمقارنة مع الأصحاء، ولكن مستويات LDH انخفضت بشكل ملحوظ في المجموعة الفرعية للبيولوجيا بالمقارنة مع المجموعات الفرعية للعلاج الكيميائي والعلاج الكيميائي الحيوي. ليس لتغيير أنواع العلاج أي تأثير على رفع مستوياتACPA ، والزنك، والنحاس، إلا أنه له تأثير على مستويات LDH لم تظهر المجموعة الفرعية للبيولوجيا أي فرق كبير بين المرضى والاشخاص الاصحاء.

الكلمات المفتاحية: الأجسام المضادة الببتيدية المضادة للسيترولين، المناعة الذاتية ،النحاس، الانزيم النازع لهيدروجين اللاكتات، التهاب المفاصل الروماتويدي (RA)،التهاب الغشاء المفصلي، الزنك.