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ORIGINAL A R T I C L E

Some Trace Elements and Oxidative Stress Status in Patients with Chronic Rheumatoid Arthritis

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Abstract

Background Rheumatoid arthritis (R.A.) is a complex polygenic, autoimmune inflammatory disease. It was disturbing that almost 1-2% of people depended on that geographic spreading worldwide. R.A. can result from the interaction of genetic, environmental, and autoimmunity. It is characterized by non-organ-specific self-reactive antibody production and chronic synovitis leading to the damage of cartilage and bone.
Objectives To evaluate the sera of trace elements and oxidative stress levels in patients detected with chronic rheumatoid arthritis.
Determination of some trace elements such as copper, zinc, and iron in the sera of patients.
Patients and Method A case-control study was done on the Iraqi population from Al-Najaf, an Iraqi city. Blood samples were collected from 135 volunteers from September 2021 to February 2022 from Al-Sadder Medical City (Al-Najaf). The 180 volunteers in our study were divided into two groups patient group consisting of 90 individuals ages range: (20–70 years), male and female, and a control group consisting of 45 individuals. Blood was drawn from the patients to measure the copper, zinc, and iron concentration level using the Colorimetric method technique.
Results The average zinc concentration was lower in the patient's group than in the reference category. The average copper concentration was more significant in the patient's group than in the reference category. In addition, the average Zn/Cu ratio was lower in the patient's group compared to the reference category. There was no statistical variation in average serum iron between patients and the reference category. However, the average Zn/Fe ratio was lower in the patient's group compared to the reference category control group.
Conclusion Lower levels of zinc and a higher level of copper suggest a role for those trace elements on that pathogen of R.A.

Keywords: Rheumatoid arthritis; Copper; Zinc; Iron

1 Introduction

Rheumatoid arthritis (R.A.) is an autoimmune illness that was artificial via hereditary, epigenetic, and environmental variables. Novel gene variants related to disease susceptibility and distinct disease stages have received much interest in recent years [1]. Rheumatic diseases are the best-shared illnesses all over the world. They induce aches, practical weakening, and work incapacity, and they have an impact on individuals [2]. It characterizes a chronic inflammatory illness that primarily affects joints but may harm extra-articular structures like the skin, eyes, heart, lungs, digestive system, neurologic system, and vascular systems [3]. The condition affects around 1% of people and occurs two to three times more in females than in males; R.A.

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is often considered an autoimmune disease because of the expression of some distinctive autoantibodies [4].
The disease activity is the target for R.A. The various disease activity indices that have been developed typically only take a few clinical or laboratory parameters into account. In many cases, a sample of joints (such as 28 or 44 joints) is sufficient to determine the severity of the disease [5]. In addition to physical impairment, productivity, and everyday tasks may also impact emotional well-being in general [6]. Autoantibodies similar to rheumatoid factor (R.F.) and antibodies against the cyclic citrullinated peptide (anti-CCP) are created via B-lymphocytes. Patients with R.A. are heterogeneous, indicating that many pathophysiological pathways may be involved in the onset and course of the disease, according to differences in anti-CCP and R.F. expression, percentage of illness appearance, and changeability of reaction to the medication. Only some of the characteristics of R.A. can be attributed to genetic heterogeneity [7].
Trace elements (T.E.s) play critical roles in various vital bodily functions, including nerve conduction, the release of hormones and enzymes, muscular contraction, structural support, and mineral balance maintenance [8].
Due to several T.E.s being co-factors in metabolic methods affecting collagen with bone construction or immune system purposes, the significance of T.E.s in R.A. was of great concentration. Active R.A. is associated with elevated levels of the cytokines interleukin-1(IL-1) and tumor necrosis factor-α (TNF-α) within IL-6, which may impact the bioavailability of that T.E.s via stimulating the change of metal-binding proteins at the liver or the intestine. The increased synthesis of metallothionein may affect the sequestration of the metal ions to prevent their circulation in the blood. The antioxidant enzymes contain many of these T.E.s. R.A. has been linked to the increased formation of that free radical (F.R.s) in inflammatory joints with impairment of this antioxidant system [9].
According to research using different T.E.s to lessen pain and promote joint mobility, trace elements can be involved at the start, development, and cure of the illness [10]. Most enzymes require trace elements as cofactors, and these deficiencies have a variety of detrimental impacts on human health. The inflammatory response in R.A. may contribute to the homeostatic changes in the metabolism of trace elements. Regulating the blood concentrations and association of zinc, copper, and Iron in R.A. patients and healthy controls was the target of the current investigation [11].
Lower zinc and higher copper levels correlate with active disease [12]. It was reported that increased IL-1 levels in patients could increase metallothionein levels, which may chelate circulating zinc [13]. moreover, zinc-containing proteins accumulate in the liver and inflamed joints, reducing plasma zinc levels in patients [14]. Patients supplemented with zinc showed improved laboratory and clinical parameters for R.A. [15]. zinc has a bone-forming effect and reduces osteoclast activity [16]. Thus, zinc deficiency may play an essential role in the inflammatory process of R.A. Increased levels of copper are present in the serum of patients with R.A. Copper levels rise due to the increased synthesis of ceruloplasmin by the liver [14].
Copper (Cu) and zinc (Zn) are essential trace elements that act as ion co-factors in proteins, hormones, and receptors and also as co-factors in numerous enzymatic reactions [17]. They are structural ions of S.O.D. [18] and reduce O.S. by induction of metallothionein synthesis [19, 20]. Because of their pivotal role in the redox mechanisms, their imbalanced status may increase the susceptibility to oxidative damage [21–23]. While acute Zn deficiency causes a decrease in innate and adaptive immunity, a chronic deficiency increases inflammation [24]. On the other hand, excess Cu is probably associated with an inflammatory response, although it is not clear whether copper has prooxidant or antioxidant effects. This is because ceruloplasmin, the main copper-containing protein, has acted as an antioxidant and prooxidant in different conditions [25].

2 Material and method

The 135 volunteers, including (90) patients group ages range (20-70 years) male and female and (45) control group, were in this case-control study. All of them attended the isolation wards at Al-Sadder Medical City on the Iraqi population from Al-Najaf- Iraq, from April 2021 to February 2022.The. Blood was drawn from the patients to measure the copper, zinc, and iron concentration level using the Colorimetric method technique. For trace elements such as copper, a measurement method is Colorimetric Test with Dibrom-PAESA, Company is the Egyptian Company for Biotechnology (S.A.E.). Obour city industrial area. Block 20008 piece 19 A. Cairo. Egypt.
Another trace element is zinc; a measurement method is Colorimetric Test; Company is SPINREACT, S.A./S.A.U. Ctra.Santa Coloma, 7 E-17176 SANT ESTEVE DE BAS (GI) SPAIN. Furthermore, another trace element is iron; a measurement method is Colorimetric Test, made in France.

2.1 Inclusion Criteria

All patients who were previously or newly diagnosed by physicians as having autoimmune rheumatoid arthritis were included in the current study. All patients diagnosed by a rheumatologist according to 2010 ACR/EULAR Criteria and get > or =6 score of this criterion, age between 20 – 70 years.

2.2 Exclusion Criteria

- Non-autoimmune rheumatoid arthritis.
- Patients with other autoimmune diseases such as renal failure, S.L.E., and Celiac disease.
- Nonrheumatic disorders include acute or chronic hepatic, cardiovascular, cerebrovascular, and benign and malignant diseases.
- Pregnant females or females who are on contraceptive pills.

3 Statistical analysis

Information was composed, shortened, investigated, and obtainable via statistical platform used for societal sciences (SPSS) variety 23 and Microsoft Office Excel 2010. Qualitative (categorical) variables were stated for example sum and ratio, while, quantitative (numeric) variables were primarily calculated and used for regularity delivery via the Kolmogorov-Smirnov test, and then consequently typically spread numeric variables were stated such as mean (an index of central tendency) and standard deviation (an index of dispersion). The next statistical test was used:

1. **The chi-square test** was used to calculate the relationship among some 2 definite variables providing fewer than 20 percent to the cell has an estimated total of fewer than 5.
2. **Independent samples t-test** was used to calculate that change in the mean of numeric variables among some 2 categories providing that this variable was typically spread.
3. **Spearman correlation** that use to calculate the relationship among some 2 numeric variables and that effect was uttered such as relationship coefficient (r) and that level of significance (P). The significance levels were measured at a P- the value of like or fewer than 0.05. The levels of great significance were measured at a P- the value of like or fewer than 0.01.

4 Result

4.1 Clinical Demographic Features of reference and disease subjects

A comparison of inflammatory markers among reference and disease subjects is presented in Table 1. Patients with positive C-reactive protein (C.R.P.) accounted for 34 (37.8 %), whereas, none of the control subjects had positive C.R.P. and that variation was statistically significant ($p < 0.001$). In addition, patients with positive rheumatoid factor (R.F.) accounted for 39 (43.3 %), whereas, none of the control subjects had positive R.F. and that variant was statistically significant ($p < 0.001$). Moreover, the average erythrocyte sedimentation rate (E.S.R.) in the patient's group was higher significantly than that of the reference category, 48.31 ±16.96 mm/hr versus 9.42 ±4.55 mm/hr, respectively (p < 0.001).

Table 1: Comparison of inflammatory markers among reference and disease subjects.

Characteristic	Patients $n = 90$	Control $n = 45$	P
C.R.P.			
Positive n (%)	34 (37.8 %)	0 (0.0 %)	< 0.001 C ***
Negative n (%)	56 (62.2 %)	45 (100.0 %)	
Rheumatoid factor			
Positive n (%)	39 (43.3 %)	0 (0.0 %)	< 0.001 C ***
Negative n (%)	51 (56.7 %)	45 (100.0 %)	
E.S.R. (mm/Hr)			
Average ±SD	48.31 ±16.96	9.42 ±4.55	< 0.001 I***
Range	19 -95	2 -22	

4.2 Contrast of levels of trace elements among reference and disease subjects

A comparison of trace elements among reference and disease subjects is presented in Table 2. Average zinc concentration was statistically lower in the disease group in comparison with the reference category, 119.44 ±29.70 μg/dl versus 140.38 ±26.45 μg/dl, respectively (p < 0.001). On the other hand, the average copper concentration was statistically greater in the disease group in comparison with the reference category, 116.63 ±28.32 μg/dl versus 102.40 ±26.56 μg/dl, respectively ($p = 0.006$). In addition, the average Zn/Cu ratio was statistically lower in the disease group compared with the reference category, 1.09 ±0.40 versus 1.45 ±0.38, respectively ($p < 0.001$). There was no statistical variation in average serum iron among the reference and disease groups ($p = 0.511$). However, the average Zn/Fe ratio was lower in the disease group compared with the reference category, 1.22 ±0.39 versus 1.40 ±0.38, respectively ($p = 0.012$).

Table 2: Comparison of trace elements among reference and disease subjects.

Characteristic	Patients $n = 90$	Control $n = 45$	P
Zinc (μg/dl)			
Average ±SD	119.44 ±29.70	140.38 ±26.45	< 0.001 I***
Range	65 -198	85 -192	
Copper (μg/dl)			
Average ±SD	116.63 ±28.32	102.40 ±26.56	< 0.001 I **
Range	64 -172	49 -155	
Zn/Cu ratio			
Average ±SD	1.09 ±0.40	1.45 ±0.38	< 0.001 I***
Range	0.41 -2.23	0.77 -2.45	
Iron (μg/dl)			
Average ±SD	102.42 ±24.34	105.56 ±29.20	< 0.511 I NS
Range	51 -162	66 -155	
Zn/Fe ratio			
Average ±SD	1.22 ±0.39	1.40 ±0.38	< 0.012 I *
Range	0.52 -2.92	0.8 -2.39	

4.3 Correlation of severity of disease to markers of trace elements

The correlation of disease severity to markers of trace elements in diseased individuals is presented in Table 3. It was negatively and significantly correlated to zinc and zinc/copper ratio ($p < 0.001$), but positively and significantly correlated to serum copper ($p < 0.001$).

Table 3: Correlation of severity of disease to markers of trace elements in diseased individuals.

Characteristic	Severity of disease	
	r	P
Zinc	-0.468	<0.001 ***
Copper	0.379	<0.001 ***
Zn/Cu ratio	-0.633	<0.001 ***
Iron	-0.126	0.235
Zn/Fe ratio	-0.197	0.063

5 Discussion

5.1 Clinical demographic markers of inflammation among reference and disease subjects

In this research, positive C-reactive protein (C.R.P.) accounted for 34 (37.8 %). A surplus of pro-inflammatory cytokine found in that R.A. synovium boosts the liver's synthesis of C.R.P., making it a favorable choice as a disease activity biomarker [26]. C.R.P. measurement in R.A. is not error-free, though. For instance, truncal obesity in women with R.A. has been independently linked to higher C.R.P. levels, regardless of articular association or biological treatments [27].

In our results, positive rheumatoid factor (R.F.) accounted for 39 (43.3 %). Antibodies targeting the Fc region of immunoglobulin (Ig) G are known as rheumatoid factors. Though IgA and IgG R.F. occur, IgM R.F. is most frequently measured in clinical practice. Up to 80% of people with R.A. have R.F. However, their specificity is limited because they can also develop from a variety of added inflammatory diseases that cause chronic antigenic stimulus. This comprises, then is not restricted to, added rheumatologic disorders (such as systemic lupus erythematosus, Sjogren's syndrome), infective illnesses (such as hepatitis C virus, subacute bacterial endocarditis, Epstein-Barr virus), malignancies (such as B-cell neoplasms), well people, and infectious diseases [28]. Additionally, smoking has been linked to a higher incidence of R.F. [29]. About 30- 45 percent of individuals with early rheumatoid arthritis do not possess R.F.; even though, some of them can have R.F. later in the disease course [30].

In this research, the average erythrocyte sedimentation rate (E.S.R.) in the patient's category was significantly greater than that of the reference category. That level at the erythrocytes pass done plasma while deferred in an upright tube was known as the E.S.R., and it serves as a secondary indicator of the concentrations of the acute-phase reactant (mostly fibrinogen). Red blood cell size, shape, and number, as well as other components of plasma such as immunoglobulins, all have an impact on E.S.R. levels. Increased E.S.R. levels can be brought on by tissue damage, end-stage renal disease, nephrotic syndrome, infection, cancer, local or systemic inflammation, infection, or obesity. Age-

related increases in E.S.R. levels are slightly greater in women than in males. Additionally, various causes may be to blame for falsely low E.S.R. levels, including irregular erythrocyte shape, severe leukocytosis, heart failure, and cachexia. The E.S.R. is not a particular indicator of inflammation, which is not surprising [31].

5.2 Contrast of levels of trace elements among reference and disease subjects

In this research, the average zinc concentration was significantly lower in the disease group compared to the reference category. Consistent with our findings and based on the research of Zoli et al [32], When R.A. patients were related to good controls, blood zinc concentrations were considerably lower and serum copper levels were significantly greater. An acute phase reaction that eliminates zinc (and Iron, but not copper) from the plasma can be brought on by inflammation. Interleukin-1 (IL-1) from macrophages, cortisol from the adrenal gland, and adrenocorticotropic hormone (ACTH) from the pituitary gland are all involved in this reaction. Nitric oxide (NO) production by IL-1 activates Zip14 in the liver, which results in zinc sequestration [33].

In this research project, the average copper concentration was statistically greater in the disease group compared to the reference category. Chakraborty et al [34] 2015 performed research to evaluate serum copper levels in 50 diseased individuals in comparison with control subjects and found that sera levels of copper were significantly higher in the patient's category in comparison within the reference category; therefore we agree with the results of Chakraborty et al [34].

These results are consistent with that of research completed by Xin et al. [35], Strecker et al.[36], and Shatha Rouf Moustafa et al. [37]. For keep its bigger necessity via lysyl oxidase, superoxide dismutase, glycyl histidine complex, etc., copper may have been released from its reserves, primarily the liver [38]. Ceruloplasmin is also claimed to act as an anti-inflammatory agent in and of itself. Ceruloplasmin is an acute-phase protein that is elevated in rheumatoid arthritis [34].

5.3 Correlation of severity of disease to markers of trace elements

Our findings concur with those of Chakraborty et al. [34], who discovered a significant and positive relationship between serum copper and the severity of that disease in R.A. patients. This correlation may be the result of copper being released as of its supplies, mainly the liver, to change the enlarged demand for lysyl oxidase, superoxide dismutase, glycyl histidine complex, and further enzymes [38].

Ceruloplasmin is also claimed to act as an anti-inflammatory agent in and of itself. Ceruloplasmin, an acute-phase protein elevated in rheumatoid arthritis, may have a further function [34].

6 Conclusion

The inflammation is associated with symptoms of Rheumatoid arthritis. The lower level of zinc and a higher level of copper are suggestive of the role of those trace elements in the pathogenesis of R.A.

Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at University of Al-Qadisiyah, Al Diwaniyah, Iraq.

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