
Clinical Correlations Between Cesium, Cobalt, Manganese, Rubidium and Rhenium with the Pathogenesis of Rheumatoid Arthritis

Shatha Rouf Moustafa

Clinical Analysis Department, College of Pharmacy, Hawler Medical University, Havalan City, Erbil, Iraq

Email address:

shatha003@yahoo.com

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Abstract: Background and Objectives: Rheumatoid arthritis is one of the most common inflammatory diseases. Studies indicated that increased oxidative stress or defective antioxidant status with inflammation contribute to the pathogenesis of disease. This study was emphasized that levels of some trace elements altered due to oxidative stress and inflammatory process which are associated with the pathogenesis of rheumatoid arthritis. This study was aimed to assess the serum levels of cesium, cobalt, manganese, rubidium and rhenium in patients group as compared with the control group and investigate the effect of other confounding factors like rheumatoid factor, age, gender and finally estimate the correlation between studied parameters. It was hypothesized that there were an alteration in levels of parameters due to oxidative stress and inflammatory process which are associated with the etiology and pathogenesis of rheumatoid arthritis. Method: This case control study conducted on 56 Iraqi patients of both genders 30 men and 26 women with the average age (40-57) years and 56 of age –gender matched apparently healthy adults were also enrolled in this study as a control group. The patients were free from any diseases except rheumatoid arthritis and this was confirmed by clinical examination and biochemical and hematological tests. Levels of parameters were estimated using atomic absorption spectrophotometers. Results: There were no significant differences between RF positive and negative groups regarding the studied parameters. There were a significant reduction in cesium and rubidium and a significant elevations in cobalt, manganese and rhenium in patients as compared with the control group. There were no significant differences between rheumatoid factor positive and negative groups regarding focused parameters in men and women groups, except for age factor in women group, there were no significant differences between different age categories in rheumatoid factor positive and negative regarding focused parameters. In addition, there was no significant correlation among studied parameters. Conclusion: Levels of parameters were significantly altered in patients group. These alterations proved the possible association with pathogenesis of rheumatoid arthritis. Therefore, the estimation of these parameters could be a useful complementary non-invasive diagnostic tool to determine trace elements status for treatment and diagnosis of disease. These variations are probably responsive to oxidative stress concomitant with inflammation induced by cytokines and resulted from defensive mechanism of patients. Inflammatory mediators affect on trace elements homeostasis in rheumatoid arthritis.

Keywords: Rheumatoid Arthritis, Cesium, Cobalt, Manganese, Rubidium and Rhenium

1. Introduction

1.1. General View

Rheumatoid arthritis (RA) is a chronic, inflammatory and systemic disease of unknown etiology. Although the cause of RA is still unknown, much points towards a multi-factorial etiology such as environmental factors and genetic factors which play a role in the development and progression of the

RA [1].

Inflammation and oxidative stress (OS) have been implicated in the pathogenesis of rheumatoid arthritis [2].

Rheumatoid arthritis is characterized by increased activity of macrophages, which in cooperation with other inflammatory cells infiltrates the synovial tissue. The activated macrophages, monocytes and granulocytes generate reactive oxygen species (ROS) which have been suggested to be mediators of inflammation, together with the pro-

inflammatory cytokines.

It has been suggested that ROS and trace elements (TEs) play a role in the etiology and pathogenesis of rheumatoid arthritis (RA). Deficiencies of TEs in patients with RA occur in response to chronic inflammation.

There is a shift toward oxidant/antioxidant imbalance favor to lipid peroxidation, which could lead to the tissue damage. Elevated free radicals production in inflamed joints and dysfunction of antioxidant system have been implicated in RA [3]. Many of these TEs are incorporated into antioxidant enzymes.

The increased levels of inflammatory mediators like cytokines such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α) and IL-6 are associated with active RA which may affect the bioavailability of these TEs by stimulation the production of metal-binding proteins in the liver or intestine. The increased production of metallothionein may affect the level of metal ions so that they are deficient in blood circulation.

Physiological concentration of ROS may be beneficial in process such as intracellular signaling and defense against micro-organisms. Nevertheless, higher amounts of ROS play a role in the aging process as well as in a number of human diseases including inflammatory state, rheumatoid arthritis, cancer, failure in immunity and endocrine functions.

However, many studies showed that there was an association between TEs status with RA.

Trace elements are enrolled in many important processes associated to health, structural support, contraction of muscle, enzyme / hormones release nerve conduction, and maintenance of mineral balance in human body [4].

The importance of the TEs in RA is of great interest because many of these TEs are co-factors in metabolic processes involving collagen and bone structure, articular tissues or immune system functions [5].

Trace elements may play a role in the initiation, progression and curing of the disease as investigated by supplying different TEs to decrease pain and increase joint mobility [6].

1.2. Cesium (Cs)

Caesium is known as cesium in the USA. Cesium is one of the most alkaline elements and raises the pH of the body's cells.

This metal is characterized by a spectrum containing two bright lines in the blue (accounting for its name). It is silvery gold, soft, and ductile. It is the most electropositive and most alkaline element. It is liquid at or around room temperature which reacts explosively with cold water, and reacts with ice above -116°C. Cesium hydroxide is a strong base and attacks glass.

Maintaining proper body tissue pH is critical for staying healthy. Alkaline tissue holds 20 times more oxygen than does acidic tissue and this oxygen rich environment is critical for supporting health.

Cesium has been found to be capable of significantly raising the pH of malignant cancer cells to the point of the cells dying off—usually within days without harming normal cells.

Cesium not only kills cancer (even in stage 4 patients), but also relieves pain by neutralizing the lactic acid that cancer makes from fermenting sugar for energy. The cells that die are absorbed and eliminated by the body.

Cesium salts may be useful in the treatment of manic-depressives. It is used to supports the body's immune system and regulates cardiac rhythm.

1.3. Cobalt (Co)

Cobalt is valuable in cases of headaches, migraines, vasomotor disorders, vertigo and tinnitus. This is due to the sympathicolytic effect that Co exerts on vascular receptors. Cobalt has a regulating influence on stomach and bowel receptors Cobalt, and other heavy metals are essential TEs, but they are toxic when their concentrations are relatively high. Possible mechanisms of action of these metals might include denaturation of protein, inhibition of enzymes, or increased susceptibility to infection due to immunosuppression. Metal exposure may occur also by contamination of food and drinking water.

Several researchers have reported that the ingestion of one or more heavy elements may be important in the etiology of some rheumatic diseases like RA.

Cobalt is required as a constituent of vitamin B12 and its metabolism is the same as for vitamin B12, Co is also a cofactor of enzymes involved in amino acid metabolism and DNA biosynthesis [7]. It acts as a co-factor in antioxidant therapy for the enzyme catalase. It is essential for the growth and development of healthy nervous system.

Deficiencies are reflected in abnormal bone development [8]. It is also necessary co-factor for making the thyroid hormone and deficiency lead to slow growth and development conditions [8], 30% of the population are deficient in Co and could benefit from Co supplementation.

Because of its low retention rate, Co toxicity is rare, but an excess can lead to enlargement of the thyroid gland.

1.4. Manganese (Mn)

Manganese is one of TEs that are necessary for bone health, 36-90% of the population are deficient in Mn and could benefit from Mn supplementation. Manganese deficiency can lead to abnormal bone formation. An excess of Mn affect iron metabolism (poor iron metabolism) [9].

It is an essential part of many enzymes associated with protein and fat metabolism, energy production and bone formation, it is also required for the utilization of vitamin E and vitamin B1, formation of cartilage and synovial fluid of the joints. Manganese is biochemically essential as an enzyme activator [9], synthesis of acid mucopolysaccharides such as chondroitin sulphate which is utilized to form collagen, bone and cartilage, strong fibrous connective material that builds tissue. Manganese is involved in glycoprotein synthesis and it is a co-factor in phosphohydrolases and phosphotransferases involved in the synthesis of proteoglycans in cartilage. Consequently skeletal deformities occurs when the Mn intake is not sufficient [10].

Manganese is important in mental facilities and functions. It aids memory and modulates neurotransmitter activity related to nerve/muscle dysfunction.

Manganese is a part of enzymes involved in urea formation, pyruvate metabolism and the galactotransferase of connective tissue biosynthesis [11].

Carpal Tunnel Syndrome, a painful condition in which arm tendons are weak or damaged, is a sign of manganese deficiency.

Deafness, if due to damage of the cartilage of the ear, can be attributed partially to a deficiency in Mn.

Manganese is stored half in the bones and the remainder in the liver, pancreas, pituitary gland, and the kidneys.

A deficiency of Mn concentration may affect brain health and skeletal and cartilage formation, it is a constituent of metalloenzymes antioxidant enzyme superoxide dismutase which prevents damage by superoxide free radicals [12].

It is used for therapy of RA, allergies, arthritis, fatigue, headache, migraine, inflammation, thyroid disorders, respiratory problems, sinusitis, sinus infection.

1.5. Rhenium (Re)

Rhenium is silvery white element. It is expensive but useful as a trace alloying agent.

¹⁸⁶Re sulphide colloid offers a local, relatively non-invasive therapeutic technique for the treatment of arthritic joint conditions in medium-sized joints such as the hip and ankle, shoulder, elbow and wrist.

1.6. Rubidium (Rb)

Rubidium is a soft, silvery white metallic element. It is used in some laboratory studies and clinical applications. Rubidium stimulates metabolism.

Rubidium chloride is used to induce cells to take up DNA, Rb ions are taken up by cells of living organisms similar to potassium ions to replace potassium that is taken up by animal cells and plant. It has a spectral absorption range, making it a target for laser manipulation of atoms. As a result of variation in the blood brain barrier in brain tumors, brain tumors have a higher concentration of Rb than normal brain tissue, allowing the use of rubidium-82 in nuclear medicine to locate and image brain tumors [13].

Depressed patients show deficient in Rb concentration, so supplementation may be necessary for those patients [14]. It is used in high PH therapy and to decrease tumor growth, muscle pain, multiple sclerosis, tetany, spasmophilia. Depletion of Rb affects minerals (zinc, copper, phosphorus, calcium, magnesium, iron, sodium and potassium) status.

Accordingly, the aim of the present study was undertaken to assess the probable variations in the serum levels of Ce, Co, Mn, Rb and Rh in patients with RA. In addition, to investigate their relationship with other confounding factors RF, age, gender and finally evaluate the correlation coefficient between all studied parameters.

It was hypothesized that there were an alteration in serum profile of interested parameters due to OS concomitant with

inflammatory process which are associated with the etiology and pathogenesis of RA.

2. Patients and Methods

This study was performed to assess the association between the serum level of focused parameters with the pathogenesis of RA. This study was done at Hawler Medical University, College of Pharmacy in period between 2014 and 2015.

2.1. Study Design

This case control study conducted on 56 Iraqi patients of both genders 30 men (16 men with rheumatoid factor positive and 14 men with rheumatoid factor negative) and 26 women (12 women with rheumatoid factor positive and 14 women with rheumatoid factor negative) with the average age (40-57) years, in addition an equal number of apparently healthy adults randomly selected were also participated in this study as a control group. Serum trace elements were determined using Atomic Absorption Spectrophotometer in Baghdad city at Ministry of Science and Technology /Department of Research of Biochemical Science. The protocol of the study was approved by Ethical Committee of College of Pharmacy. Verbal consent was obtained from all subjects before participation.

Samples were collected under the guidance of expert rheumatologist. All reagents and chemicals were of high analytical grade. Exclusion criteria: None of the patients and controls were smokers or consuming alcohol or had any other chronic disease except RA and this is confirmed by clinical examination and laboratory estimations of biochemical and hematological tests.

2.2. Sample Collection

The Protocol of the Study: Ten ml of the fasting blood (overnight for 12–14 hours) samples was collected from the vein of the participants (healthy adults and patients with RA) of both genders without using tourniquet. The blood samples were left for 30 minutes for coagulation purpose, and then centrifuged for 15 minutes at 2500-3500 revolution per minutes (rpm). The sera of the patients were separated and divided into several parts and put them into several plastic plain tubes to do the biochemical tests of the current study.

The sera of the patients were stored at (-80 C °) till the day of the analysis within (1-2 months). The sera samples were prepared for measurement by warming the frozen sera at room temperature.

2.3. Statistical Analysis

The SPSS 18.0 software was used for statistical analysis. Statistical significance was defined as $P < 0.05$.

3. Results

The patient samples were divided into two groups rheumatoid factor (RF) positive and RF negative

groups. The demographic distribution of patients was shown in (Table 1).

Table 1. The demographic distribution of patients group.

Gender	Rheumatoid factor		Total		p		
	Negative	Positive					
Male	14	46.7	16	53.3	30	100	0.592
Female	14	53.8	12	46.2	26	100	
Total	28	50	28	50	56	100	

There were no significant differences between RF positive and negative groups regarding the studied parameters (Table 2).

Accordingly, there was no RF effect on the serum levels of studied parameters.

Table 2. Comparison between RF positive and negative groups regarding the studied parameters.

	RF	N	Mean	±SD	p
Age	Negative	28	49.18	4.78	.027
	Positive	28	46.21	4.95	
Co	Negative	28	.07	.01	.214
	Positive	28	.07	.01	
Mn	Negative	28	.03	.00	.457
	Positive	28	.03	.00	
Ce	Negative	28	23.31	3.68	.981
	Positive	28	23.34	3.75	
Rb	Negative	28	22.78	3.85	.099
	Positive	28	24.38	3.24	
Rh	Negative	28	28.21	5.09	.889
	Positive	28	28.39	4.37	

Table 3. Comparison between patient and control groups regarding studied parameters in RF positive and negative groups.

	Patients group ng/ml	Control group ng/ml	P value
Cs			
RF-	23.3107±3.678	30±4.3	0.001
RF+	23.3350±3.749		
Co			
RF-	0.06596±0.008	0.035±0.001	0.001
RF+	0.06942±0.011		
Mn			
RF-	0.03130±0.004	0.025±0.003	0.001
RF+	0.03042±0.004		
Re			
RF-	28.21±5.087	25±3.47	0.001
RF+	28.39±4.374		
Rb			
RF-	22.7836±3.846	35±2.9	0.001
RF+	24.3764±3.236		

There were significant differences between patient and control groups regarding the studied parameters. There were significant elevations in the serum levels of Co, Mn, Re and Rb in patients group as compared with the control group. Moreover, there were significant reduction in the serum levels of Cs and Rb in patients group as compared with the control group (Table 3).

There were no significant differences between different age categories regarding all studied parameters in RF negative group (Table 4) except for Mn (age= 55+, p=0.005) and Rb (age= 40-44, p=0.044).

Table 4. Comparison between different age categories the regarding studied parameters in RF negative group.

Dependent Variable	(I) Age_Cat	(J) Age_Cat	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Co	40-44	45-49	.003433	.005179	.514	-.00725	.01412
		50-54	-.003036	.004613	.517	-.01256	.00648
		55+	.000433	.005179	.934	-.01025	.01112
		40-44	-.003433	.005179	.514	-.01412	.00725
		50-54	-.006470	.004340	.149	-.01543	.00249
		55+	-.003000	.004938	.549	-.01319	.00719
	50-54	40-44	.003036	.004613	.517	-.00648	.01256
		45-49	.006470	.004340	.149	-.00249	.01543
		55+	.003470	.004340	.432	-.00549	.01243
		40-44	-.000433	.005179	.934	-.01112	.01025
		45-49	.003000	.004938	.549	-.00719	.01319
		50-54	-.003470	.004340	.432	-.01243	.00549
Mn	40-44	45-49	.004600	.002379	.066	-.00032	.00952
		50-54	.003655	.002029	.085	-.00054	.00785
		55+	.007033*	.002278	.005	.00232	.01175
		40-44	-.004600	.002379	.066	-.00952	.00032
		45-49	-.000945	.002029	.646	-.00514	.00325
		55+	.002433	.002278	.297	-.00228	.00715
	50-54	40-44	-.003655	.002029	.085	-.00785	.00054
		45-49	.000945	.002029	.646	-.00325	.00514
		55+	.003379	.001909	.090	-.00057	.00733
		40-44	-.007033*	.002278	.005	-.01175	-.00232
		45-49	-.002433	.002278	.297	-.00715	.00228
		50-54	-.003379	.001909	.090	-.00733	.00057
Ce	40-44	45-49	-2.98400	2.15612	.179	-7.4340	1.4660
		50-54	-2.83945	1.92050	.152	-6.8032	1.1243
		55+	.23433	2.15612	.914	-4.2157	4.6843
	45-49	40-44	2.98400	2.15612	.179	-1.4660	7.4340
		50-54	.14455	1.80713	.937	-3.5852	3.8743

Dependent Variable	(I) Age_Cat	(J) Age_Cat	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval		
						Lower Bound	Upper Bound	
Rb	50-54	55+	3.21833	2.05578	.131	-1.0246	7.4612	
		40-44	2.83945	1.92050	.152	-1.1243	6.8032	
		45-49	-.14455	1.80713	.937	-3.8743	3.5852	
		55+	3.07379	1.80713	.102	-.6559	6.8035	
		40-44	-.23433	2.15612	.914	-4.6843	4.2157	
		45-49	-3.21833	2.05578	.131	-7.4612	1.0246	
	55+	50-54	-3.07379	1.80713	.102	-6.8035	.6559	
		45-49	-4.80967*	2.25786	.044	-9.4697	-.1497	
		40-44	-2.84709	2.01112	.170	-6.9978	1.3037	
		55+	-2.01800	2.25786	.380	-6.6780	2.6420	
		40-44	4.80967*	2.25786	.044	.1497	9.4697	
		45-49	1.96258	1.89240	.310	-1.9431	5.8683	
	40-44	55+	2.79167	2.15278	.207	-1.6515	7.2348	
		40-44	2.84709	2.01112	.170	-1.3037	6.9978	
		45-49	-1.96258	1.89240	.310	-5.8683	1.9431	
		55+	.82909	1.89240	.665	-3.0766	4.7348	
		40-44	2.01800	2.25786	.380	-2.6420	6.6780	
		45-49	-2.79167	2.15278	.207	-7.2348	1.6515	
	Rh	50-54	50-54	-.82909	1.89240	.665	-4.7348	3.0766
			45-49	.933	3.229	.775	-5.73	7.60
			40-44	1.964	2.876	.501	-3.97	7.90
			55+	1.933	3.229	.555	-4.73	8.60
		45-49	40-44	-.933	3.229	.775	-7.60	5.73
			50-54	1.030	2.706	.707	-4.56	6.62
55+			1.000	3.079	.748	-5.35	7.35	
40-44			-1.964	2.876	.501	-7.90	3.97	
55+		50-54	-1.030	2.706	.707	-6.62	4.56	
		55+	-.030	2.706	.991	-5.62	5.56	
		40-44	-1.933	3.229	.555	-8.60	4.73	
		45-49	-1.000	3.079	.748	-7.35	5.35	
40-44	50-54	.030	2.706	.991	-5.56	5.62		

*. The mean difference is significant at the 0.05 level.

There were no significant differences between different age categories regarding the studied parameters. Accordingly, there was no age effect, in RF positive group. (Table 5).

Table 5. Comparison between different age categories the regarding studied parameters in RF positive group.

Dependent Variable	(I) Age_Cat	(J) Age_Cat	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Co	40-44	45-49	.003750	.006774	.585	-.01030	.01780
		50-54	-.000667	.005830	.910	-.01276	.01142
		55+	-.004500	.009033	.623	-.02323	.01423
	45-49	40-44	-.003750	.006774	.585	-.01780	.01030
		50-54	-.004417	.007713	.573	-.02041	.01158
		55+	-.008250	.010348	.434	-.02971	.01321
	50-54	40-44	.000667	.005830	.910	-.01142	.01276
		45-49	.004417	.007713	.573	-.01158	.02041
		55+	-.003833	.009756	.698	-.02407	.01640
	55+	40-44	.004500	.009033	.623	-.01423	.02323
		45-49	.008250	.010348	.434	-.01321	.02971
		50-54	.003833	.009756	.698	-.01640	.02407
Mn	40-44	45-49	-.003071	.002315	.198	-.00787	.00173
		50-54	.001429	.001993	.481	-.00270	.00556
		55+	-.004571	.003087	.153	-.01097	.00183
	45-49	40-44	.003071	.002315	.198	-.00173	.00787
		50-54	.004500	.002636	.102	-.00097	.00997
		55+	-.001500	.003537	.676	-.00883	.00583
	50-54	40-44	-.001429	.001993	.481	-.00556	.00270
		45-49	-.004500	.002636	.102	-.00997	.00097
		55+	-.006000	.003335	.086	-.01292	.00092
	55+	40-44	.004571	.003087	.153	-.00183	.01097
		45-49	.001500	.003537	.676	-.00583	.00883
		50-54	.006000	.003335	.086	-.00092	.01292

Dependent Variable	(I) Age_Cat	(J) Age_Cat	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Ce	40-44	45-49	1.30536	2.12097	.544	-3.0721	5.6828
		50-54	-2.04214	1.65803	.230	-5.4642	1.3799
		55+	1.67786	2.82795	.559	-4.1588	7.5145
	45-49	40-44	-1.30536	2.12097	.544	-5.6828	3.0721
		50-54	-3.34750	2.29090	.157	-8.0757	1.3807
		55+	.37250	3.23983	.909	-6.3142	7.0592
	50-54	40-44	2.04214	1.65803	.230	-1.3799	5.4642
		45-49	3.34750	2.29090	.157	-1.3807	8.0757
		55+	3.72000	2.95754	.221	-2.3841	9.8241
	55+	40-44	-1.67786	2.82795	.559	-7.5145	4.1588
		45-49	-.37250	3.23983	.909	-7.0592	6.3142
		50-54	-3.72000	2.95754	.221	-9.8241	2.3841
Rb	40-44	45-49	-1.79607	1.79779	.328	-5.5065	1.9144
		50-54	-.91357	1.40539	.522	-3.8142	1.9870
		55+	3.46643	2.39705	.161	-1.4808	8.4137
	45-49	40-44	1.79607	1.79779	.328	-1.9144	5.5065
		50-54	.88250	1.94183	.654	-3.1252	4.8902
		55+	5.26250	2.74616	.067	-.4053	10.9303
	50-54	40-44	.91357	1.40539	.522	-1.9870	3.8142
		45-49	-.88250	1.94183	.654	-4.8902	3.1252
		55+	4.38000	2.50689	.093	-.7940	9.5540
	55+	40-44	-3.46643	2.39705	.161	-8.4137	1.4808
		45-49	-5.26250	2.74616	.067	-10.9303	.4053
		50-54	-4.38000	2.50689	.093	-9.5540	.7940
Rh	40-44	45-49	-.143	2.207	.949	-4.70	4.41
		50-54	3.232	1.725	.073	-.33	6.79
		55+	-6.143*	2.942	.048	-12.22	-.07
	45-49	40-44	.143	2.207	.949	-4.41	4.70
		50-54	3.375	2.384	.170	-1.54	8.29
		55+	-6.000	3.371	.088	-12.96	.96
	50-54	40-44	-3.232	1.725	.073	-6.79	.33
		45-49	-3.375	2.384	.170	-8.29	1.54
		55+	-9.375*	3.077	.006	-15.73	-3.02
	55+	40-44	6.143*	2.942	.048	.07	12.22
		45-49	6.000	3.371	.088	-.96	12.96
		50-54	9.375*	3.077	.006	3.02	15.73

*. The mean difference is significant at the 0.05 level.

There were no significant differences between RF positive and negative groups in males group (Table 6).

Table 6. Comparison between RF positive and negative groups in males group.

	RF	N	Mean	SD	p
Age	Negative	14	49.14	4.72	.235
	Positive	16	46.94	5.17	
Co	Negative	14	.07	.01	.538
	Positive	14	.07	.01	
Mn	Negative	14	.03	.00	.610
	Positive	14	.03	.00	
Ce	Negative	14	23.46	3.54	.817
	Positive	16	23.14	3.95	
Rb	Negative	14	23.34	4.07	.381
	Positive	16	24.56	3.41	
Rh	Negative	14	29.64	6.45	.638
	Positive	16	28.63	5.26	

a. Gender = Male

There were no significant differences between RF positive and negative groups in females group (Table 7)

Table 7. Comparison between RF positive and negative groups in females group.

	RF	N	Mean	SD	p
Age	Negative	14	49.21	5.01	.049
	Positive	12	45.25	4.69	
Co	Negative	14	.07	.01	.235
	Positive	12	.07	.01	
Mn	Negative	13	.03	.00	.563
	Positive	12	.03	.00	
Ce	Negative	14	23.16	3.94	.773
	Positive	12	23.60	3.63	
Rb	Negative	14	22.22	3.68	.170
	Positive	12	24.14	3.12	
Rh	Negative	14	26.79	2.78	.264
	Positive	12	28.08	3.00	

There were no significant correlations among the studied parameters in RF negative group, except the correlation between Mn and age (p=0.013,r=-0.472) (Table 8).

Table 8. Correlation coefficient among studied parameters in RF negative group.

		Co	Mn	Ce	Rb	Rh	Age
Co	Pearson Correlation	1	-.085	.024	-.235	.268	.010
	Sig. (2-tailed)		.674	.902	.229	.167	.959
	N	28	28	28	28	28	28
Mn	Pearson Correlation	-.085	1	.084	.099	-.284	-.472*
	Sig. (2-tailed)	.674		.678	.624	.150	.013
	N	28	28	28	28	28	28
Ce	Pearson Correlation	.024	.084	1	.002	-.343	-.038
	Sig. (2-tailed)	.902	.678		.992	.074	.850
	N	28	28	28	28	28	28
Rb	Pearson Correlation	-.235	.099	.002	1	-.155	.141
	Sig. (2-tailed)	.229	.624	.992		.430	.475
	N	28	28	28	28	28	28
Rh	Pearson Correlation	.268	-.284	-.343	-.155	1	-.163
	Sig. (2-tailed)	.167	.150	.074	.430		.407
	N	28	28	28	28	28	28
Age	Pearson Correlation	.010	-.472*	-.038	.141	-.163	1
	Sig. (2-tailed)	.959	.013	.850	.475	.407	
	N	28	28	28	28	28	28

There were no significant correlations among the studied parameters in RF positive group (Table 9).

Table 9. Correlation coefficient among studied parameters in RF positive group.

		Co	Mn	Ce	Rb	Rh	Age
Co	Pearson Correlation	1	.222	-.200	-.019	.079	.018
	Sig. (2-tailed)		.277	.327	.926	.701	.929
	N	28	28	28	28	28	28
Mn	Pearson Correlation	.222	1	-.251	-.082	.163	.100
	Sig. (2-tailed)	.277		.216	.692	.427	.626
	N	28	28	28	28	28	28
Ce	Pearson Correlation	-.200	-.251	1	-.036	-.363	.007
	Sig. (2-tailed)	.327	.216		.857	.057	.973
	N	28	28	28	28	28	28
Rb	Pearson Correlation	-.019	-.082	-.036	1	-.075	-.020
	Sig. (2-tailed)	.926	.692	.857		.706	.920
	N	26	26	28	28	28	28
Rh	Pearson Correlation	.079	.163	-.363	-.075	1	-.002
	Sig. (2-tailed)	.701	.427	.057	.706		.991
	N	28	28	28	28	28	28
Age	Pearson Correlation	.018	.100	.007	-.020	-.002	1
	Sig. (2-tailed)	.929	.626	.973	.920	.991	
	N	28	28	28	28	28	28

a. RF = Positive

4. Discussion

4.1. General View

It has been suggested that oxidative stress (OS), inflammatory process and TEs play a role in the pathogenesis and etiology of rheumatoid arthritis (RA). Deficiencies of TEs in patients with RA occur in response to OS and chronic inflammation.

The role of these TEs in chronic inflammatory conditions such as RA is of great interest because many of them are co-factors in metabolic processes involving collagen and bone or immune system function.

In peripheral tissues, within inflammatory cells, many of these trace metallic elements are incorporated into antioxidant enzymes. Antioxidant metalloenzymes interfere

with the production of free radicals by inactivating reactive oxygen molecules in tissues and immune cells. Although the physiologic role for these TEs may be reasonably well substantiated, their therapeutic usefulness is less compelling.

Inflammation concomitant with OS have been implicated in the pathogenesis of rheumatoid arthritis [2].

This study was undertaken to examine the association between the levels of some TEs with the pathogenesis of RA. It has been suggested that levels of some TEs altered due to OS concomitant with inflammatory process which are associated clinically with RA.

The aim of this study was to assess the association between the serum levels of interested elements in a sample of Iraqi patients with incidence of RA and to investigate their relationship with other confounding factors RF, age, gender and finally evaluate the correlation coefficient between all

studied parameters. So, this study was designed to investigate the probable changes in the levels of some TEs in RA.

In the present study, it was observed that RA was characterized by increased RF level which is a marker of inflammation. This proved the involvement of inflammation with incidence of RA. Rheumatoid factor was independent significant predictor of altered serum levels of interested parameters regarding RF positive group.

The demographic characteristics of the patients group was presented in (Table1).

The comparison between RF positive and RF negative groups was shown in (Table2).

4.2. The Effect of Rheumatoid Arthritis on the Serum Levels of Focused Parameters

4.2.1. Cesium

The serum level of cesium was significantly decreased in patients group as compared with the control group (Table 3).

Cesium is alkaline elements and raises the pH of the body's cells.

Maintaining proper body pH is important for staying healthy. Alkaline tissue holds 20 times more oxygen than does acidic tissue and this oxygen rich environment is critical for supporting health, this fact is compatible with current result that there was a significant reduction in serum level of Cs in patients with RA. So, supplementation with cesium as a therapeutic measure must be considered.

The result of the current study was not consistent with the previous result [15] who reported that, the serum levels of cesium in patients with rheumatoid arthritis were high.

Since there was a significant reduction in serum levels of this parameter, so supplementation with this TE could be necessary for RA therapy or as complementary for treatment of RA and even more important to individuals who are at high risk of developing RA. Studies of the nutritional status of patients with active RA frequently demonstrate deficiencies in micronutrient.

The increase in levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α) and IL-6 seen in the setting of active RA may affect the availability of TEs by inducing the production of metal-binding proteins, metallothioneins, in the liver or intestine. The increased metallothionein production may result in sequestration of these metal ions so that they are deficient [16].

4.2.2. Cobalt

The serum level of cobalt was significantly elevated in patient group as compared with the control group (Table3).

The result of the current study was consistent with the previous result [17] While, the result of current study was not agreeable was with previous results [18], who reported that the mean serum levels of cobalt was significantly lower than control group.

There was no any information to explain this significant elevation in serum levels of Co in patients with RA in all previous researches that deal with the association of RA with Co element.

4.2.3. Manganese

The serum level of manganese was significantly elevated in patient group as compared with the control group (Table3).

The result of the current study was concordant with previous results [15, 18, 19].

The explanation for this significant elevation, the scientific researches were carefully reviewed and detected, no any information about this variation in serum levels of Mn in patients with RA. So, need further researches to explain this significant elevation of Mn.

4.2.4. Rhenium

The serum level of Re was significantly elevated in patient group as compared with the control group (Table 3).

The scientific researches were carefully reviewed and detected that there were no any previous results dealing with the association of RA with the serum levels of Re, accordingly, this research was the first study dealing with the changes in the serum levels of Re in patients as compared with control group.

The exact explanation for the significant elevation in the serum levels of Re was not clear and need further studies to explain this clinical correlation between serum levels of Re with RA.

4.2.5. Rubidium

There was a significant reduction in serum levels of rubidium in patients group as compared with the control group (Table 3), so supplementation with this TE could be important for treatment of RA and even more necessary to individuals who are at high risk of developing RA.

These variations in the serum level of focused parameters may provide opportunity to the physician to diagnose individuals who are at high risk to develop RA for correcting these imbalance of these elements.

The variation of TEs in sera of patients with RA can enable us to focus and shade more light on the role of TEs in physiological and pathological conditions.

This findings proved the possible association between altered levels of interested TEs with RA.

It could be suggested that the deficiency of Cs and Rb might be used as complementary non-invasive parameters for early diagnosis and treatment of RA.

The scientific researches were carefully reviewed and detected that there were no any previous results dealing with the association of RA with the serum levels of Rb, accordingly, this research was the first study dealing with the changes in the serum levels of Rb in patients with RA as compared with control group.

4.3. Gender-Factor

Rheumatoid arthritis is 2-3 times more common in women than in men. But in current study, there was no gender effect, there were 30 men (16 men with rheumatoid factor positive and 14 men with rheumatoid factor negative) and 26 women (12 women with rheumatoid factor positive and 14 women with rheumatoid factor negative) (Table 1).

4.4. Age –Factor

The onset of the disease occurs at all ages [20], but the incidence is highest between the ages of 35 and 50 years [21], this result was concordant with the finding of the current study. In the current study the age of patients range from (40- 57).

There were no significant differences between different age categories regarding all studied parameters in RF negative group (Table 4) except for Mn (age= 55+,p=0.005) and Rb (age= 40-44, p=0.044).

There were no significant differences between different age categories regarding all studied parameters in RF positive group (Table 5). Accordingly, there was no age effect.

It was reported that, the groups showed no significant age differences [22].

4.5. Gender – Effects

There were no significant differences between RF positive and negative groups in males and females groups regarding all studied parameters (Tables 6,7) respectively.

4.6. Correlation Coefficient

There were no significant correlations among the studied parameters in RF negative group, except the correlation between Mn and age (p=0.013, r=-0.472) (Table 8).

There were no significant correlations among the studied parameters in RF positive group (Table 9).

These results give a good opportunity to the physicians to correct these TEs imbalance to improve the pathological status of the patients.

These variations are probably responsive to inflammation, OS and may be a part of autoimmune process in patients induced by cytokines and resulted from defensive mechanism of patients.

Accordingly, these results postulated that these TEs might play a role in pathophysiology of RA. These findings proved the possible association between altered levels of interested parameters with RA.

5. Conclusion

The variation of TEs in sera of patients with RA can enable us to high light on the role of TEs in both physiological and pathological status.

Since there is a significant reduction in serum levels of Cs and Rb, so supplementation of these TEs could be important to get a benefit from TEs rebalance in serum, so supplementation with TEs could be necessary for RA therapy and even more important to individuals who are at high risk of developing RA.

The serum levels of Co, Mn, Re were significantly elevated in patients with RA as compared with the control group.

There were no significant differences in different age categories regarding interested parameters. There were no significant differences between RF positive and negative groups in males and females groups.

Further investigations are needed to study inununocytokines together with TEs and antioxidant enzymes activities in patients with RA.

Abbreviations: Co: Cobalt; Cs: cesium; IL: Interlukine; Mn: Manganese; OS: oxidative stress; RA: rheumatoid arthritis; Re: Rhenium; Rb: Rubidium; RF: rheumatoid factor; ROS: reactive oxygen species; TEs: Trace elements; TNF- α : Tumor necrosis factor- α

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