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Serum Trace Element Concentrations in Rheumatoid Arthritis

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Abstract Rheumatoid arthritis (RA) is a condition that is associated with oxidative stress. Serum trace elements and their related transport proteins, e.g., albumin and ceruloplasmin, play an important role in the antioxidant defense. Trace element status may therefore be involved in the pathogenesis of RA or be affected by the disease activity of this chronic inflammatory condition. The study participants were 110 patients with RA and 100 sex- and age-matched healthy volunteers. Serum concentrations of albumin, ceruloplasmin, selenium, zinc, copper, and zinc/copper ratio were measured in all subjects. The relationship between these parameters and disease activity score was also assessed. Lower concentrations of serum Alb, Zn, and Se were independently related to disease activity index. High concentrations of serum copper were associated with the presence of RA. Serum Cu concentrations were positively related to disease activity as assessed by the disease activity score. Low serum concentrations of Zn and Se, and high serum Cu concentrations may be associated with the presence of RA or be a consequence of this condition. Of the trace elements that were investigated in the present study, only serum Cu was positively correlated with disease activity.

Keywords Zinc · Selenium · Copper · Albumin · Ceruloplasmin · Zinc to copper ratio · Rheumatoid arthritis · DAS28ESR · Trace elements

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic autoimmune diseases and affects 0.5 to 1 % of the adult population [1, 2]. Early treatment of RA is necessary to prevent irreversible joint damage and to improve disease prognosis [3]. The etiology of RA is still unknown, but it is established that immune mechanisms, including enhanced production of inflammatory cytokines (TNFα, IL-1, IL-6) and deregulated cell-mediated immunity, play an important role [4–8]. Oxidative stress appears to be involved in the genesis of RA and may arise as either cause or consequence of inflammation [9, 10]. Trace elements such as selenium (Se), zinc (Zn), and copper (Cu) are cofactors for several antioxidant enzymes which prevent cellular damage caused by free radicals such as superoxide radicals and other reactive oxygen species [11, 12]. Cu^{2+} ions are important structural components of several enzymes such as superoxide dismutase, lysyloxidase, cytochrome coxidase, factor V, and tyrosinase but can also be involved in the generation of free radicals via the Fenton reaction [13, 14]. Zn is a

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component of nearly 250 human proteins, such as enzymes like angiotensin-converting enzyme inhibitors, alkaline phosphatase, carbonic anhydrase, metallothionein, superoxide dismutase, and DNA and RNA polymerases. Zn also plays an important role in cell division and apoptosis [15, 16]. Cu and Zn are influenced by chronic inflammatory responses [17].

Se is another trace element involved in cell immunity and selenoproteins, such as glutathione peroxidase, play a crucial role in the biological antioxidant defense [18]. Increased RA disease activity may be associated with a heightened oxidative burden and these deregulations might be due to alterations in trace element levels. Therefore, owing to the important role of immune imbalances and antioxidant depletion in RA, we aimed to assess serum concentrations of trace elements—which have an influence on both immunological and oxidative status, in patients with RA and also investigate the association between trace element levels and disease activity [19].

Methods

Study Population

One hundred and ten patients with RA were recruited during their visit to the Rheumatic Diseases Research Center (RDRC), Mashhad, Khorasan-e-Razavi province, Iran. All participants were resident in the Khorasan-e-Razavi province, and a diagnosis of RA was based on meeting at least four of the seven criteria specified by the American College of Rheumatology [20]. One hundred healthy volunteers were recruited from among patients' relatives and medical staff who were resident in the same community. The controls did not receive any dietary supplement during the previous year. Exclusion criteria included the following: those <18 years of age or with a history of an autoimmune disease other than RA, individuals taking dietary supplements containing trace elements in the preceding year, malabsorption with clinically relevant symptoms (e.g., chronic diarrhea), malignancy, a glomerular filtration rate (GFR) below 80 mL/min per 1.73 m., pregnant or lactating women, and those residing outside the Province of Khorasan-e-Razavi were also excluded from the study.

Demographics

A total of 210 participants were recruited into this study, including 110 RA patients (85.3 % women and 14.7 % men) and 100 healthy controls [82.3 % women and 17.7 % men]. Both study and control groups were of similar socioeconomic status with similar dietary habits. Healthy control subjects did not have any history of autoimmune diseases, symptoms such as joint pain and swelling, other autoimmune diseases, or hormone replacement therapy. The study was approved by the Ethics Committee of the Ghaem Hospital (Mashhad, Iran), and written informed consent was obtained from all enrolled subjects. There was no statistical difference between the two groups for gender distribution ($p=0.3$). The mean age of patients and controls was 44.7±12.6 and 41.5±11.9 years, respectively, and there was no statistical difference between the groups ($p=0.06$, $t=1.9$). The average disease duration was 4 months with an interquartile range of 2–288 months. The frequency of patients with active disease (DAS≥2.6) and those in remission (DAS<2.6) was 89 and 11 %, respectively. Other classifications for DAS scores have been used; a value lower than 3.2 (DAS<3.2) has been defined as inactive, between 3.2 and 5.1 (3.2<DAS<5.1) was considered as active, and greater than 5.1 (DAS≥5.1) was categorized as hyperactive. Seventy-two percent of the RA patients had three or more swollen joints, 90 % had six painful joints and 41.9 % had an elevated ESR estimated by patients' age. In clinical practice, the degree of pain relief which is assessed by visual analogue scale (VAS) is often considered as a measure of the treatment efficacy [21]. The average value of the VAS for the patients was 50. Ninety-five percent of the patients were treated with hydroxycholoroquine, 67.3 % with methotrexate and 72.7 % with prednisolone at the time of this study. Less than 5 % of patients were taken biological therapies such as infliximab, etanerecept, or rituximab. Adjustments of trace elements were made for risk factors such as sex and age by using the residuals method.

Disease Activity Index

RA disease activity was assessed using the DAS28-ESR questionnaire at the time of blood sampling. DAS is a quantitative measure of disease activity used to monitor the treatment of RA. DAS28, which stands for "disease activity score," and is calculated using a formula that includes the number of tender or swollen joints [22]. The data were collected based on the clinical examination performed by a consultant rheumatologist with taking into account the number of swollen and painful joints and the erythrocyte sedimentation rate (ESR). ESR is a simple and inexpensive laboratory test for assessing the inflammatory response [23, 24]. The International Committee for Standardization in Hematology (ICSH) recommends the use of the Westergren method [23]. Data were then calculated using the following formula for the final calculation of DAS28 for every patient.

$$[\mathrm{DAS28} = 0.56*\mathrm{sqrt}[\mathrm{tender28}] + 0.28*\mathrm{sqrt}[\mathrm{swollen28}] + 0.70*\ln[\mathrm{ESR}] + 0.014*\mathrm{GH}].$$

The DAS28 provides a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis in a patient. A DAS28 above 5.1 means high disease activity, whereas a DAS28 below 3.2 indicates low disease activity. Full remission is associated with a DAS28 score of <2.6.ESR.

Measurement of Trace Elements

Serum Se was determined by electrothermal atomic absorption spectrometry with Zeeman background correction using a palladium chloride chemical modifier [25]. Serum copper and zinc concentrations were measured by flame atomic absorption spectrometry (Perkin Elmer 3030 USA 1980) following making a 1:4 dilution with distilled water as previously described [26]. The reference ranges for the serum copper and zinc were as follows: copper, men 10.99–21.98 (μmol/L), women 12.56–24.34 (μmol/L), and zinc, 10.7–18.4 (μmol/L) for both men and women [27]. Wavelengths used for analyzing Cu, Zn, and Se were 324, 213, and 196 nm, respectively. Typical between-batch precision (CVs) for these assays were 3.6 and 2.7 %, respectively. Serum albumin was measured using the bromocresol green photometric method [28]. Cp was measured by radial immuno-diffusion, as previously described [25].

Statistical Analysis

Statistical analysis was performed using the SPSS 16 program (SPSS Inc, Chicago, IL, USA). Parametric and nonparametric tests were used to analyze data with and without a normal distribution (determined using the Klomogrov-Smirnov test), respectively. For the statistical study of quantitative variables with normal distribution, Student's *t*, one-way ANOVA, and Pearson's correlation tests were used, while the statistical tests utilized for quantitative variables without a normal distribution included Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman's correlation. Cutoff values between patients and healthy volunteers for trace elements were selected from a receiver operating characteristic (ROC) curve analysis using MedCalc software 11.5.1. Positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR−), sensitivity, specificity, and the Youden Index for the estimated cutoff points were calculated using MedCalc 11.5.1 software. Binary logistic regression analysis was used to assess association between serum Se, Zn, Cu, CP, Alb, and Zn/Cu ratio and RA disease activity using the binary model of the DAS: DAS <2.6 and DAS ≥2.6. Statistical power was calculated using the PS software version 3.0 [29].

Results

Comparison of Biochemical Markers and Trace Elements Between Patients with RA and Healthy Controls

Serum concentrations of Zn, Alb, and Se and the Zn to Cu ratio (Zn/Cu) were significantly lower in patients compared with the healthy group (Table 1). In contrast, serum Cp and Cu concentrations were higher in patients compared with those in the healthy group.

Correlation of Biochemical Markers and Trace Elements with Disease Activity

Comparison of measured biochemical parameters between patients with active and inactive disease (according to DAS) demonstrated that serum concentrations of Alb, Zn, Cu, Se, and Cp were different between the two groups. We also compared serum concentrations of the given parameters among patients that were characterized using the tertiary classification, and similar results were obtained as with the binary classification, although Cu was higher in patients compared with healthy subjects and was associated with disease activity. However, after adjustment for potentially confounding factors including age and sex, there were no significant association with disease activity (Table 2). Pearson's correlation coefficient showed that ESR was strongly correlated with serum Zn and Alb (p=0.7, p=0.64), while it had weak correlation was found with Se, Cu, Cp, and Zn/Cu ratio (p=0.24, p=0.003, p=0.044, p=0.02). The presence of tender joints was strongly related with serum Cp and Se and showed a weak correlation with serum Cu, Zn, and Alb, while it had a moderate correlation with Zn/Cu ratio; swollen joints showed a moderate correlation with serum Se (p=0.4) and had a weak correlation with other parameters; VAS and DAS show a strong correlation with Se (p=0.82, p=0.64), while these had weak correlation with other parameters. Finally, age showed a strong correlation Se, Zn, Zn/Cu ratio, and Cu, while had week correlation with albumin and Cp (Table 3). The study of the biochemical relationship with pharmaceutical regimens according to Spearman's correlation coefficient revealed that the concentration of serum Cu, Se, Alb, and Zn/Cu ratio had a weak correlation with the dose of hydroxycholoroquine, while Zn and Cp show a moderate correlation with the dose of hydroxycholoroquine taken by the patients. Serum Cu, CP, and Zn/Cu ratio concentrations showed a weak correlation with the dose of methotrexate taken by the patients, while the Se and Alb had strong correlation with the dose of methotrexate taken by the patients. These results indicated that Zn

Table 1 Comparison of serum trace element values between RA patients and healthy controls

	RA patients (n=110)	Healthy controls (n=100)	p Value	Power
Se)μg/L(	110.11±18.59	90.92±22.77	<0.0001	100 %
Cp)mg/L(	392.56±101.86	429.16±122.26	0.0150	64 %
Zn)μg/L(	902.56±158.69	748.87±162.11	<0.001	100 %
Copper)μg/L(	990.75±239.54	1124.21±315.78	<0.001	91 %
Zn/Cu	0.97±0.29	0.72±0.23	<0.001	100 %
Albumin)g/dL(	5.60±0.92	5.17±0.89	0.004	91 %

Cp ceruloplasmin

had moderate correlation with the dose of methotrexate. Serum Cu, Se, Cp, Alb, and Zn/Cu ratio show a weak correlation with the dose of prednisolone and serum Zn concentration had a strong correlation with the dose of prednisolone taken by the patients (Table 4). There was no association between age and any of the trace elements, although serum CP increased with age in the patients (Table 3). Many studies have shown that disease duration can effect the response to treatment [30, 31]. In the present study, it was found that disease duration did not correlate with serum concentrations of trace elements and proteins.

Correlation Among Trace Elements

Using Pearson correlation tests, several biochemical parameters were positively associated with each other; although serum Se was inversely related to albumin and Cu, respectively. Moreover, serum Zn and Cu were not significantly associated with each other. Pairwise correlations among biomarkers is lacking for some of them, for example CP was positively correlated only with Cu (Table 5).

MedCalc Analysis

The biochemical parameters that were significantly different between case and control groups or between active and inactive disease groups were analyzed to calculate their optimum cutoff values differentiating between the aforementioned groups. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for those cutoff points were determined using MedCalc software as summarized in Table 6.

Regression Analysis

Table 7 shows the results of regression analysis of Alb, Se, Zn, Cu, CP, and Zn/Cu ratio against age in the healthy subjects. There was no significant difference in age between the patient and healthy groups (p=0.07). It was found that higher serum Alb, Zn, and Se were all associated with increased risk of RA, while age was associated with decreased risk of RA. Logistic regression analysis using the forward conditional model did not reveal any association between serum Se, Zn, Cu, CP, Alb, and Zn/Cu ratio with RA disease activity using the binary model of DAS (DAS<2.6 and DAS≥2.6).

Discussion

The main finding of this study was that serum concentrations of Zn, Alb, Se, and Zn/Cu were lower in RA patients than in healthy age- and sex-matched controls and also higher Cu and Cp in subjects with RA. Moreover, serum Zn and Alb concentration showed a strong correlation with ESR, and serum Se, Cu, Cp, and Zn/Cu ratio were weakly correlated with ESR. Regression analysis showed that serum Alb, Zn, and Se concentrations were all associated with increased risk of RA, while age was associated with decreased risk of RA.

Table 2 RA disease activity and trace elements

DAS (tertiary classification)					
Trace elements	A<3.2 (n=18)	3.2≤B≤5.1 (n=41)	C>5.1 (n=45)	p Value[a]	p Value adjusted
Albumin(gr/L)	5.34±0.9	5.4±0.86	4.99±0.77	0.069	0.612
Zn (μg/L)	725.72±111.83	737.80±153.64	674.44±183.79	0.440	0.52
Zn/Cu R	0.7340±0.23	0.7536±0.238	0.3798±0.22	0.304	0.5
Cp (mg/L)	433.62±140.86	407.80±115.04	451.54±123.23	0.218	0.87
Cu (μg/L)	1043.39±239.56	1068.93±323.14	1215.29±321.12	0.046	0.437
Se (μg/L)	79.8778±22.58	78.0±15.53	84.3778±28.17	0.427	0.311

p Value between each two groups (Tukey-Kramer test): A and B (p=0.900), A and C (p=0.100), B and C (p=0.070). p Value adjusted: adjusted for sex and age

Se selenium, *Zn* zinc, *Cu* copper, *Cp* ceruloplasmin, *Zn/Cu R* Zn/Cu ratio

[a] Logarithmic values were used in this analysis (analysis of variance)

Table 3 Pearson's correlation coefficients between trace elements and DAS, components of the DAS and age

Variables *p* (*r*)	ESR	*N* (tender joints)	*N* (swollen joints)	VAS	DAS	Age (years)
Albumin (g/dl)	0.640 (−0.44)	0.20 (−0.120)	0.060 (−0.180)	0.100 (−0.150)	0.120 (−0.150)	0.090 (0.380)
Se (μg/L)	0.240 (0.110)	0.700 (0.030)	0.40 (−0.081)	0.823 (0.042)	0.641 (0.440)	0.601 (0.0521)
Zn/Cu ratio	0.020 (−0.236)	0.321(−0.080)	0.021 (0.840)	0.206 (−0.110)	0.111 (−0.161)	0.950 (0.012)
CP (mg/L)	0.044 (0.202)	0.552 (0.555)	0.070 (0.170)	0.200 (0.11)	0.111 (0.150)	0.011 (0.900)
Zn (μg/L)	0.700 (0.04)	0.111 (0.144)	0.100 (0.132)	0.220 (0.120)	0.260 (0.111)	0.680 (0.040)
Cu (μg/L)	0.003 (0.291)	0.026 (0.12)	0.178 (0.137)	0.081 (0.165)	0.005 (0.271)	0.891 (0.010)

Se selenium, *Zn* zinc, *Cu* copper, *Cp* ceruloplasmin, *ESR* erythrocyte sedimentation rate, *VAS* visual analogue scale, *DAS* disease activity scores

However, among the trace elements measured, only serum Cu showed a positive correlation with disease activity as assessed by the DAS28-ESR using logistic regression analysis. In the present study, the control group was recruited from patients' relatives who might share susceptible genes and living environments with patients. Environmental and genetic risk factors have been identified, but no single risk factor has emerged as necessary or sufficient to cause the disease. Several studies have found that the utilizing of relative has useful aspect in this disease. When relatives are used, they share similar patterns of distribution of potential confounders such as genetic and environmental risk factors, including socioeconomic status and dietary habits [32, 33].

Trace Elements and RA

Oxidative stress is a major cause of cell damage in RA [34]. Antioxidative enzymes such as superoxide dismutase and glutathione peroxidase are important biological defenses against detrimental effects of oxidative stress. Superoxide dismutase expedites reduction of superoxide ions. For this enzyme, Cu and Zn are major cofactors [34]. Furthermore, Se is an important component of glutathione peroxidase. Many of the nutritional effects of Se can be explained by its critical role in glutathione peroxidase activity [35]. It has been reported that the serum activities of these two enzymes are reduced in active RA [36]. In the current study, we showed that higher serum Alb, Zn, and Se concentrations were all associated with increased risk of RA. Other studies have also demonstrated that the serum concentrations of several trace elements (Se, Cu, and Fe) are altered in RA, but these changes might be affected by an acute-phase response, which were altered as a part of defense strategies of the organism that was induced by stress hormone release [37, 38]. Moreover, MedCalc analysis revealed a significant difference between case and control groups and it was used to calculate the optimum cutoff values for differentiating aforementioned groups.

RA and Albumin Concentrations

Serum Alb concentrations in patients were obviously lower than healthy controls. Since Alb decreases due to inflammation [39], the Alb reduction in patients with RA might be expected. Yazar et al. [40] showed that several plasma trace element (Se, Cu, Fe) concentrations, excluding Zn, change in inflammatory RA. These alterations in trace element concentrations in inflammatory RA might be a result of the changes in the immune-regulatory cytokines. In the present study, serum albumin concentrations were also studied together with some important indices of disease activity, including the DAS and drug treatment. There was an inverse relationship between

Table 4 Correlation between trace elements and doses of anti-inflammatory drugs

Variables	Prednisolone (mg/day) *p* (*r*)	Methotrexate (mg/week) *p* (*r*)	Hydroxychloroquine (mg/day) *p* (*r*)
Cu (μg/L)	0.140 (−0.140)	0.010 (0.230)	0.050 (−0.190)
Se (μg/L)	0.020 (0.220)	0.930 (0.008)	0.040 (0.190)
CP(mg/L)	0.130 (−0.140)	0.010 (−0.220)	0.300 (−0.090)
Albumin (g/dL)	0.011 (−0.233)	0.540 (−0.060)	0.180 (−0.140)
Zn (μg/L)	0.890 (0.010)	0.340 (0.090)	0.380 (0.090)
Zn/Cu ratio	0.200 (0.120)	0.007 (0.260)	0.020 (0.220)

Se selenium, *Zn* zinc, *Cu* copper, *Cp* ceruloplasmin

Table 5 Pairwise correlation between biochemical markers

Variables	*r*	*p*
Albumin and Cu	0.191	0.007
Albumin and Se	−0.009	0.001
Albumin and Zn	0.268	0.001
Se and Cu	−0.226	0.001
Zn and Cu	0.008	0.905
Cu and CP	0.618	0.001
Se and Zn	0.268	0.001

Se selenium, *Zn* zinc, *Cu* copper, *CP* ceruloplasmin

Table 6 Cutoff values for the measured biochemical parameters for RA patients and healthy controls

	Cutoff values	Sens (%)	Spec (%)	(+LR)	(−LR)	(+PPV)	(−PPV)
Se (μg/L)	>92.4	72.12	84.62	4.69	0.33	84.3	72.6
	95 % CI	62.5–80.5	75.5–91.3	4–5.4	0.2–0.6	75–91.1	63.1–80.8
Albumin (g/dL)	≤5.8	86.87	34.41	1.32	0.38	58.5	71.1
	95 % CI	78.6–92.8	24.9–45	1–1.8	0.2–6.0	50.1–66.6	55.7–83.6
Zn (μg/L)	>820	78.43	64.44	2.21	0.33	71.4	72.5
	95 % CI	62.2–86	53.7–74.3	1.8–2.7	0.2–0.5	62.1–79.6	61.4–81.9
Cu (μg/L)	≥868	81.73	36.26	1.28	0.50	59.4	63.5
	95 % CI	72.9–88.6	26.4–47	1–1.7	0.3–0.8	50.9–67.6	49–76.4
Zn/Cu	≥0.787	67.33	67.42	2.07	0.48	70.1	64.5
	95 % CI	57.3–76.3	56.7–77	1.7–2.5	0.3–0.7	60–79	53.9–74.2
CP (mg/L)	>440	33.33	76.6	1.42	0.87	61.4	50.7
	95 % CI	24.4–43.2	66.7–84.7	1.1–1.9	0.6–1.3	47.6–74	42.2–59.2

Sens sensitivity, *Spec* specificity, *+LR* positive likelihood ratio, *−LR* negative likelihood ratio, *+PPV* positive predictive value, *−PPV* negative predictive value

serum albumin concentrations and the dose of prednisolone. A positive correlation between serum concentrations of Alb, Se, and Zn was also observed. Since Alb is a binding protein for zinc and is also a negative acute phase reactant; these findings were expected.

RA, Cu, and Cp Concentrations

Significantly higher serum Cu and Cp concentrations were observed in RA patients compared with healthy individuals. These results are in accordance with previous studies that have investigated the relationship between serum Cu, Cp, and RA [41–43]. High serum Cu concentrations may be found in other connective tissue diseases, including SLE [44]. Cp is an acute phase reactant and also a Cu-carrying protein. Elevated Cu and Cp concentrations in RA may be due to the increase in the production of acute reactive phase proteins. In the current study, we also found a parallel correlation between Cu and Cp serum concentrations. We found a significant positive correlation between Cu and DAS ($p<0.046$) and its component ESR ($p<0.020$); therefore, it may be a potential index for disease activity [45]. Some previous studies have shown higher serum Cu concentrations in older RA patients [42]. Strecker et al. revealed that Cu level was significantly higher in RA patients' serum and hair compartments. The Cp concentration was also higher in serum of RA patients. A statistically significant, positive correlation between the Cp serum concentration and the ESR values was found [46]. In the present study, weekly dosage of methotrexate was positively correlated with serum Cu concentrations. This may also be a surrogate reflection of disease activity. In line with previous studies, we found a direct increase in Cu and CP. However, serum CP concentration did not correlate with disease activity. The increase in Cu and CP is considered as an anti-inflammatory response in RA and other joint diseases and can also be regarded as inflammatory markers [43, 47].

Table 7 Logistic regression analysis on the influence of trace elements and confounding factor in contrast to RA development

Independent factors	*p* Value	*β*	OR	CI (95 %)
Age (years)	0.070	−0.040	0.950	0.92–0.990
Serum Albumin (g/dl)	0.002	0.810	2.200	1.33–3.800
Serum Zn (μg/L)	0.001	0.005	1.000	1.002–1.007
Serum Cu (μg/L)	0.010	−0.002	0.990	0.99–1.00
Serum Se (μg/L)	0.001	0.070	1.080	1.05–1.100

RA and Zn Concentrations

Compared to the control group, serum Zn concentrations were lower in RA patients. There have been similar previous reports that investigated serum concentration in RA [48–50]. However, Yazar et al. did not observe a significant difference in serum Zn concentrations in patients with RA compared with healthy subject [40]. There is evidence from previous studies showing that Zn distribution in the body is influenced by inflammation [51]. Data from previous studies have suggested a correlation between the extent of inflammation and serum Zn depletion [51, 52]. Some studies pointed to the protective role of Zn in RA [52]. Although, in the current study, there was no relationship between serum concentrations of trace elements and albumin with the age of participants, some previous studies have reported that serum Zn concentrations for normal people decreases with age [1]. In this study, serum Zn concentrations did not have any correlation with disease activity but was correlated with Cu, Se, and Alb.

RA and Zn/Cu Ratio

The reduced serum Zn/Cu ratio in RA has been reported previously [1]. This may either occur because of a decrease in Zn or an increase in Cu levels or both. We found that serum Zn/Cu ratio is markedly lower in RA patients compared with healthy controls. Some studies have shown the association between changes in Zn/Cu ratio and early atherosclerosis [53]. Low Zn/Cu ratio is an indicator of malnutrition [54]. In this study, the relationship between Zn/Cu ratio and disease activity was investigated for the first time but no correlation was observed. However, Zn/Cu ratio was positively correlated with methotrexate and hydroxychloroquine dosage.

RA and Serum Se Concentrations

Serum Se concentrations in the RA patients were lower than those of the control group. Se is an important constituent of glutathione peroxidase, which plays an important role in the anti-oxidative defense system. Interestingly, Se may influence the eicosanoid pathway to promote anti-inflammatory products and modulate cell-mediated immunity [55]. Selenoproteins play an important role in reproduction, thyroid hormone synthesis, and immunomodulation. Several studies have shown the inverse relationship between serum Se concentrations and risk of cancer [19]. We found, as in most previous studies, that serum Se serum Zn concentrations were significantly lower in RA patients compared with healthy controls [41, 19]. However, no relationship was found between serum Se levels and DAS. In some studies, disease exacerbation was associated with decreased serum concentrations of Se [19]. Unlike the results obtained by O'Dell et al. [19], we found a positive association between serum Se concentrations and doses of hydroxychloroquine and prednisolone therapy. Serum Se concentrations have a direct relationship with those of albumin and Zn and an inverse relationship with Cu. Results by Yazar et al. [40] also confirmed the negative correlation between Se and Cu in RA patients. In other study, Onal et al. [41] indicated that serum Cu concentration are higher and those of Se and Zn are lower in patients compare with healthy subjects.

Conclusion

Results of the present study suggest that serum Cu and Cp concentration are elevated while Zn, Se, and Alb levels are reduced in patients with RA. Elevated serum Cu concentrations were also found to be associated with disease activity. These results suggest that alterations in serum trace elements may be associated with RA. However, further longitudinal studies are warranted to clarify if altered levels of trace elements, Alb and Cp are causally related to RA disease activity.

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