

Relationship between Serum Levels of Some Trace Elements, Disease Duration and Severity in Patients with Knee Osteoarthritis

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Abstract

Background: Many trace elements in the biological system, including boron, are involved in various vital processes related to health and diseases. Boron has been proved to have a role in decreasing inflammatory pain, joint stiffness and other disabling symptoms associated with osteoarthritis (OA). **Aims and Objective:** The purpose of the present study was to evaluate the relationship between serum concentrations of copper (Cu), zinc (Zn), selenium (Se), manganese (Mn) and magnesium (Mg) with disease duration and severity in patients with knee OA. **Methods:** A total of 43 patients with knee OA were clinically evaluated and serum concentrations of Cu, Zn, Se, Mn and Mg were measured, and the results were compared with those of healthy controls. Trace elements levels were correlated with disease duration and severity. **Results:** Serum Cu and the value of Cu/Zn were significantly elevated in OA patients and positively correlated with disease duration and severity. Serum Zn, Se and Mn were significantly lower in patients compared with controls; Zn and Se were found to be negatively and significantly correlated with disease duration and severity. **Conclusion:** Patients with knee OA had higher levels of Cu and larger value of Cu/Zn and lower levels of serum Zn and Se; these changes were potentially correlated with the duration and severity of disease.

Keywords

Knee OA, Trace Elements, Disease Severity, Disease Duration

1. Introduction

Osteoarthritis (OA) is a chronic disorder characterized by progressive degenerative changes in the cartilage and

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articular tissues. Multiple etiologies are suspected to contribute to the formation of OA, including defective articular cartilage structure and biosynthesis, joint trauma, joint instability, congenital and developmental abnormalities, and inflammatory conditions [1]. Oxidative damage to essential cell components caused by oxygen free radicals is a mechanism in the pathobiology of degenerative joint disease [2]. Many trace elements have been recognized to play an important role in the pathogenesis and progression of many diseases, including osteoarthritis. However, it is difficult to precisely identify the relationship between these elements and disease severity because of the multifactorial variations of these elements in the biological fluids [3] [4]. A relationship was observed between OA and trace elements in many research studies. In many cases, changes in the metabolism of these elements were demonstrated. Naturally occurring minerals such as magnesium (Mg), copper (Cu), manganese (Mn), selenium (Se) and zinc (Zn) have shown anti-inflammatory effects in both animal and human studies. Animal model of OA, a deficiency of dietary Mg was shown to accelerate cartilage damage [5]. Furthermore, increased intake of dietary Mg may influence inflammation through decreasing the release of C-reactive protein [6]. Copper is an essential cofactor in enzymes such as super oxide dismutase (SOD) that also needs Zn and Mn as cofactors. Many studies revealed a role for oxidative stress in the pathogenesis of OA, whereby ROS generation and impaired antioxidant status of the joint might result in the degradation of cartilage joint remodeling [7]. Selenium is also an essential co-factor for glutathione peroxidase which may have a role in reducing the incidence of osteoarthritic lesion [8]. Positive roles have also been suggested for trace minerals such as boron and manganese in reducing the symptoms and slowing the pathogenesis of OA [9]. It is not known whether trace element status leads to disease or whether diseases set in due to the deficiency of trace elements. Although it is generally believed that a strict metabolic control delays the development of late complications OA.

2. Methods

A total of 43 knee OA patients and 18 controls were enrolled in this case-control study between December 2014 and April 2015. The controls were selected to have similar age and gender distributions compared to those of the knee OA patients. The knee OA patients were diagnosed according to the ACR Guidelines for Medical Management of Osteoarthritis of the knee 2000 [10] by senior orthopedist, and patients were excluded from the study if they had comorbid diseases that affect immunity, or overlapped with other connective tissue diseases, or were alcohol drinker, or received a systemic therapy which may interfere with the inflammatory condition for the last 4 weeks before blood sample collection, and pregnant women. All controls were free of remarkable musculoskeletal disorders by medical history, physical and laboratory examinations. Patients also underwent clinical examinations and record disease duration, while disease severity score was calculated according to the Ahlback classification and the Kellgren and Lawrence system [11] [12]. All subjects were mainland Kurdish ethnicity and gave written informed consent for the study under a protocol approved by the ethics board of the Faculty of Medical Sciences, Sulaimani University.

Fasting blood samples were collected in plain tubes and centrifuged for 15 min at 1500 rpm at room temperature. After centrifugation, serum samples were collected and stored at -20°C until analysis. Hemolyzed samples were excluded from the study. Utmost care was taken to avoid potential pre-analytical contamination during specimen acquisition and treatment. A conventional wet acid digestion method was used to digest serum as previously described [13]. Briefly, 0.4 ml of serum sample and 3 ml of nitric acid (65%) were added into a 25 ml beaker, and digested at 70°C - 80°C on an electric hot plate for 90 min. Thereafter, 1.5 ml of hydrogen peroxide (30%) was added into the beaker and continued for digestion. When the remaining volume was about 0.5 - 1 ml, the liquid was all transferred into a 5 ml of volumetric flask after cooling, and a final volume of 5 ml was obtained by adding the nitric acid stock standard solution. The reference material was treated in the same manner before analysis. ICP atomic absorption spectrophotometer (Perkin Elmer, USA) was used for determination of serum Cu, Zn, Se, Mn and Mg concentrations according to standard procedures. All the results were expressed as mean \pm SD. The data were analyzed by using Graph Pad Prism 5.1 software (Graph Pad Software Inc., San Diego, CA, USA). Unpaired *t*-test with Welch's correction was utilized for statistical evaluation of the differences between the means. The correlation between element and disease duration and severity and Cu/Zn ratio was detected by Spearman correlation analysis. Difference was considered significant if *P* value (FDR corrected) < 0.05 .

3. Results

Table 1 indicates that serum concentrations of Zn, Se and Mn were significantly decreased ($P < 0.0001$) in OA

patients group compared with that in controls (137%, 66% and 27%, respectively). Meanwhile, serum Cu concentrations in OA patients were significantly elevated (129%; $P < 0.0001$) compared with that reported in control group. **Table 1** also shows serum Mn concentrations were not significantly changed in OA patients ($P > 0.05$). Additionally, Cu/Zn ratio was highly and significantly elevated in OA patients (595%; $P < 0.0001$) compared with control group. **Figure 1** shows the correlation between duration of OA in the patients group with se-

Table 1. Serum levels of zinc, copper, selenium, manganese, and magnesium, and copper/ration in patients with knee OA compared with healthy subjects.

Element	Control subjects (n = 18)	OA patients (n = 43)	P value
Serum Zinc ($\mu\text{g/ml}$)	2.1 ± 0.54	0.73 ± 0.17	<0.0001
Serum Copper ($\mu\text{g/ml}$)	1.33 ± 0.35	3.05 ± 0.81	<0.0001
Serum Selenium ($\mu\text{g/ml}$)	0.16 ± 0.03	0.054 ± 0.002	<0.0001
Serum Manganese ($\mu\text{g/ml}$)	0.64 ± 0.06	0.47 ± 0.11	<0.001
Serum Magnesium ($\mu\text{g/ml}$)	18.9 ± 2.3	18.01 ± 1.7	0.16
Copper/Zinc ratio	0.69 ± 0.29	4.8 ± 3.1	<0.0001

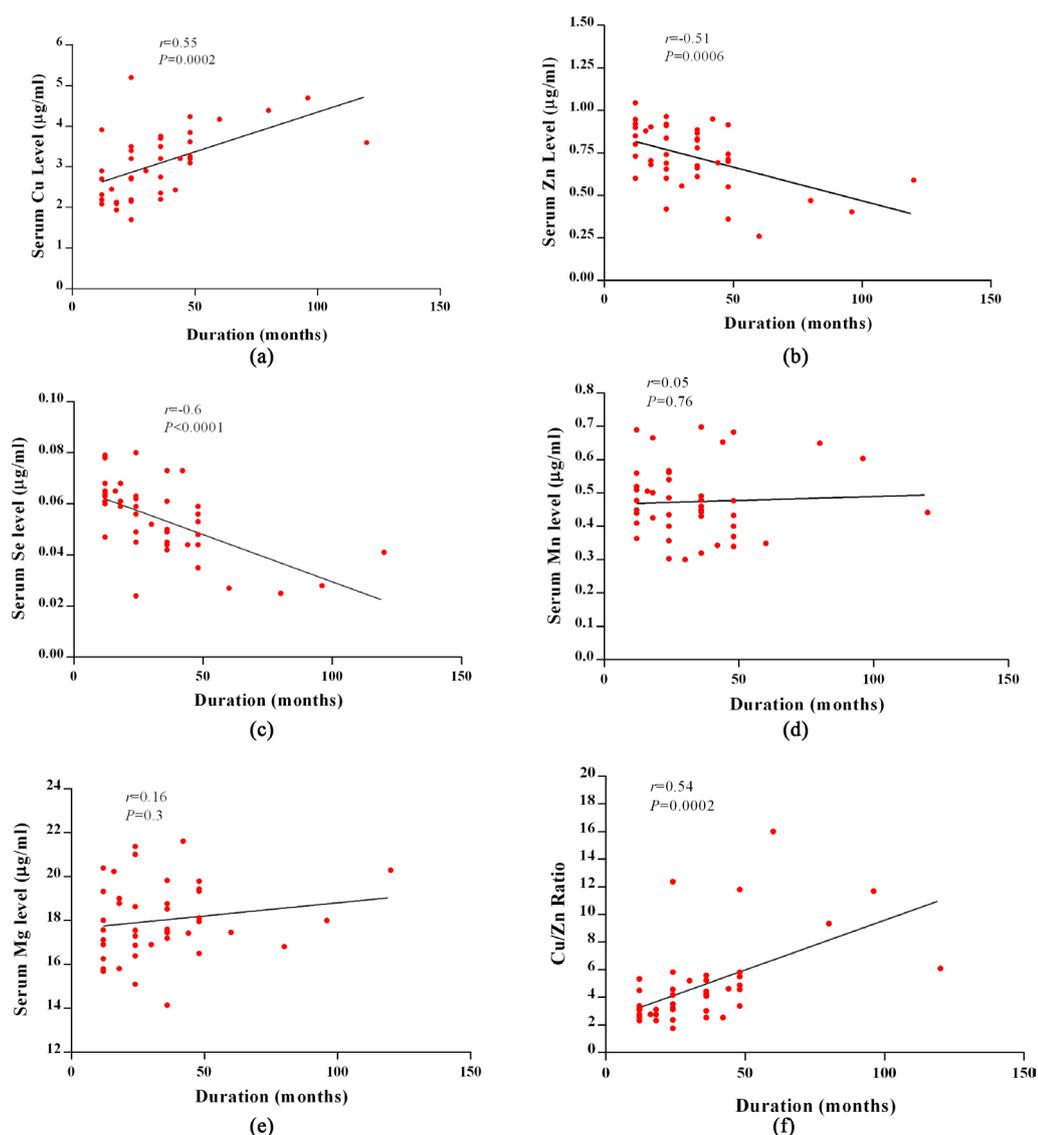


Figure 1. Correlation between disease duration and serum levels of trace elements and Cu/Zn ratio in patients with knee OA; r = Spearman correlation coefficient; significance at $P < 0.05$.

rum concentrations of trace elements, and strong positive and significant correlation was reported ((a) and (f)) with serum Cu and Cu/Zn ratio ($r = 0.55$ and $r = 0.54$, respectively). Meanwhile, strong negative correlation was reported with serum concentrations of Zn and Se ((b) and (c)) ($r = -0.51$ and $r = -0.6$, respectively). In the same regard, **Figure 1** indicates weak and non-significant correlation between disease duration and serum concentrations of Mn and Mg ((d) and (e)) ($r = 0.05$ and $r = 0.16$, respectively). In **Figure 2**, serum concentrations of Cu and Cu/Zn ratio ((a) and (f)) were highly and positively correlated with the disease severity score ($r = 0.89$ and $r = 0.86$, respectively), while serum concentrations of Zn and Se ((b) and (c)) were highly and negatively correlated with disease severity score ($r = -0.77$ and $r = -0.91$, respectively). Moreover, weak and non-significant correlations were reported with serum concentrations of Mn and Mg ($r = 0.006$ and $r = 0.08$, respectively) (**Figure 2(d)** and **Figure 2(e)**). In **Figure 3(a)**, serum concentration of Se was highly and negatively correlated with the Cu/Zn ratio ($r = -0.81$) while poor negative and non-significant correlation was reported for serum Mn concentrations (**Figure 3(b)**) with Cu/Zn ratio ($r = -0.04$).

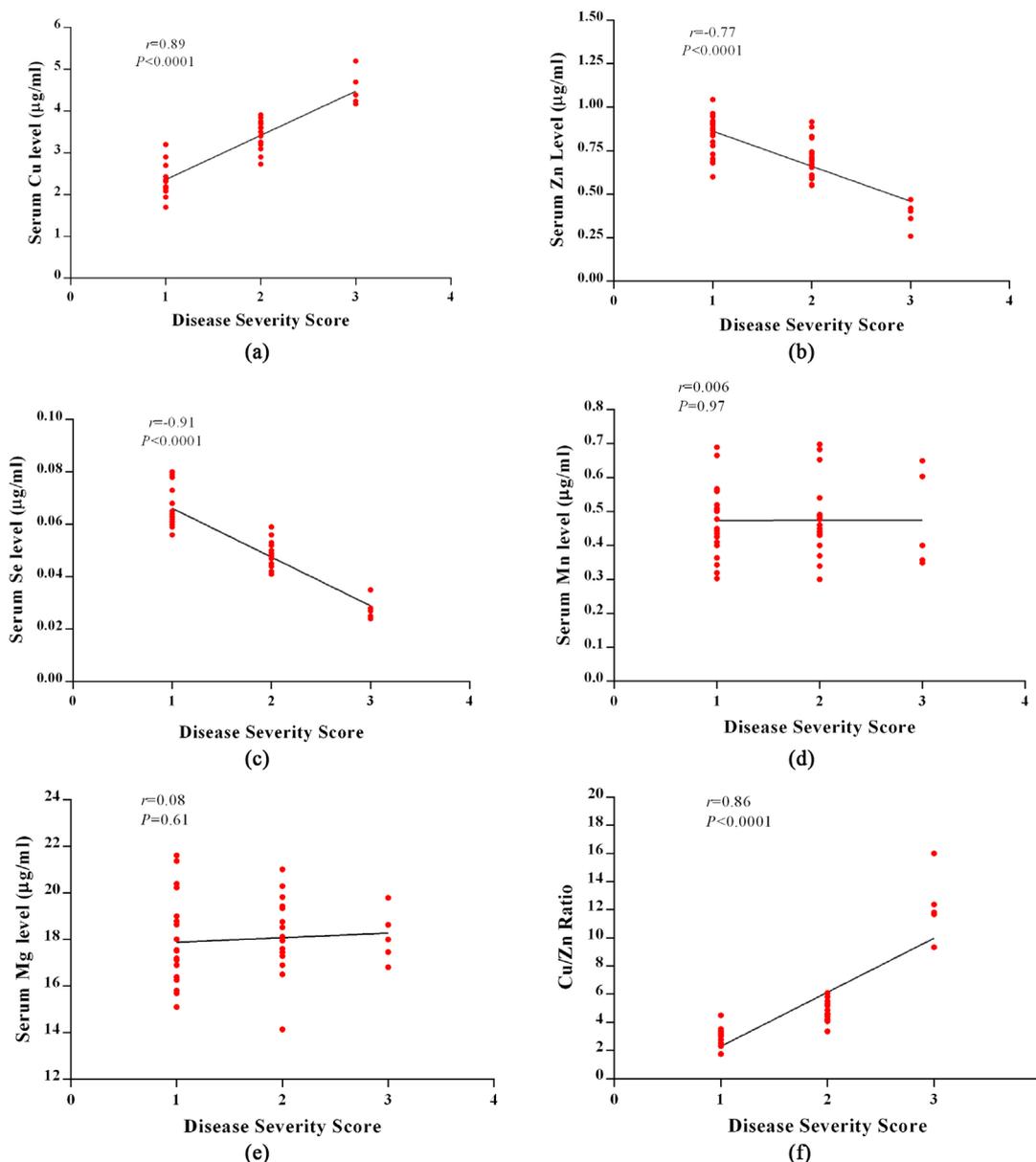


Figure 2. Correlation between disease severity score and serum levels of trace elements and Cu/Zn ratio in patients with knee OA; $r =$ Spearman correlation coefficient; significance at $P < 0.05$.

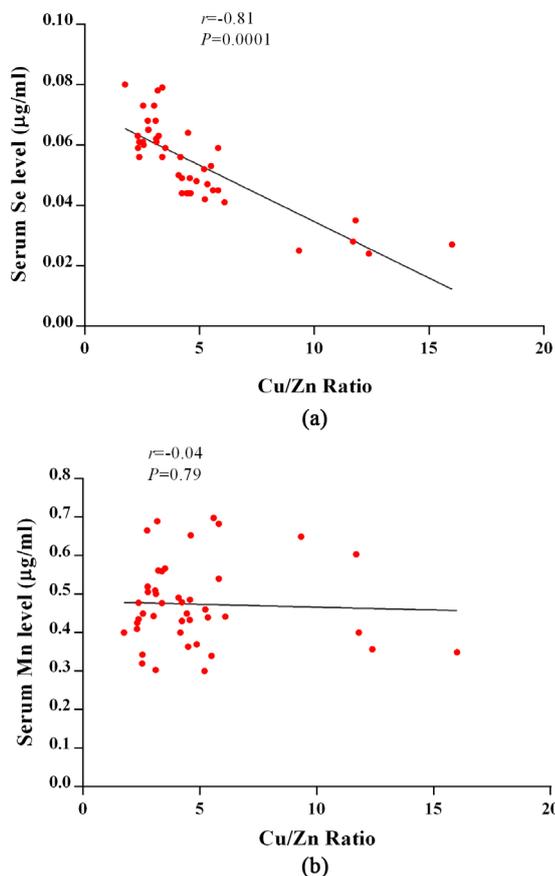


Figure 3. Correlation between Cu/Zn ratio and serum levels of Se and Mn in patients with knee OA; r = Spearman correlation coefficient; significance at $P < 0.05$.

4. Discussion

The present study explored the associations between serum levels of 5 trace elements and the duration and severity of knee OA, demonstrating lower concentrations of Zn, Se and Mn and higher concentrations of Cu and Cu/Zn ratio in patients with knee OA compared with controls; in addition to strong association of disease duration and severity with serum concentrations of Cu, Zn and Se. However, the association between Mn and Mg with the mentioned factors was not significant. Selenium is an important constituent of glutathione peroxidase enzyme and its deficiency resulting in a marked decline in glutathione peroxidase activity of many tissues, which leads to increased oxidative stress [14]. In the present study, serum Zn and Se concentrations were low in knee OA patients and negatively associated with the duration and severity of the disease, this is in good agreement with many results reported about Zn and Se status and many other diseases [15] [16]. In the presented study, the serum Cu level in patients with knee OA, confirmed the reports of some other investigators who have shown higher serum (or plasma) concentration of this element in the patients with OA and other inflammatory disorders including RA, compared to the control group [17] [18]. According to some other authors, this increased blood serum Cu concentration was even considered to be a marker of clinical activity of this disease [19]. Decreased levels of Se and the activity of selenium-dependent enzymes have also been studied in other diseases, including epilepsy, which showed a strong correlation between their reduction and severity of the disease [20]. Decreased serum Se levels in humans is unlikely to happen, but may be the etiological factor of some serious disorders such as Keshan disease (endemic cardiomyopathy) and Kashin-Beck disease (endemic osteoarthritis), which are successfully managed with Se supplements [21]. Understanding that Se is a cofactor of some enzymes with antioxidant activity; we can suggest that reduced serum levels of this element renders the individual prone to various damages mediated through oxidative stress [22]. Given that in evaluation of zinc and selenium levels various studies have shown some discrepancies, differences and changes in climate and minerals

in soil, as well as type of race and other conditions included in the studies (for example, time of the year when samples were collected, and so forth) may lead to changes in these parameters in the serum, and eventually result in harmful states. Increased serum concentrations of Mn has been known to induce tissue damage, elevated levels of this trace element were reported to accumulate in the mitochondria [23]. In animal study, Mn toxicity has been involved in DNA fragmentation [24], which may be, in part, responsible for articular tissue damage, though the reported elevated levels showed poor correlation with the severity and duration of OA. Several limitations in the present study should be considered. First, the data revealed changes of trace element levels in peripheral blood (serum), and further researches still need to precisely determine whether such changes reflect relevant alterations in the articular tissue. Second, due to absence of some variables, including body mass index (BMI), smoking, dietary intakes and use of anti-inflammatory agents, potential confounding biases could not be excluded. However, some study did not find any association between drug doses, and smoking status, and the changes of several trace elements, including Mn, Se, Fe, Cu and Zn [17]. Additionally, even if the socioeconomic and nutritional status of cases and controls are similar, it is still impossible to rule out the possibility that various genetic profiles might play a role in the pathogenicity and severity of knee OA [25]. The present study also has some significant advantages. The first strength is the simultaneous estimation of 5 trace elements under the same experimental conditions.

5. Conclusion

Patients with knee OA had higher levels of Cu and value of Cu/Zn and lower levels of serum Zn and Se; these changes were potentially correlated with the duration and severity of disease. Zinc and selenium supplementation to reduce severity of knee OA should be further investigated.

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Conflict of Interest

The author declares that there is no conflict of interest.

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