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ORIGINAL ARTICLE

Serum trace element and heavy metal levels in patients with sepsis

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ABSTRACT

Background and objectives: Sepsis is defined as a life-threatening organ dysfunction syndrome, which occurs when the body's immune response to infection is impaired. The aim of the present study was to investigate serum Iron, Copper, Zinco, Cobalt, Chromium, Selenium, Vanadium, Nickel, Cadmium, and Aliminium levels in patients with sepsis.

Materials and methods: This prospective and observational study was conducted at a tertiary care university hospital of Turkey from 2015 to 2016, and comprised patients with sepsis. Serum concentrations of 10 elements were analyzed using inductively coupled plasma mass spectrometry. Analyses were performed at the laboratory of Düzce University Scientific and Technological Research Application and Research Center. A total of 87 participants (52 men, 35 women; average age, 74.11 ± 14.26) were enrolled.

Results: When evaluated in terms of trace elements, a significant difference was noted between the sepsis and control groups in terms of the levels of the five elements. Chromium, Iron, Nickel, Copper, and Cadmium levels were significantly higher in the sepsis group.

Conclusion: Our study indicated in particular, Iron, Copper, Chromium, Nickel, and Cadmium levels were elevated in patients with sepsis.

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Introduction

Sepsis is defined as a life-threatening organ dysfunction syndrome, which occurs when the body's immune response to infection is impaired [1]. With increasing prevalence, sepsis affects approximately 30 million people worldwide, resulting in high mortality and morbidity [2]. Sepsis can develop due to nearly any type of microorganism that causes community or hospital-acquired infections. The most common site of infection is the lungs, followed by the abdomen, blood circulation, and genitourinary system [3,4].

Nutritional status is considered as one of the crucial determinants of resistance to infection and of general well-being. Trace elements are vital for several reactions in the body. These elements must be present in the body in an appropriate amount. Trace elements, which act as cofactors for several enzymes, mediate important biochemical reactions [5]. Serum trace elements affect the functions of the cells of the immune system such as lymphocytes and granulocytes, and certain immune and inflammatory responses can alter the distribution of these chemicals in the body [6].

Data obtained from literature supports the immunological functions of various trace elements. However, there are also publications reporting that trace element deficiencies do not have an effect on the mortality and duration of hospitalization and intensive care unit (ICU) stay in critical patients. Serum iron (Fe) and zinc (Zn) levels are decreased during infection and inflammation [6,7]. Cobalt (Co) is a crucial component of vitamin B12, which is essential in folate and fatty acid metabolism [8]. Selenium (Se) plays an important role in maintaining the immune system. It also functions as a common factor for metalloenzymes, such as glutathione peroxidase [9]. Copper (Cu), Zn, Se, and Fe have been investigated in certain acute and chronic infections such as tuberculosis, otitis media, sepsis, and viral hepatitis [10]. The function of chromium (Cr) during inflammation remains unclear, but it was reported to show beneficial effects on the regulation of blood glucose in diabetic patients with insulin resistance [11].

Nickel (Ni), which is one of the trace elements that are considered carcinogenic for humans, can be included in the enzyme structure that contributes to

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the virulent behavior of certain bacteria such as *Helicobacter pylori* [12]. Cadmium (Cd) is another well-known carcinogenic trace element [13]; however, to the best of our knowledge, serum Cd levels in cases of infection have not yet been studied. Aluminum (Al) is considered to be responsible for cell death due to irreversible structural changes in protein structures in Alzheimer's disease [14]. To date, to the best of our knowledge, no human studies have been conducted on Vanadium (V), which is included in the possibly essential trace element category. However, *in vitro* and *in vivo* studies have shown that the use of V may be beneficial in the treatment of viral and bacterial infections as well as cardiovascular and neurological disorders [15].

The aim of the present study was to investigate serum Fe, Cu, Zn, Co, Cr, Se, V, Ni, Cd, and Al levels in patients with sepsis.

Materials and methods

This prospective and observational study was conducted at a tertiary care university hospital in Düzce city in the western Black Sea region of Turkey from December 2015 to December 2016, and comprised patients with sepsis. The study was approved by the ethics committee of Düzce University Medical faculty and written informed consent was obtained from the patients and their relatives.

Sepsis was defined in accordance with the International Sepsis Definitions Conference [1]. After patients were diagnosed with sepsis, blood samples were collected from the patients at admission. The control group comprised healthy volunteers who were living in the same area and did not use vitamin supplements. Patients under the age of 18 years, pregnant patients, and patients who refused to have their blood drawn were not included in the study. Serum samples were stored at $-70\,^{\circ}C$ until further analysis.

Age, sex, mortality, severity indices for patients with sepsis, length of stay in the ICU, and length of stay in the hospital were recorded. We used Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) scores, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores for determining the severity indices for critically ill patients from patients' clinical data obtained within first 24 h of admission. In addition, the presence of comorbidities (trauma, heart disease, hypertension, malignancy, history of surgery, chronic obstructive pulmonary disease, diabetes mellitus, kidney failure, and goiter) and the mortality on day 14 were recorded.

Serum concentrations of 10 elements were analyzed using inductively coupled plasma mass spectrometry (ICP-MS; Perkin Elmer NexION 350X, USA). Analyses were performed at the laboratory of Düzce University Scientific and Technological Research Application and Research Center (DUBIT). The reference levels of serum trace elements were evaluated on the basis of the limits specified by Forrer et al. [16].

Statistical analyses were performed using the SPSS v.22 software package. For continuous variables, comparisons between the groups were made using Independent samples *t*-test or Mann–Whitney *U* test, depending on the distribution of the variables. Pearson chi-square or Fisher's exact test was used for analyzing categorical data. Spearman rho correlation analysis was performed for analyzing linear relationships between variables. $p < 0.05$ was considered statistically significant in all analyses.

Results

Of the 87 patients included in the study with the diagnosis of sepsis, 52 (59.8%) were male and 35 (40.2%) were female. Half of the 22 individuals who constituted the control group were male and half were female. No significant difference was noted between the sepsis and control groups in terms of gender ($p = 0.407$). While the mean age of the sepsis group was 74.11 ± 14.26, the mean age of the control group was 31.05 ± 7.31, and this difference was noted to be significant ($p < 0.001$). The mean length of hospital stay was 11 (1–135) days in the sepsis group, and the mortality rate was 63.2%. The mean GCS, APACHEII and SOFA scores of the patients were 9 (3–15), 27 (13–49), and 10 (1–18), respectively. There were diabetes mellitus 18 (20.6%), chronic renal failure 17 (19.5%), chronic obstructive pulmonary disease 16 (18.3%), cerebrovasculer obstruction 17 (19.5%), hypertension 57 (65.5%), congestive heart failure 28(32.1%), coronary artery disease 15(17.2%), and malignancy 6 (6.8%) cases. In patients with sepsis, the most commonly occurring infection was pneumonia with 70.1%, followed by urinary system infection with 13.4%.

When evaluated in terms of trace elements, a significant difference was noted between the sepsis and control groups in terms of the levels of the five elements (Cr, Fe, Ni, Cu, and Cd). Cr ($p < 0.001$), Fe ($p = 0.004$), Ni ($p = 0.001$), Cu ($p < 0.001$), and Cd ($p < 0.001$) levels were significantly higher in the sepsis group. Although Zn was lower in the sepsis group, the difference was not statistically significant ($p = 0.113$). No difference was noted between the sepsis and

Table 1. Median trace element values of sepsis and control group [median (min-max)] (Serum trace element levels were measured in μg/L.).

Trace element	Sepsis ($n = 87$)	Control ($n = 22$)	p Value
Al	6.98 (2.19–334.70)	8.61 (1.41–19.03)	0.572
V	5.23 (0.68–9.94)	5.22 (0.08–7.86)	0.298
Cr	7.94 (1.44–38.77)	0.31 (0.20–0.65)	***<0.001***
Fe	2591 (133–26,140)	1318 (892–2980)	***0.004***
Co	2.48 (0.00–23.24)	2.99 (0.06–3.81)	0.846
Ni	5.43 (0.24–80.87)	2.74 (0.66–15.24)	***0.001***
Cu	927 (1–4232)	434 (324–731)	***<0.001***
Zn	915 (36–81,820)	1248 (645–2347)	0.113
Se	37.96 (3.62–58.90)	28.03 (23.13–5.99)	0.106
Cd	0.30 (0.00–8.36)	0.08 (0.01–0.58)	***<0.001***

Al: Aluminium; V: Vanadium; Cr: Chromium; Fe: Iron; Co: Cobalt; Ni: Nickel; Cu: Copper; Zn: Zink; Se: Selenium; Cd: Cadmium.

Table 2. Correlation of trace elements.

		Al	V	Cr	Fe	Co	Ni	Cu	Zn	Se	Cd
Al	*r*		0.055	**−0.455**	**−0.354**	0.157	0.070	**−0.392**	**0.317**	**−0.372**	0.087
	p		0.613	**0.000**	**0.001**	0.148	0.519	**0.000**	**0.003**	**0.000**	0.424
V	*r*			0.112	−0.046	**0.321**	**0.449**	**0.236**	**0.429**	**0.215**	0.074
	p			0.304	0.676	**0.003**	**0.000**	**0.029**	**0.000**	**0.047**	0.499
Cr	*r*				**0.734**	0.081	0.191	**0.867**	0.017	**0.797**	−0.076
	p				**0.000**	0.457	0.078	**0.000**	0.879	**0.000**	0.488
Fe	*r*					0.085	0.053	**0.687**	0.094	**0.686**	−0.097
	p					0.437	0.629	**0.000**	0.391	**0.000**	0.375
Co	*r*						−0.098	**0.332**	**0.729**	**0.245**	−0.111
	p						0.369	**0.002**	**0.000**	**0.023**	0.310
Ni	*r*							0.160	**0.266**	**0.242**	0.137
	p							0.142	**0.013**	**0.025**	0.209
Cu	*r*								**0.253**	**0.824**	−0.144
	p								**0.019**	**0.000**	0.186
Zn	*r*									**0.252**	0.027
	p									**0.019**	0.806
Se	*r*										−0.039
	p										0.723
Cd	*r*										
	p										

control groups in terms of Al, V, and Se levels ($p > 0.05$) (Table 1).

Positive correlations were observed between some of the trace elements (Cr and Fe, $r = 0.734$, $p < 0.001$; Cr and Cu, $r = 0.867$, $p < 0.001$; Cr and Se, $r = 0.797$, $p < 0.001$; Co and Zn, $r = 0.729$, $p < 0.001$; and Cu and Se, $r = 0.824$, $p < 0.001$). The positive and negative correlations between the 10 elements that were investigated are presented in Table 2.

The relationship between trace elements and mortality was investigated, and a significant correlation was noted between Cd levels and mortality on day 14 ($p = 0.030$) (Table 3).

Table 3. Comparison of trace elements with 14th day mortality ([median (min-max)]).

	Survived ($n = 56$)	Ex ($n = 31$)	p Value
Al	7.15 (3.70–334.70)	7.06 (2.19–237.00)	0.891
V	5.30 (1.06–9.93)	5.09 (0.68–9.94)	0.628
Cr	7.01 (1.75–34.76)	17.93 (1.71–38.77)	0.457
Fe	2191 (133–17,570)	2911 (519–26,140)	0.061
Co	2.22 (0.00–23.24)	3.05 (0.11–20.57)	0.214
Ni	6.15 (0.95–80.87)	4.94 (0.99–28.75)	0.237
Cu	799 (211–4232)	1484 (1–4070)	0.422
Zn	877 (266–81820)	1055 (72–67,930)	0.371
Se	35.42 (7.93–158.90)	48.74 (5.37–133.60)	0.844
Cd	0.21 (0.00–5.17)	0.46 (0.01–8.36)	***0.030***

Discussion

In the present study, we aimed to determine the levels of serum trace elements and heavy metals in patients with sepsis and compare the results with healthy volunteers. Several studies have been conducted on Zn, Se, and Fe that emphasize the protective effects of these elements against oxidative damage to cells in various inflammatory diseases [17,18]. However, studies investigating the levels of Co, Cu, Cr, V, Ni, Cd, and Al in patients with sepsis are very scarce. To the best of our knowledge, this is one of the studies in which the highest number of trace elements and heavy metals have been investigated in patients with sepsis.

In the study by Mertens et al., Zn and Se concentrations were reduced in critically ill patients particularly in patients with sepsis [10,19]. In the present study,

although no statistically significant difference was noted between the sepsis and the healthy control groups ($p = 0.113$), serum Zn level was lower in patients with sepsis. In another study, it was observed that Zn deficiency increased the mortality rate in a mouse model of polymicrobial sepsis [20]. We were expecting similar results in our study, but when we analyzed the relationship between serum Zn levels and mortality on day 14 in patients with sepsis, there was no difference between the two groups ($p = 0.371$). In previous trials, it was shown that plasma Se concentration decreased in early acute response in sepsis [9,10,21]. In these studies, serum Se levels were measured for identifying Se deficiency. However, some sources state that Se deficiency cannot be detected by serum levels alone. This is because, in case of inflammation, selenoenzymes are translocated as a result of increased vascular permeability, and Se passes into the tissues. Therefore, serum Se levels may not represent the actual level of Se in the body [22]. Unlike previous studies, no statistically significant difference was noted in serum Se levels between sepsis and control groups in the present study ($p = 0.106$).

Fe is crucial for cell growth and numerous metabolic processes. In addition, Fe is a critical factor for the survival and virulence of pathogenic microorganisms. Therefore, Fe therapy has been associated with acute infections and exacerbation of sepsis [23]. Contrary to previous studies, serum Fe levels were significantly higher in the sepsis group in the present study ($p = 0.004$). Similarly, it was reported that serum Fe level was high in patients with chronic otitis media, and this was a precipitating factor for recurrent infection [24]. Heavy metals, such as Co, may accumulate in different organs of the body and inhibit vital enzymes. Co is a component of vitamin B12. In the present study, no significant difference was noted in serum Co levels between sepsis and control groups ($p = 0.846$).

Cu is important for collagen synthesis, antioxidant activity, and Fe transport and can act as a cofactor for oxidative metalloenzymes [25]. In one study, serum Cu levels were found to be low in Peyronie's disease associated with inflammation [26]. Contrary to this study, Tanrıkulu et al. reported that serum Cu levels were elevated in patients with COPD [27]. Elevated Cu values have also been associated with nutritional abnormalities, oxidative stress, inflammation, and immune dysfunction [28]. Consistent with the literature, Cu level in the present study was significantly higher in the sepsis group compared with that in the control group ($p < 0.001$). In several studies evaluating the relationship between Cr and infection, no significant correlation was found between serum Cr levels and infection [29,30]. In the present study, however, serum Cr levels were significantly higher in the sepsis group ($p < 0.001$). Although *in vitro* studies have demonstrated the interaction between V compounds and DNA and the beneficial effects of these compounds on tissues, they are not yet used in humans [15]. Serum V levels, to the best of our knowledge, were investigated for the first time in the present study, and no significant difference was noted in serum V levels between sepsis and control groups ($p = 0.298$).

One of the important findings of the present study was that the serum Ni level was higher in patients with sepsis compared with that in the control group ($p = 0.001$). Similarly, in another study, Ni level was found to be significantly higher in patients suffering from viral hepatitis infection [31]. Another important finding was that the serum level of Cd, which is known to be toxic and carcinogenic in humans similar to that of Ni, was higher in patients with sepsis compared with that in the control group ($p < 0.001$). No difference was noted between the sepsis and control groups in terms of the serum level of Al, which is another toxic element.

The primary limitations of the present study are as follows: the number of patients in the control group was less and the mean age differed between the groups. Serum samples obtained from patients with sepsis were not standardized (fasting or postprandial, etc.). Another limitation of the study was the lack of follow-up measurement of serum element levels due to limited resources.

Our study indicated that altered trace and heavy element status is associated with sepsis. In particular, Fe, Cu, Cr, Ni, and Cd levels were elevated in patients with sepsis. Therefore, further research investigating the clinical significance of these trace and heavy elements and their association with in patients with sepsis is required.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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