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The Effect of β-Glucan on Trace Element Levels in Intra-Abdominal Sepsis in Rats

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Abstract Sepsis is associated with the development of progressive damage in multiple organ systems. The beneficial effect of glucans has been attributed to modulation of immune function and enhances defense against bacterial, viral, fungal, and parasitic infections. The aim of this study was to investigate the putative protective effect of ß-glucan on changes of trace element levels in various tissues after experimental sepsis in rats. Sepsis was induced by cecal ligation and perforation (CLP) in 28 male Wistar albino rats. To evaluate this, rats were divided into four groups as sham operated, ß-glucan treated sham operated, CLP, and ß-glucan-treated CLP. Sixteen hours after operation, rats were decapitated and zinc (Zn) and copper (Cu) levels were determined in the liver, kidney, heart, diaphragm, and lung tissues. The results demonstrate that sepsis significantly decreased zinc and copper levels of all tissues. The decrease in tissue zinc and copper levels demonstrates the role of trace elements in sepsis-induced tissue damage. Our results indicated that ß-glucan administration did not return the zinc and copper levels to the control group level, and it seems likely that the given dose of ß-glucan was insufficient to prevent sepsis-induced organ injury.

Keywords Sepsis · β-Glucan · Zinc · Copper · Rat tissue

Introduction

Sepsis is defined as a systemic response to microorganisms and toxins. In spite of the developments in sophisticated monitoring, antibiotic therapy, surgical technique, and

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supportive treatment, sepsis is the most frequent cause of death in intensive care units [1]. Research during the last quarter of the twentieth century clearly established the importance of adequate trace element nutrition for protection of animals and humans against infections [2]. Zinc and copper have received the majority of attention. The extent of the impairment in the immune system due to trace element deficiency can be sufficient to increase the risk of morbidity and mortality due to viral, microbial, and parasitic infections; and reversal of the trace element deficiency restores immunocompetence. Moreover, there is increasing evidence that some cell types and effector activities appear to be particularly sensitive to marginal and moderate deficiencies of the trace elements. Recent reviews should be consulted for specific details about the relationship between the nutritional status of trace elements and the function of the immune system [2].

Antioxidants might counteract the toxicity of oxygen radicals and that free radical ablation for the treatment of sepsis could be useful in the clinical setting of sepsis [3]. It has been shown that the increase in tissue and plasma oxidative stress correlates in intra-abdominal sepsis [4]. However, trace element status needs to be taken into account in regard to the involvement of trace elements in the antioxidant responses, inflammation, wound healing, and immune responses [5]. Trace elements act as major antioxidant enzyme cofactors; variations of β-glucans are glucose polymers found in the cell walls of yeast, fungi, and cereal plants. The beneficial effects on the immune system and the lack of toxic or adverse effect had focused the studies on β-glucan molecule. Several mechanisms were proposed for the protective effect of β-glucan; one of them is related to antioxidant capacity of the molecule [6]. There are several studies in which the relationship between sepsis and trace elements has been investigated [4]. However, the effects of β-glucan on the trace elements metabolism or its alterations have not been studied.

In this study, we investigated the possible protective effects of β-glucan on the alteration of trace element levels of liver, lung, kidney, heart, and diaphragm tissues in experimental model of intra-abdominal sepsis established by cecal ligation and puncture in rats.

Materials and Methods

All experimental protocols were performed in accordance with the National Institutes of Health guidelines and the approval of the Istanbul University, Cerrahpasa Medical Faculty Animal Care and Use Ethics Committee.

Animals and Induction of Sepsis

Twenty-eight male Wistar albino rats, weighing 200–250 g, were kept in individual wire-bottom cages in a room at a constant temperature (22±2°C) with 12-h light and dark cycles, and fed standard rat chow. The rats were divided into the following four groups of seven rats each: sham-operated control (C), sham-operated+β-glucan-treated group (Glucan), cecal ligation and perforation (CLP) group, and cecal ligation and perforation+β-glucan-treated (β-glucan+CLP) group.

Sepsis was induced by CLP (cecal ligation and perforation) technique [7]. General anesthesia was induced by injection of intraperitoneal ketamine hydrochloride (Ketalar, Parke-Davis, USA). All procedures were performed under sterile conditions. The cecum was exposed, ligated just distally to the ileocecal valve to avoid intestinal obstruction, punctured twice with a 22-gauge needle, squeezed gently to force out a small amount of feces, and then returned to the abdominal cavity and the laparotomy was closed with 4.0 silk sutures (Fig. 1).

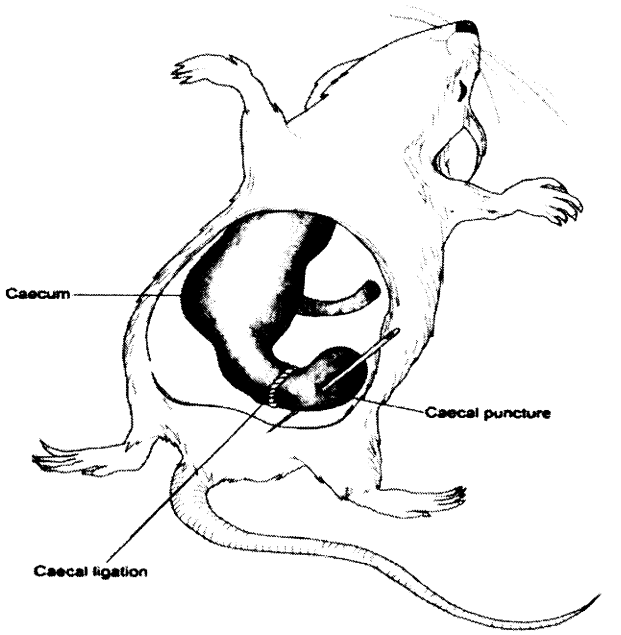

Fig. 1 CLP (cecal ligation and perforation) technique

At the end of the operation, all rats were resuscitated with saline, 3 ml/100 g body weight given subcutaneously. Postoperatively, the rats were then returned to their cages with free access to food and water [8]. The sham-operated group rats underwent laparotomy, but the cecum was neither ligated nor perforated.

β-Glucan Treatment

The β-glucan (Mustafa Nevzat Company, Turkey) we used in this study is 1,3-1,6 β-D-glucan in the microparticulate form which is prepared from *Saccharomyces cerevisiae* yeast. β-Glucan was suspended in saline. β-Glucan 50 mg/kg per oral (po) was given by intragastric gavage once a day for 10 days. The rats were decapitated 16 h after the CLP procedure, and kidney, liver, lung, heart, diaphragm tissue samples, and blood were taken and tissue samples were stored at −70°C [6].

Measurements of Trace Elements

In order to eliminate adsorbed metals on the glassware being use, all the glassware was kept in 10% (*v*/*v*) nitric acid solution before use. These were then cleaned with distilled water and dried in an oven overnight at 100°C [9]. The tissue samples were weighed and transferred into metal-free glass tubes for digestion. The samples were first digested with 2 ml of concentrated nitric acid at 100°C in the furnace for 1 h, and 2 ml of perchloric acid (60%) was added to the cooled materials. The materials were then completely digested at 120°C until the materials diminished to half of the original total volume. Digested materials were diluted with deionized water to 10 ml. The last dilutions of the samples were mixed on a shaker for 15 min just before measurement. Zn and Cu levels of the kidney, liver, lung, heart, and diaphragm were measured by flame atomic absorption spectrophotometer (Shimadzu AA-680). Results were calculated as μg/g wet weight [10].

Histopathological Examination

Samples of kidney, liver, lung, heart, and diaphragm tissue were fixed in 10% formaldehyde and processed routinely for embedding in paraffin. Paraffin sections were stained with hematoxylin–eosin and azan examined under a light microscope. The histopathological examination was performed by a histologist who was unaware of the groups of the specimens. Histopathological analysis was based on the scoring system described by Sener et al. [11]. Histological changes were scored from 0 to 4 and the means of the scores were taken. The following scale was used: 0, no pathological findings; 1, mild (fewer than three fields); 2, moderate (three to six fields); 3, severe (more than six fields).

Criteria for the microscoping scoring of lung tissue damage are congestion, alveolar structural disturbance, inflammatory cell infiltration, and interstitial edema; for liver are vacuolization of hepatocytes, congestion, Kupffer cell infiltration, and enlargement of sinusoids; for kidney are congestion, degeneration of proximal and distal tubules, and interstitial edema; and for diaphragm and heart are degeneration of muscle fibers and inflammatory cell infiltration.

Statistical Analysis

All data are expressed as mean (M)±standard deviation (SD). Statistical analyses were performed with Statistical Products and Service Solution package (SPSS for Windows, 10.0.1 version, Chicago, IL, USA). Statistical significance was defined by a p value less than 0.05.

Results

The zinc levels in the lung and liver tissues were significantly lower in the CLP group than in the controls ($p<0.001$). In the CLP group, kidney, diaphragm, and heart tissue zinc levels were significantly lower than in controls ($p<0.01$, $p<0.01$, and $p<0.05$, respectively). In the CLP+β-glucan group, zinc levels of liver ($p<0.001$), lung ($p<0.01$), kidney ($p<0.05$), heart ($p<0.05$), and diaphragm ($p<0.05$) were found to be significantly lower than those of controls (Table 1). No significant differences were found in the liver, lung, kidney, heart, and diaphragm zinc levels between the CLP and CLP+β-glucan groups ($p>0.05$) (Table 1).

In the CLP group, liver, kidney, and diaphragm copper levels were found to be significantly lower than in control group ($p<0.001$). Copper levels of lung and heart was

Table 1 Zinc Levels of Liver, Lung, Kidney, Heart, and Diaphragm Tissues in Control, β-Glucan, Cecal Ligation and Perforation (CLP), and CLP+β-Glucan (μg/g Wet Weight)

	Control	β-Glucan	CLP	CLP+β-glucan
Liver	69.42±13.60	64.49±19.28	36.62±4.92***	40.03±6.59***
Lung	77.84±13.49	70.25±20.49	35.52±12.72***	47.12±20.46**
Kidney	53.04±12.18	59.96±9.80	26.71±9.57**	36.18±9.73*
Heart	56.62±5.15	65.79±23.91	31.18±18.30*	40.15±19.14*
Diaphragm	68.34±15.58	66.00±24.52	31.72±22.03**	53.24±32.37*

Values are expressed as means±standard deviation

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control groups

Table 2 Copper Levels of Liver, Lung, Kidney, Heart, and Diaphragm Tissues in Control, β-Glucan, Cecal Ligation and Perforation (CLP), and CLP+β-Glucan (μg/g Wet Weight)

	Control	β-Glucan	CLP	CLP+β-glucan
Liver	9.80±3.46	6.50±1.43	4.15±0.65***	4.24±0.73***
Lung	7.37±3.14	2.62±1.63	2.17±1.52*	2.32±0.57*
Kidney	10.47±3.27	7.09±2.25	4.83±0.94***	5.16±0.73***
Heart	6.31±1.94	6.00±1.10	4.27±0.77*	4.51±0.93*
Diaphragm	3.14±0.66	2.10±0.93	1.87±0.37***	2.36±0.70*

Values are expressed as means±standard deviation

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control group

found to be significantly lower than those of control group ($p<0.05$) (Table 2). When CLP group compared with CLP+β-glucan group, no significant statistical differences were observed in copper levels of the liver, kidney, lung, heart, and diaphragm tissues ($p>0.05$) (Table 2).

Table 3 shows copper/zinc ratios all groups. There was no significant difference found in the tissues. In our study, β-glucan treatment reduced tissue damage according to histological criteria in this experimental sepsis model in rats (Table 4). Representative example of control groups was liver in the copper/zinc ratios of all tissues.

Histological evaluation in liver tissue of control group is indicated in Fig. 2. Histological evaluation in the liver tissue samples of sepsis group found vacuolization of hepatocytes, mononuclear cell infiltration, and fibrosis (Fig. 3). Histological evaluation in kidney tissues of control group are indicated in Fig. 4. Sepsis-induced histological damage was seen in the kidney tissue demonstrating degeneration of Bowman space and glomeruli, vascular congestion and interstitial edema, and degeneration of proximal and distal tubules (Fig. 5).

Discussion

Sepsis is associated with the development of progressive damage in multiple organs, and is an important cause of patient mortality in intensive care units. The site of infection on injury dictates the first organ system exposed to the various inflammatory mediators during

Table 3 Copper/Zinc Ratios of Liver, Lung, Kidney, Heart, and Diaphragm Tissues in Control, β-Glucan, Cecal Ligation and Perforation (CLP), and CLP+β-Glucan

	Control	β-Glucan	CLP	CLP+β-glucan
Liver	0.15±0.08	0.11±0.05	0.11±0.02	0.11±0.03
Lung	0.09±0.04	0.05±0.05	0.06±0.02	0.06±0.03
Kidney	0.20±0.06	0.16±0.04	0.20±0.08	0.15±0.05
Heart	0.11±0.03	0.10±0.04	0.17±0.09	0.13±0.06
Diaphragm	0.05±0.02	0.04±0.02	0.08±0.05	0.06±0.03

Values are expressed as means±standard deviation

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control group

Table 4 The Total Histological Scores of the Liver, Lung, Kidney, Heart, and Diaphragm Tissues in Control, β-Glucan, Cecal Ligation and Perforation (CLP), and CLP+β-Glucan

	Control	β-Glucan	CLP	CLP+β-glucan
Liver	0.11±0.10	0.13±0.11	8.80±0.10***	6.70±0.40***
Lung	0.12±0.09	0.20±0.18	9.00±0.00***	7.50±0.30***
Kidney	0.23±0.17	0.18±0.10	8.00±0.00***	6.90±0.50***
Heart	0.19±0.10	0.16±0.12	6.00±0.10***	5.00±0.30***
Diaphragm	0.00±0.00	0.12±0.15	5.50±0.00***	3.20±0.00***

Values are expressed as means±standard deviation

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control group

sepsis events. The heart/lung axis is the primary response organ system during systemic sepsis, whereas the liver is the primary response organ for intestinally derived events [12, 13]. Although it is widely recognized that essential trace elements are required for the differentiation, activation, and performance of numerous functions of immune cells, the specific roles of these inorganic micronutrients in these processes remain largely undefined. Trace elements are required for the activity of a number of acute-phase proteins and immune cells that directly participate and interact in host defense processes. During infection, there is a flux of both free and protein-bound, essential as well as non-essential, trace elements between blood and the tissues involved by the disease [2].

Acute infectious diseases are most often accompanied by changes in the concentrations of several trace elements in plasma/serum. The most consistent responses include a decrease in plasma levels of Fe and Zn and an increase in Cu levels. These essential trace elements are crucial for the host defense, including the development of inflammation and the growth and virulence of many microorganisms [2, 14, 15]. However, it is not known whether trace element changes in whole blood in infected individuals are similar in magnitude and direction as in serum/plasma, because concentrations in blood cells are virtually unknown. Determination of blood Cu and Zn can be used to indicate ongoing infectious and inflammatory disease, but blood levels cannot be used to predict levels of

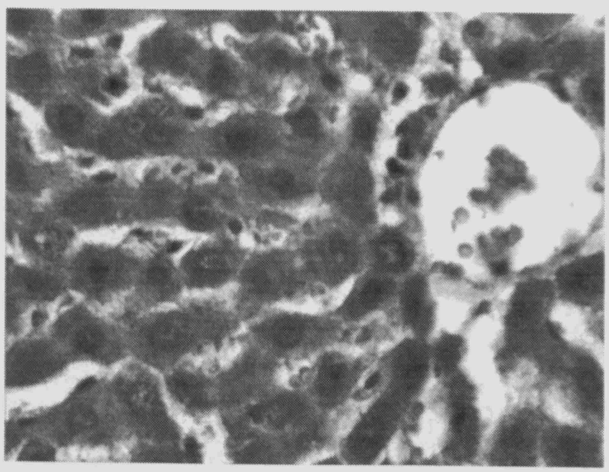

Fig. 2 Normal liver histology in control groups (hematoxylin–eosin ×40)

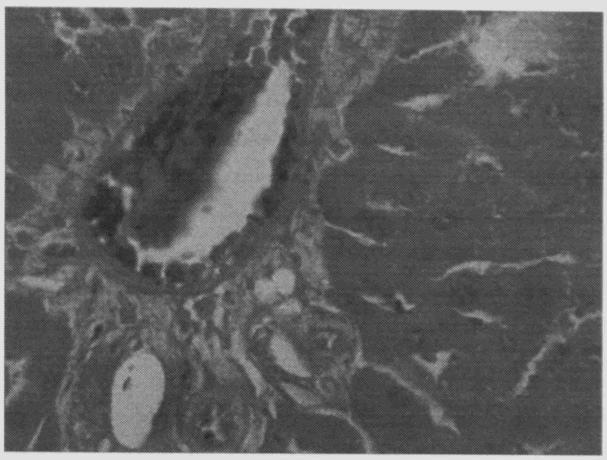

Fig. 3 Liver histology in sepsis group. The view of liver vacuolization of hepatocytes, mononuclear cell infiltration, and fibrosis (hematoxylin–eosin ×40)

these elements in inflammatory tissues [16]. Therefore, the levels of these elements in all tissues were determined in sepsis.

According to the findings of the present study, the Zn levels in the liver, lung, kidney, heart, and diaphragm were significantly decreased when compared to control groups (Table 1). The Cu levels were also lower in the experimental groups than the same parameter of the control groups (Table 2). These finding indicates that zinc and copper levels decrease by a correlation of the severity of infection. The observed alterations can reflect either decreased activities of individual cells, a reduction in the total number of effector cells in one or more tissues, or a combination of fewer cells with each cell having diminished capacity [15].

Trace elements are redistributed in infection; for instance, the Cu/Zn ratio is increased in serum because of the release of ceruloplasmin from the liver, concomitant to Zn uptake in the liver, which is typical to infectious diseases regardless of etiology [2]. Saner et al. [17] investigated serum Zn, Cu levels and Cu/Zn ratios in infants with sepsis, sepsis syndrome, and septic shock. They found that serum Zn and Cu levels were lower in infants with sepsis compared to healthy infants and infants with mild infection but significant differences were

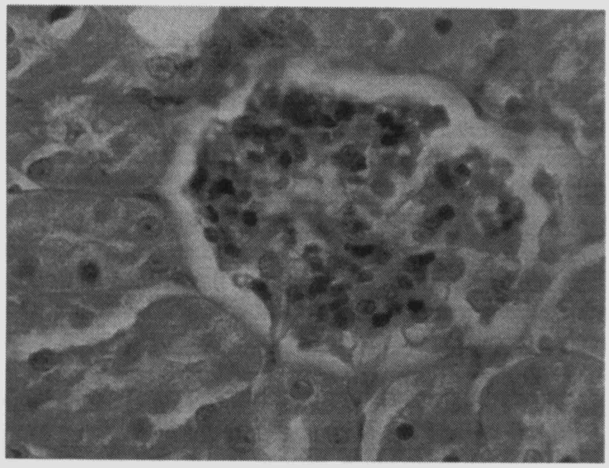

Fig. 4 Normal kidney histology in control groups (azan ×40)

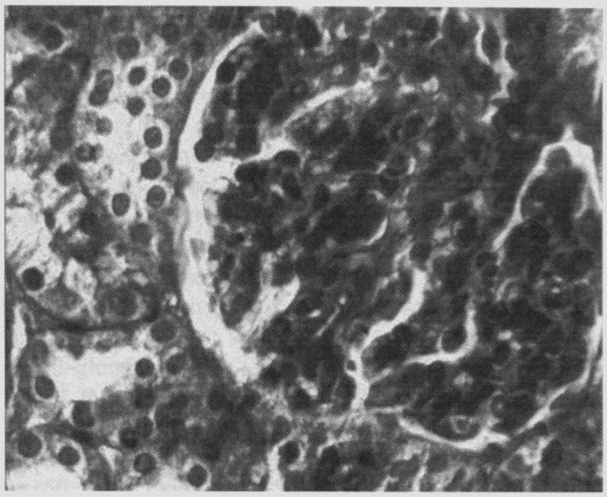

Fig. 5 Kidney histology in sepsis group. The view of kidney vascular congestion, degeneration of Bowman space and glomeruli, interstitial edema, degeneration of proximal, and distal tubules (azan ×40)

not found. Frisk et al. [18] showed that Cu/Zn ratio increased in serum as a response to the infection. Gupta et al. [19] found an association between lower zinc levels and consequently an increased Cu/Zn ratio and carcinoma of the gallbladder. Some authors have reported a strong correlation between the stage of various malignancies and elevated serum Cu levels and Cu/Zn ratio and decreased serum Zn levels. Gallante et al. [20] reported that increased blood level of Cu and a decreased level of Zn resulting in an increased Cu/Zn ratio suggest a persistent low grade "acute-phase reaction" in patients with aortic valve sclerosis. Some investigators emphasize the role of Cu/Zn ratio in human pathology, but in our study tissue Cu/Zn ratios were not significantly different in the CLP and CLP+β-glucan group from control group values (Table 3).

Sepsis is associated with heightened oxidative stress. There is increasing evidence that oxidative stress has an important role in the development of sepsis-induced multi-organ failure. Kolgazi et al. [21] observed that induction of sepsis resulted in a significant oxidative damage in lung and kidney tissue, as evidenced by increased lipid peroxidation with a concomitant decrease in endogenous antioxidant glutathione levels. Diminished antioxidative defenses, superoxide dismutase, catalase, and glutathione, also contribute to oxidative stress [4]. Recent studies have reported increased levels of lipid peroxides and decreased antioxidant enzyme activity in experimental sepsis, indicating an exhaustion of the antioxidant system [22–25]. Ritter et al. [26] showed that malondialdehyde (MDA) and plasma superoxide dismutase levels are markers of early mortality in septic rats. Increased concentrations of lipid peroxidation products are found in rats with sepsis and tissue MDA levels are increased in septic shock induced by cecal ligation and perforation in rats. Both copper and zinc act as antioxidants mainly through their associated enzyme Cu, Zn superoxide dismutase and ceruloplasmin. Zn and Cu containing superoxide dismutase have been much reported in the literature and are important to antioxidant defense and catalyze the conversion of two O_2— to O_2 and H_2O_2 in the cytosol [9]. Thus, it is clear that Cu and Zn play an important role in the development of oxidative stress. Cu can act both as a pro-oxidant and as a component of the antioxidant system. Zinc is involved in antioxidant defense [27].

β-Glucans are glucose polymers found in the cell wall of yeast, fungi, and cereal plants. The beneficial effects on the immune system and the lack of toxic or adverse effect had focused the studies on β-glucan molecule [28, 29]. Currently, β-glucan is accepted to be

one of the most powerful immune response modifiers [30]. Sener et al. [6] showed that treatment with β-glucan significantly reversed the elevations in MDA levels in the liver, kidney, heart, lung, diaphragm, and brain tissues. Babayigit et al. [8] investigated the protective effect of β-glucan on lung injury after cecal ligation and puncture in rats. They also found that β-glucan treatment decreased lung damage according to both morphological and functional criteria in their experimental sepsis model in rats. Konukoglu et al. [31] indicated that Cu, Zn, and Fe had important effects on peroxidation events in *Escherichia coli*-induced peritonitis. They observed the presence of *E. coli*-induced lipid peroxidation in peritoneum and this is accompanied by an increase in Fe, Zn, and Cu levels. However, the relationship between the kidney, liver, lung, heart, and diaphragm tissues trace elements levels and β-glucan administration in sepsis has not been defined.

We examined the effects of β-glucan therapy on the trace elements levels in experimental sepsis. The results of the present study demonstrate that sepsis causes decrease of Zn and Cu in the liver, lung, kidney, heart, and diaphragm tissues, and these data suggest that the sepsis-induced damages in these tissues have not returned to control levels with given β-glucan dose (50 mg/kg) treatment. Therefore, additional Cu and Zn may be needed in the treatment of injured rats to prevent the extension of damage in multiple organ system and the given β-glucan dose must be adjusted.

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