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Original scientific paper

Serum Concentration of Zinc, Copper, Manganese and Magnesium in Patients with Liver Cirrhosis

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A B S T R A C T

The role of trace elements in the pathogenesis of liver cirrhosis and its complications is still not clearly understood. Serum concentrations of zinc, copper, manganese and magnesium were determined in 105 patients with alcoholic liver cirrhosis and 50 healthy subjects by means of plasma sequential spectrophotometer. Serum concentrations of zinc were significantly lower (median 0.82 vs. 11.22 μmol/L, p<0.001) in patients with liver cirrhosis in comparison to controls. Serum concentrations of copper were significantly higher in patients with liver cirrhosis (median 21.56 vs. 13.09 μmol/L, p<0.001) as well as manganese (2.50 vs. 0.02 μmol/L, p<0.001). The concentration of magnesium was not significantly different between patients with liver cirrhosis and controls (0.94 vs. 0.88 mmol/L, p=0.132). There were no differences in the concentrations of zinc, copper, manganese and magnesium between male and female patients with liver cirrhosis. Only manganese concentration was significantly different between Child-Pugh groups (p=0.036). Zinc concentration was significantly lower in patients with hepatic encephalopathy in comparison to cirrhotic patients without encephalopathy (0.54 vs. 0.96 μmol/L, p=0.002). The correction of trace elements concentrations might have a beneficial effect on complications and maybe progression of liver cirrhosis. It would be recommendable to provide analysis of trace elements as a routine.

Key words: *zinc, copper, manganese, magnesium, liver cirrhosis, trace elements*

Introduction

The role of trace elements in pathogenesis of liver cirrhosis and its complications is still not clearly understood. In fibrogenesis the initial occurrence is hepato-cellular necrosis. In the early phase, inflammation cell products, proteinases and reactive oxygen radicals, may initiate hepato-cellular necrosis with consecutive releasing of numerous cytokines. Following hepatic injury, there is the increase in extracellular matrix, the activation of stellate cells, the increase in rough endoplasmatic reticulum and expression of smooth muscle specific α--actin[1]. Activated stellate cells are influenced by numerous cytokines. Some of them have proliferative effect on stellate cells while others stimulate fibrogenesis[2].

Zinc, copper, manganese and magnesium are essential trace elements whose role in liver cirrhosis and its complications is still a matter of research. There are contrary reports about their serum concentrations in patients with liver cirrhosis. Zinc is associated with more than 300 enzymatic systems[3]. Zinc augments the natural defense of reactive oxygen radicals by Zn-enzyme Cu-Zn superoxide dismutase[4]. Zinc acts as an antioxidant, a membrane and cytosceletal stabilizator, an anti-apoptotic agens, an important co-factor in DNA synthesis, an anti-inflammatory agens etc[5].

Copper is an essential trace element which participates in many enzymatic reactions. Its most important role copper has in redox processes. Reactive copper can participate in liver damage directly or indirectly, through Kupfer cell's stimulation[6]. Scientists agree that copper's toxic effects are related to oxidative stress[7].

Manganese is a structural part of arginase, which is an important enzyme in the urea metabolism. Manganese acts as an activator of numerous enzymes in Krebs cycle, particularly in the decarboxilation process.

Magnesium is important for the protein synthesis, enzyme activation, oxidative phosphorilation, renal potassium and hydrogen exchange etc.

Since zinc, copper, manganese and magnesium have a possible role in the pathogenesis of cirrhotic complica-

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tions**,** the aim of this study was to investigate the serum concentrations of mentioned trace elements in patients with liver cirrhosis and compared them with concentrations in controls.

Material and Methods

Subjects

The study included 105 patients with diagnosed liver cirrhosis of ethylic etiology who were hospitalized from 2000 to 2005 in the Division of Gastroenterology at Dubrava University Hospital, with median age 55 years. Seventy eight (74%) of them were male and twenty seven (26%) were female. According to the Child-Pugh classification patients with liver cirrhosis were divided in Child--Pugh A, B and C group. There were 35 subjects in every Child-Pugh group.

Inclusion criteria were liver cirrhosis (diagnosed by anamnestic data of alcohol consumption, laboratory and pathohistological findings, negative markers of viral hepatitis and normal values of ceruloplasmine), ability to sign the Informed consent and age 18 to 70.

Exclusion criteria were vegetarianism, Wilson's disease, malign disease, acute liver failure, impaired renal function (creatinine clearance <60 ml/min), multiorganic failure and inability to sign the Informed consent.

The control group consisted of 50 healthy subjects (median age 52 years) who were performed laboratory analysis as part of systematic medical examinations. There were 35 (70%) males and 15 (30%) females.

The Informed consent was obtained from all study subjects. The study protocol was approved by the Ethics Committee of Dubrava University Hospital. The protocol was carried out in accordance with the ethics guidelines of the Helsinki Declaration.

Methods

Blood samples were collected without anticoagulans and serum was stored in a freezer on –20°C until processing. In processing 1 ml of serum was taken, 1.5 ml of concentrated nitric acid and 0.5 ml 30% H_2O_2 were added on account of the digestion. After the digestion the sample was cooling for 20 minutes. The solution was transferred into a 10 ml container and was supplemented with ultra clean water. The concentrations of trace elements were determined by means of plasma sequential spectrophotometer TraceScan (Thermo Jarrell Ash, USA). Data were presented with median and 5–95 percentile range and compared using Wilcoxon and Kruskal-Wallis non--parametric tests. Statistics was done using MedCalc software (MedCalc Software, Mariakerke, Belgium). Only $p<0.05$ was considered significant.

Results

The serum levels of zinc, copper, manganese and magnesium in patients with liver cirrhosis and controls are presented in Table 1. The levels of zinc were significantly lower in patients with liver cirrhosis in comparison to controls (0.82 μmol/L vs. 11.22 μmol/L, $p<0.001$). The serum concentration of copper was significantly higher in patients with liver cirrhosis in comparison to controls (21.56 μmol/L vs. 13.09 μmol/L, $p<0.001$) as well as manganese concentration (2.50 μmol/L vs. 0.02 μmol/L, $p<0.001$). The concentration of magnesium was not significantly different between patients with liver cirrhosis and controls (Table 1, $p=0.132$). There were no differences in the concentrations of zinc, copper, manganese and magnesium between male and female patients with liver cirrhosis (Table 2).

The data in Table 3 show that the serum levels of manganese were significantly different between Child--Pugh groups ($H=9.21$, $p=0.036$). An additional analysis showed that the serum levels of manganese were significantly higher in patients with Child-Pugh C liver cirrhosis (6.30 μmol/L) in comparison to patients with Child--Pugh A (2.00 μmol/L, $z=–3.09$, $p=0.002$) and B liver cirrhosis (2.10 μmol/L, $z=–2.06$, $p=0.039$). The concentrations of zinc, copper, and magnesium did not differ significantly between Child-Pugh groups (Table 3).

The serum concentrations of zinc, copper, manganese and magnesium in cirrhotic patients with and without hepatic encephalopathy are represented in Table 4. The concentration of zinc was significantly lower in patients with hepatic encephalopathy in comparison to cirrhotic patients without encephalopathy (0.54 μmol/L vs. 0.96 μmol/L, $p=0.002$). There were no differences in serum concentrations of other trace elements between patients with or without encephalopathy. The serum concentrations of zinc, copper, manganese and magnesium in cirrhotic patients with and without ascites are represented

TABLE 1
SERUM CONCENTRATIONS OF ZINC, COPPER, MANGANESE AND MAGNESIUM IN PATIENTS WITH LIVER CIRRHOSIS AND CONTROLS

Trace elements	Subjects (N=105) median and 5–95 percentiles	Controls (N=50) median and 5–95 percentiles	Statistics	
			z	p
Zinc (μmol/L)	0.82 (0.24–1.74)	11.22 (9.23–15.10)	10.05	<0.001
Copper (μmol/L)	21.56 (11.17–30.60)	13.09 (11.17–19.95)	–7,66	<0.001
Manganese (μmol/L)	2.50 (0.01–29.65)	0.02 (0.01–0.40)	–8,21	<0.001
Magnesium (mmol/L)	0.94 (0.63–1.36)	0.88 (0.56–1.12)	–1.51	0.132

TABLE 2
SERUM CONCENTRATIONS OF ZINC, COPPER, MANGANESE AND MAGNESIUM IN MALE AND FEMALE PATIENTS WITH LIVER CIRRHOSIS

Trace elements	Male (N=78) median and 5–95 percentiles	Female (N=27) median and 5–95 percentiles	Statistics	
			z	p
Zinc (μmol/L)	0.84 (0.25–1.70)	0.74 (0.20–1.99)	–0.32	0.750
Copper (μmol/L)	21.18 (9.86–30.07)	23.56 (15.49–32.12)	1.58	0.113
Manganese (μmol/L)	2.10 (0.01–31.20)	3.70 (0.08–29.55)	1.45	0.146
Magnesium (mmol/L)	0.96 (0.58–1.40)	0.88 (0.71–1.36)	–1.05	0.293

TABLE 3
SERUM CONCENTRATIONS OF TRACE ELEMENTS IN CHILD-PUGH GROUPS

Trace elements	Child-Pugh A (N=35) median and 5–95 percentiles	Child-Pugh B (N=35) median and 5–95 percentiles	Child-Pugh C (N=35) median and 5–95 percentiles	Statistics	
				H	p
Zinc(μmol/L)	1.06 (0.38–1.49)	0.78 (0.26–1.94)	0.54 (0.14–1.45)	19.24	0.053
Copper (μmol/L)	19.98 (13.75–29.84)	22.30 (10.51–31.65)	23.20 (9.75–29.76)	1.00	0.608
Manganese (μmol/L)	2.00 (0.12–9.42)	2.10 (0.01–27.62)	6.30 (0.01–35.75)	9.21	0.036
Magnesium (mmol/L)	0.93 (0.65–1.18)	0.96 (0.65–1.38)	0.88 (0.40–1.53)	5.34	0.084

TABLE 4
SERUM CONCENTRATIONS OF TRACE ELEMENTS IN CIRRHOTIC PATIENTS WITH AND WITHOUT HEPATIC ENCEPHALOPATHY

Trace elements	Without encephalopathy (N=83) median and 5–95 percentiles	With encephalopathy (N=22) median and 5–95 percentiles	Statistics	
			z	p
Zinc (μmol/L)	0.96 (0.25–1.77)	0.54 (0.19–1.11)	–3.07	0.002
Copper (μmol/L)	21.56 (13.07–31.43)	21.31 (9.85–29.31)	–1.21	0.227
Manganese (μmol/L)	2.20 (0.01–31.38)	4.90 (0.01–26.94)	0.66	0.506
Magnesium (mmol/L)	0.95 (0.63–1.36)	0.90 (0.53–1.37)	–1.72	0.086

TABLE 5
SERUM CONCENTRATIONS OF TRACE ELEMENTS IN CIRRHOTIC PATIENTS WITH AND WITHOUT ASCITES

Trace elements	Without ascites (N=45) median and 5–95 percentiles	With ascites (N=60) median and 5–95 percentiles	Statistics	
			z	p
Zinc (μmol/L)	0.97 (0.36–1.57)	0.69 (0.18–1.78)	1.77	0.077
Copper (μmol/L)	20.25 (11.84–30.47)	22.42 (10.74–30.82)	–0.28	0.778
Manganese (μmol/L)	1.80 (0.01–11.20)	4.10 (0.01–31.80)	–3.43	<0.001
Magnesium (mmol/L)	0.92 (0.64–1.13)	0.94 (0.54–1.46)	–0.58	0.564

in Table 5. Only manganese concentration was significantly different between patients with and without ascites. Namely, serum manganese concentration was higher in cirrhotic patients with ascites in comparison to cirrhotic patients without ascites (4.10 μmol/L vs. 1.80 μmol/L, $p<0.001$).

Discussion

Mechanisms linked on ethanol metabolism, especially oxidative stress, redox potentials and acetaldehyde, participate in the emergence of liver damage. Trace elements play an important role in oxidative stress and redox potentials. A possible role of zinc, copper, manganese and magnesium in pathogenesis of liver cirrhosis and its complications is still subject of researches.

In our research the serum levels of zinc were significantly lower in patients with liver cirrhosis in comparison to controls (Table 1, median 0.82 μmol/L in patient with liver cirrhosis and 11.22 μmol/L in controls, $p<0.001$). The results confirm Kugelmans' research[8], who explained low zinc levels with low ingestion due to pro-

tein reluctance, increased loss in gastroenterological system due to diarrhea or intestinal malabsorption and increased urinary losses. The assumption is also based on the research of McClain[9] and Extremera[10]. Protein deficiency occurs frequently due to poor dietary intake. Our results confirm findings of decreased serum concentrations of zinc in patients with liver cirrhosis. Possible explanations for the decreased zinc levels in cirrhotic patients are mentioned above.

In Celik's research[11] the decrease in both serum and ascites zinc content was found in patients with liver cirrhosis. The interaction between zinc and copper in their intestinal absorption and their competition for binding sites on the carrier proteins and cellular uptake may be regulators of their homeostasis. Maybe this can explain inverse concentrations of zinc and copper**.** Zinc binds on albumin, transferrin and metalloproteins in the cell, so relative concentrations of these proteins might regulate the serum concentration of zinc[11,12].

The serum copper content was found significantly increased in patients with liver cirrhosis in comparison to the control group (Table 1, median 21.56 μmol/L in patient with liver cirrhosis and 13.09 μmol/L in controls, $p<0.001$). It could be explained with copper's role in the redox process. Redox cycling between Cu^{2+} and Cu^{1+} can catalyze the production of toxic hydroxyl radicals[13,14]. It is a well known fact that redox processes and oxidative stress play an important role in the pathogenesis of liver cirrhosis.

Serum concentrations of manganese were significantly higher in cirrhotic patients in comparison to controls (Table 1, median 2.50 μmol/L in cirrhotic patients and 0.02 μmol/L in controls, $p<0.001$). Higher serum levels of manganese in Krieger's research[15] as well as in research of Layrargues and co.[16] were also found in cirrhotic patients.

Moscarello[17] did not find any significant difference in the concentrations of manganese between cirrhotic patients and controls. After all, it seems that serum levels of manganese are higher in patients with liver cirrhosis than in healthy people. Manganese is secreted in bile so the concentration of manganese increases in cholestatic liver disease, which could be one of the possible explanations why manganese accumulation is common in liver cirrhosis[15,18].

It has been suggested that a possible mechanism responsible for manganese accumulation in the pallidum of patients include a decrease in biliary excretion and increased systemic availability due to portosystemic shunting.

Intrahepatic shunting or portosystemic shunting also have an additional effect on manganese accumulation. In the study of Rose et al.[19] pallidal manganese concentrations were the highest in shunted rats, which confirms that shunting is a major determinant of manganese accumulation in the brain. Manganese accumulation in the brain was confirmed by several clinical studies[15,19–21].

The difference between serum concentrations of magnesium in cirrhotic patients and controls was not significant (Table 1, median 0.94 mmol/L in cirrhotic patients and 0.88 mmol/L in controls, $p= 0.132$). Results are opposite to Kosch's research[22]. In that research serum levels of magnesium were lower in patients with liver cirrhosis in comparison to patients with liver steatosis and controls. In addition, the research of Rocchi[23] and Suzuki[24] confirmed the same. Our research did not confirm lower concentrations of magnesium in patients with liver cirrhosis. That partially could be explained with influence of spironolactone on magnesium levels. Namely, in Stergiou's research[25] spironolactone in health subjects decreased urine excretion of magnesium and in cirrhotic patients antagonized magnesiuric effect of furosemide. Our patients with liver cirrhosis mostly have spironolactone in their standard therapy, but there were no differences between patients who were taking spironolactone and those who were not taking spironolactone.

There was a slight decrease in serum zinc concentrations in patients with more severe clinical state of liver cirrhosis according to Child-Pugh classification but these differences in our research were not significant.

As zinc is bound to albumin in the serum, it has been thought that the serum zinc concentration would decrease with advancing grades of hepatic fibrosis[26]. Yoshida[27] found that patients with decompensated liver cirrhosis have lower levels of zinc than patients with compensated cirrhosis. However, in Hatano's research[26] serum zinc levels did not differ significantly between grades of hepatic fibrosis.

Copper levels in our research were similar in all three Child-Pugh groups (Table 3), as well as in Hatano's research.

Serum levels of manganese were higher in patients with Child-Pugh C liver cirrhosis in comparison to those in Child-Pugh A and B cirrhosis. Our results are contrary to Spahr's research[21] who found similar concentrations of manganese in all three Child-Pugh groups. It seems that manganese concentrations are higher in patients with severe liver cirrhosis possible due to the advanced intrahepatic and portosystemic shunting.

In our study magnesium levels were similar in all Child-Pugh groups. Moscarella's research[17] also confirms similar levels in compensated and decompensated liver cirrhosis. However, Wang[28] found that magnesium deficiency occurs more frequently in severe liver disease**.**

Significantly lower zinc levels were found in cirrhotic patients with hepatic encephalopathy (Table 4, median 0.54 μmol/L in patients with encephalopathy and 0.96 μmol/L without encephalopathy, $p= 0.002$), which was confirmed in other studies[29,30]. There are some findings that zinc supplementation can cause increased releasing of glutamine from sceletal muscle and also activate glutamine synthetasis, which can decrease the level of ammonia and improve hepatic encephalopathy[29]. That can be explained with the fact that zinc supplementation increases the hepatic activity of ornithine transcarbamoy-

lase, key enzyme of the urea cycle, which consecutively increases urea formation and decreases ammonia levels[30]. The rationale for use of zinc is also its ability to induce intestinal and hepatic metallothionein synthesis. Zinc decreases copper absorption by increasing the formation of Cu-metallothionein in intestinal epithelial cells[31]. However, Riggio found that short-term zinc supplementation has no influence on hepatic encephalopathy[32].

Considering all, zinc supplementation could have a positive influence on hepatic encephalopathy but before the implementation of this result in the treatment, further researches are necessary.

The levels of manganese were not significantly different between patients with liver cirrhosis and hepatic encephalopathy and patients without encephalopathy (Table 4, $p=0.506$), which is opposite to the researches of Hauser[20] and Krieger[15]. They found increased concentrations of manganese and suggested a beneficial effect of prevention of accumulation or decreasing manganese concentration in patients with liver cirrhosis. Rose[19] and Layrargues[16] found increased concentrations of manganese in basal ganglia of cirrhotic patients in comparison to controls.

Manganese concentrations in our research were significantly higher in cirrhotic patients with ascites in comparison to those without ascites (Table 5, median 4.10 μmol/L in patients with ascites and 1.80 μmol/L in patients without ascites, $p<0.001$). The levels of zinc, copper and magnesium were within reference range. Our results are contrary to the research of Pasqualetti[33] who found significantly lower magnesium concentrations in patients with ascites. Therefore, it is necessary to research the possible role of manganese in emergence of ascites in patients with liver cirrhosis.

Finally, decreased serum concentrations of zinc and increased levels of manganese in patients with liver cirrhosis could have an important role in the pathogenesis of liver cirrhosis and its complications, especially in hepatic encephalopathy. The supplementation of zinc could improve hepatic encephalopathy. The decrease in manganese levels could also have a beneficial effect on the neurological status in patients with liver cirrhosis and hepatic encephalopathy. Increased concentrations of manganese in cirrhotic patients with ascites inspire further researches about a possible role of manganese in the pathogenesis of ascites in patients with liver cirrhosis. Maybe, decreasing of manganese levels might also have beneficial effect on prevention or volume of ascites.

Considering all that, the correction of serum trace elements concentrations would have a beneficial effect on some complications of liver cirrhosis and maybe on progression of the disease, so it would be recommendable to provide laboratory analysis of trace elements as a routine.

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SERUMSKE KONCENTRACIJE CINKA, BAKRA, MANGANA I MAGNEZIJA U BOLESNIKA S JETRENOM CIROZOM

S A Ž E T A K

Cilj istraživanja bio je odrediti serumske koncentracije cinka, bakra, mangana i magnezija u bolesnika s jetrenom cirozom i usporediti ih s koncentracijama u zdravih ispitanika. Serumske koncentracije navedenih elemenata u tragovima bile su određivane u 105 bolesnika s jetrenom cirozom i 50 ispitanika kontrolne skupine pomoću plazma sekvencijskog spektrofotometra. Serumske koncentracije cinka bile su statistički značajno niže u bolesnika s jetrenom cirozom u odnosu na ispitanike kontrolne skupine (medijan 0.82 prema 11.22 μmol/L, $p<0.001$). Koncentracije bakra bile su značajno povišene u bolesnika s jetrenom cirozom u odnosu na kontrolnu skupinu (medijan 21.56 prema 13.09 μmol/L, $p<0.001$) kao i koncentracije mangana (medijan 2.50 prema 0.02 μmol/L, $p<0.001$). Koncentracije magnezija nisu bile značajno različite između bolesnika s jetrenom cirozom i ispitanika kontrolne skupine ($p=0.132$). Koncentracije cinka, bakra, mangana i magnezija nisu bile različite u muških i ženskih bolesnika s jetrenom cirozom. Serumske koncentracije mangana bile su statistički značajno različite između Child-Pughovih skupina ($p=0.036$), dok koncentracije cinka, bakra i magnezija nisu bile značajno različite između Child-Pughovih skupina. Značajno niže serumske koncentracije cinka pronađene su u bolesnika s jetrenom cirozom i portalnom encefalopatijom u usporedbi s bolesnicima bez portalne encefalopatije (0.54 prema 0.96 μmol/L, $p=0.002$). Korekcija koncentracija elemenata u tragovima mogla bi imati pozitivan učinak na komplikacije a moguće i tijek jetrene ciroze, stoga bi bilo preporučljivo u bolesnika s jetrenom cirozom određivati serumske koncentracije elemenata u tragovima kao dio rutinske laboratorijske obrade.