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ORIGINAL ARTICLE

Abnormalities in Cu and Zn levels in acute hepatitis of different etiologies

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Abstract

Background: Copper (Cu) and Zinc (Zn) are essential trace elements which play an important role in various biological processes. Zn deficiency is common in liver diseases while Cu deficiency is rarely reported. To determine whether serum Cu and Zn concentrations differed in acute hepatitis, compared to controls and investigate possible correlations of Cu and Zn values with etiology and severity of liver diseases.

Methods: Serum Cu and Zn concentrations were determined by air acetylene flame atomic absorption spectrometer in 40 patients (acute hepatitis A, B, C, autoimmune and drug induced hepatitis) and 150 healthy controls.

Results: Compared to healthy controls, significantly higher Zn levels were found in patients (106.5 μg/dl, P <0.01). Abnormal levels of either Cu and/or Zn were found in 48% of patients vs 23.3% of the controls (P =0.01). Ten patients had abnormal Zn and fourteen had abnormal Cu levels. There was a trend for the severe hepatitis cases to have abnormal Cu values and in this subgroup Cu and Zn were positively correlated with prothrombin time and alanine aminotransferase (ALT) levels, respectively. Cu and Zn levels did not differ statistically across groups of different etiologies.

Conclusions: Abnormalities in Cu and Zn concentrations are common in acute hepatitis. Cu and Zn exhibited positive correlations with prothrombin time and ALT respectively, in severe cases. Hippokratia 2014; 18 (2):144-149.

Keywords: Trace elements, viral hepatitis, autoimmune hepatitis, drug-induced hepatitis, cryptogenic hepatitis

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Introduction

Copper (Cu) and Zinc (Zn) are essential trace elements as they act as cofactors of antioxidant enzymes to protect the body from oxidative stress[1,2]. In particular, Cu is a component of many important enzymes, including amine oxidases, ferroxidases, cytochrome c-oxidase, dopamine b- hydroxylase, superoxide dismutase and tyrosinase[1]. Zn contributes to zinc finger proteins that interact with DNA and approximately 250 proteins contain Zn including DNA polymerase, RNA polymerase and transfer RNA synthetase[3,4]. Intestinal absorption of Zn occurs by a specific process that is enhanced in pregnancy and by corticosteroids while diminished by co– ingestion of phytates, phosphates, iron, Cu, lead and calcium[5,6].

A large number of studies have shown that Cu and Zn are implicated in cardiovascular, autoimmune, cancer and degenerative diseases[7-9]. During most viral infections, the plasma levels of trace elements change[10] and their effect has been studied on a variety of infectious diseases[11]. The changes in trace element levels are induced by cytokines in response to several stimuli, including stress and infection[12].

Although there are studies about the association of trace elements with acute[13,14] or chronic viral hepatitis[15,16], there is no data about the above trace elements concerning other types of acute liver diseases (autoimmune, drug- induced, acute hepatitis B, cryptogenic) and in particular, the association of their values with the severity of the disease.

The aim of this study is to determine possible disturbances of Cu and Zn levels in patients with acute liver diseases and investigate correlations with etiology and severity of liver disease.

Methods

Study sample

Forty patients (21 men and 19 women) with acute hepatitis (ALT > 400 U/L) aged between 18 and 80 years, were evaluated in the outpatient Clinics or hospitalized in the 2nd Department of Medicine, in the time interval 2009 and 2011. One hundred fifty healthy blood donors (75 men and 75 women, in the age range 18-70 years) were included in the study with an approximate matching by age group and men/women ratio (Table 1). None of the controls received any medication. The study was approved by the Hospital Ethics Committee. Half of the patients had acute viral hepatitis (fourteen acute hepatitis B, three acute hepatitis A and three acute hepatitis C),

Table 1: Characteristics of 40 patients with acute hepatitis and 150 healthy controls.

		Acute hepatitis (n=40)		Controls (n=150)	
Age group		n	**%**	n	**%**
	≤20y	2	5.0	7	4.7
	21-30y	6	15	24	16.0
	31-40y	8	20	51	34.0
	41-50y	8	20	43	28.7
	51+y	16	40	25	16.7
Sex (M/W ratio)		21/19	53/47	75/75	50/50
Etiology	Viral (A, B, C)	20	50		
	Drug-induced	5	12.5		
	Autoimmune	8	20		
	Cryptogenic	7	17.5		
Clinical characteristics			**Mean**	**SD**	
Hemoglobin (g/dl)			13.5	1	not available
Creatinine (mg/dl)			1.0	0.2	not available
AST (U/L)			1027	600	not available
ALT (U/L)			1588	952	not available
ALP (U/L)			197	100	not available
Total bilirubin (mg/dl)			8.4	6.8	not available
Albumin (g/dl)			3.7	0.8	not available
Prothrombin time (sec)			14.4	2.7	not available

n: number, M/W: men/women, y: years, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatise, SD: Standard deviation.

five patients drug-induced, eight autoimmune and seven cryptogenic. Severe cases were defined as those with prothrombin time > 15 sec and/or albumin < 3.5 g/dl. All severe hepatitis cases were icteric and had a total bilirubin level more than 10 mg/dl.

Based on the available information, that is a ratio of approximately ¼ for cases and controls and assuming a proportion of 15% with abnormal values for Cu or Zn in the control group (Kouremenou-Dona et al, 2006)[17], we calculated a power of nearly 0.60, 0.80 and 0.90 to detect a 15, 20 and 25% higher proportion of abnormal values in the patients group considering a type I error of 0.005.

Serum samples and analytical methods

Demographics and liver biochemistry [aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP) and bilirubin], prothrombin time and albumin values were recorded at the first visit of the patient group. The etiology of acute hepatitis of viral etiology was identified as follows: Cases of acute hepatitis B were positive for IgM anti-HBc and in the vast majority the source of infection was identified; cases of acute hepatitis A were positive for IgM anti-hepatitis A virus (HAV) antibody; cases of acute hepatitis C had a recent seroconversion from anti-Hepatitis C virus (HCV) negative to anti-HCV positive status and detectable HCV RNA. A score ≥ 7 (definite) was used for the diagnosis of autoimmune hepatitis according to Simplified criteria for the diagnosis of autoimmune hepatitis[18]. In cryptogenic hepatitis cases, viral markers, autoantibodies and drug history were negative, IgG levels were normal and metabolic liver diseases as Wilson disease or hemochromatosis were excluded. All cryptogenic cases had a liver biopsy without any specific characteristics. Drug-induced acute hepatitis cases reported an administration of a suspect drug with temporal association to the illness.

Serum samples at the first visit were centrifuged and stored at 18°C. All glassware and bottles used for the isolation and analysis of serum were previously soaked in diluted nitric acid (10%) for 3 hours and rinsed thoroughly with de-ionized water. This procedure was followed in order to exclude the possibility of contamination with Zn or Cu. All samples were diluted (1:4) using water. The determination of Cu and Zn was carried out in serum samples by air acetylene flame atomic absorption spectrometer (model Spectra AA, Varian, Australia) equipped with D2 lamp background correction system. A Cu and Zn hollow cathode lamp (Varian) operating at 10 mA intensity and a spectral width of 0.7 nm was selected to isolate the 324.7 nm and 213.9 nm lines for Cu and Zn respectively. All analyses were performed in peak height mode to calculate absorbance rates. All samples were analyzed in triplicate.

Serum Cu and Zn values were expressed in μg/dl. Based on the Kouremenou-Dona's et al (2006)[17] work, we considered as reference values those between 70 and 155μg/dl for Cu and between 60 and 150μg/dl for Zn. The trace elements were measured in the Department of Forensic Medicine and Toxicology, Medical school, University of Athens.

Statistical analysis

All analyses were performed using the Stata statistical package (Stata Corporation: Stata/SE 11.0 for Windows, Lakeway Drive, College Station, TX, USA, 2009). For descriptive statistics, results are presented as number and percentage for categorical variables and mean and standard deviation for continuous variables. The median and inter-quartile range was estimated for Cu and Zn and the non-parametric test of equality of medians was applied to test differences in serum measurements between cases and controls or between men and women. The Chi square and Fisher's exact tests were used to compare the differences in the prevalence of abnormal values for Cu and zinc among cases and controls. The Spearman's rank correlation coefficients between Cu and zinc with several clinical measurements were subsequently estimated for the patients group only. Significance was generally tested at the 5% level of statistical significance ($p < 0.05$).

Results

Characteristics of patients and controls are presented in Table 1. The distribution of cases and controls across the age groups was generally equal. Gender distribution was also equal between patients and controls.

The median values and first and third quartiles for Cu and Zn are presented in Table 2 for both patients and healthy individuals, overall, by sex and age group. Levels of Cu in patients were similar to controls. For zinc, higher values were found among patients overall ($p<0.01$) and among men ($p =0.01$) and women ($p =0.03$) separately, when compared to controls (p^1). Cu and Zn values were similar between men and women in acute hepatitis group (p^2).

The distribution of patients and healthy individuals with normal and abnormal values for both trace elements are depicted in Table 3. The normal values were based on data of previous investigators from the same area[17]. Nearly half of the cases had abnormal values either for Cu and/or for Zn (47.5%). The corresponding percentage was much lower in controls (23.3%) ($p=0.01$). Most of the analysed sample for healthy individuals lied within the reference intervals (approximately 90% for Cu and 85% for Zn), while the proportions of abnormal values in both trace elements were significantly higher among cases (35% for Cu and 25% for Zn, $p <0.01$ and $p =0.15$ respectively) than among controls. Eight patients had Zn levels above normal and two below normal. Nine patients had Cu levels above normal and five below normal.

The results for Cu were more striking among men and that for zinc among women.

The analysis of the proportions of patients who had abnormal values of trace elements according to the cause of acute hepatitis showed that similar frequencies of patients with abnormal values of Cu or Zn were found across different etiologies of acute hepatitis (Table 4).

The values of both trace elements according to the severity status showed that both Cu and Zn were higher in severe than in non-severe cases and the proportions of patients with abnormal values showed that there was a trend for the severe cases to have abnormal Cu values (47.6% vs 21%) without any of the above results gaining a statistical significance (Table 5).

Table 6 presents the spearman's rank correlation coefficients of Cu and Zn with several laboratory measurements across patients. In the total of patients no signifi-

Table 2: Serum Cu and Zn median (1st and 3rd quartile) concentrations of 40 patients with acute hepatitis and 150 healthy controls, overall and by sex.

	Overall		**Acute hepatitis**		**Controls**		
Serum Cu (μg/dl)	(n=190)		(n=40)		(n=150)		
	median	(Q1, Q3)	median	(Q1, Q3)	median	(Q1, Q3)	p^1
Overall	119.5	(103; 142)	133.5	(94.5; 152.5)	118	(105; 135)	0.37
Sex							
Men	113	(99.5; 132.5)	130	(87; 152)	111	(100; 126)	0.54
Women	126	(114; 148)	138	(95; 156)	125	(115; 144)	0.60
p^2	<0,01		1.00		<0.01		
Serum Zn (μg/dl)							
	median	(Q1, Q3)	median	(Q1, Q3)	median	(Q1, Q3)	p^1
Overall	78	(66; 92)	106.5	(80; 141)	74	(63; 85)	<0.01
Sex							
Men	84	(72; 100)	110.11	(89.5; 141)	80	(68; 91)	0.01
Women	72	(62; 82)	103.16	(72; 158)	71	(61; 80)	0.03
p^2	<0.01		0.16		<0.01		

The p-values are referred to two different tests; one for the comparison cases-controls (p^1) and the other for the comparison men-women (p^2), Cu: Copper, Zn: Zinc, n: number.

Table 3: Distribution of 40 patients with acute hepatitis and 150 healthy controls with normal and abnormal serum Cu and Zn concentrations, overall and by sex.

	Overall			***Men***			***Women***		
	Acute hepatitis	**Controls**		**Acute hepatitis**	**Controls**		***Acute hepatitis***	**Controls**	
	n (%)	n (%)	p	n (%)	n (%)	p	n (%)	n (%)	p
Both Cu and Zn			0.01			<0,01			0.5
Normal Cu (μg/dl) and Zn (μg/dl)	21 (52.5)	115 (76.7)		12 (57.1)	63 (84.0)		9 (47.4)	52 (69.3)	
Normal Cu (μg/dl) and abnormal Zn (μg/dl)	5 (12.5)	21 (14.0)		1 (4.8)	8 (10.7)		4 (21.1)	13 (17.3)	
Abnormal Cu (μg/dl) and normal Zn (μg/dl)	9 (22.5)	12 (8.0)		7 (33.3)	3 (4,0)		2 (10.5)	9 (12.0)	
Abnormal Cu (μg/dl) and Zn (μg/dl)	5 (12.5)	2 (1.3)		1 (4.8)	1 (1,3)		4 (21.1)	1 (1.3)	
Cu			<0.01			<0.01			0.06
Normal Cu (70-155 μg/dl)	26 (65.0)	136 (90.7)		13 (61.9)	71 (94.7)		13 (68.4)	65 (86.7)	
Abnormal Cu (μg/dl)	14[1] (35.0)	14 (9.3)		8 (38.1)	4 (5.3)		6 (31.6)	10 (13.3)	
Zn			0.15			0.75			0.03
Normal Zn (60-150 μg/dl)	30 (75.0)	127 (84.7)		19 (90.5)	66 (88.0)		11 (57.9)	61 (81.3)	
Abnormal Zn (μg/dl)	10[2] (25.0)	23 (15.3)		2 (9.5)	9 (12.0)		8 (42.1)	14 (18.7)	

[1]Nine patients had Cu levels above normal and five below normal, [2]Eight patients had Zn levels above normal and two below normal, Cu: copper, Zn: Zinc, n: number.

Table 4: Differences in patients with acute hepatitis of different etiologies.

	Viral		**Drug-induced**		**Autoimmune**		**Cryptogenic**		
	(n=20)		(n=5)		(n=8)		(n=7)		
	Median	(Q1, Q3)	Median	(Q1, Q3)	Median	(Q1, Q3)	Median	(Q1, Q3)	p
Copper (μg/dl)	136.5	(97, 154.5)	148	(100, 160)	124	(96.5, 148)	104	(84, 147)	0.64
Zinc[1] (μg/dl)	115.1	(102, 141)	80	(75.4, 165.6)	102	(68.9, 132.3)	100.3	(73.5, 132)	0.38
	n	%	n	%	n	%	n	%	
Copper									0.41
Normal Cu (70-155 μg/dl)	12	60.0	2	40.0	6	75.0	6	85.7	
Abnormal Cu	8	40.0	3	60.0	2	25.0	1	14.3	
Zinc									0.29
Normal Zn (60-150 μg/dl)	17	85.0	2	40	5	62.5	6	85.7	
Abnormal Zn	3	15.0	3	60	3	37.5	1	14.3	

Results are presented as median (1st and 3rd quartile) for continuous variables and as number and percentage for categorical variables, Cu: Copper, Zn: Zinc, n: number. Reference values for Cu and Zn according to Kouremenou-Dona et al, 2006.

cant correlations were found. However, Cu values were positively correlated with prothrombin time (r=0.46) and Zn were positively correlated with ALT (r=0.45) in the subgroup of severe acute hepatitis cases.

Only one patient with cryptogenic hepatitis died and had abnormal levels for both Cu and Zn. No patient was transplanted.

Discussion

Although there are only a few studies on Cu and Zn levels in acute hepatitis, including a limited number of patients with only viral causes[13,14,16], the effect of these trace elements on patients with chronic hepatitis or cirrhosis has attracted the attention of many researchers. Kalkan et al[16], Grungreiff et al[19] and Cesur et al[15] calculated Cu and/or Zn levels in a different setting of patients with chronic hepatitis. Kalkan et al[16] showed significantly reduced Zn and elevated Cu levels in patients with chronic hepatitis compared to healthy control subjects. Grungreiff et al[19] and Cesur et al[15] reported similar Zn and Cu concentrations in patients with chronic hepatitis and healthy control subjects. On the other hand, patients with decompensated liver cirrhosis exhibited a more pronounced reduction in Zn concentrations[19].

Table 5. Differences in patients with acute hepatitis by severity status.

	Severe (n=21)		Non-severe (n=19)		
	Median	(Q1, Q3)	Median	(Q1, Q3)	p
Cu (μg/dl)	144	(95, 165)	110	(94, 147)	0.20
Zn (μg/dl)	110,2	(75.4, 151.6)	105	(82.8, 132)	0.86
	n	(%)	n	(%)	
Cu					0.08
Normal Cu (70-155 μg/dl)	11	52.4	15	79.0	
Abnormal Cu (μg/dl)	10	47.6	4	21.0	
Zn					0.85
Normal Zn (60-150μg/dl)	16	76.2	14	73.7	
Abnormal Zn (μg/dl)	5	23.8	5	26.3	

Note: Severe cases were defined as those with prothrombin time > 15 sec and/or albumin < 3.5 g/dl. Results are presented as median (1st and 3rd quartile) for continuous variables and as number and percentage for categorical variables. Cu: Copper, Zn: Zinc, n: number.

Table 6: Association of serum Cu (μg/dl) and Zn (μg/dl) concentrations with laboratory measurements among patients with acute hepatitis overall and by severity status.

	Overall (n=40)				Severe hepatitis[1] only (n=21)			
	Cu		Zn		Cu		Zn	
	r	p	r	p	r	p	r	p
Hemoglobin (g/dl)	-0.04	0.79	0.01	0.97	-0.10	0.66	0.09	0.72
Creatinine (mg/dl)	-0.21	0.19	0.23	0.18	-0.15	0.52	-0.09	0.72
AST (U/L)	0.07	0.68	0.12	0.46	-0.07	0.76	0.31	0.19
ALT (U/L)	-0.01	0.95	0.13	0.45	-0.41	0.06	0.45	0.05**
Total bilirubin (mg/dl)	-0.04	0.81	0.04	0.80	-0.05	0.81	-0.11	0.65
Direct bilirubin (mg/dl)	-0.01	0.95	0.03	0.86	-0.09	0.70	-0.08	0.74
Albumin (g/dl)	0.30	0.06	0.04	0.80	-0.29	0.20	-0.20	0.41
Prothrombin time (sec)	-0.16	0.31	0.10	0.55	0.46	0.03**	-0.12	0.63

r = Spearman's rank correlation coefficient, [1] Individuals with severe hepatitis were defined as those with prothrombin time>15 sec and/or albumin<3.5 g/dl, ** Correlations significant at the 5% level of significance, Cu: Copper, Zn: Zinc, N: number, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Cu and Zn are absorbed by the small intestine and are bound to plasma albumin. Cu is absorbed by a specific intestinal transport mechanism and is carried to the liver where it is incorporated into the protein transporter ceruloplasmin which delivers Cu to target tissues in the body. In the liver, Cu is stored by the storage protein metallothionein[20]. Zn after absorption by the small intestine is carried to the liver by portal circulation. Zn absorption is regulated by matallotheionin which binds both Cu and Zn and also acts as a Zn storage protein in the liver[21].

Different mechanism of Cu and Zn homeostasis may play a role in acute hepatitis compared to chronic hepatitis or liver cirrhosis. In chronic hepatitis proinflammatory cytokines and particularly increase of IL-6 may play an important role in trace element levels[22,23]. In liver cirrhosis, the changes in the albumin synthesis, intestinal resorption and use of hepatic zinc are disturbed inducing low zinc levels[18]. However, Cu concentration in liver cirrhosis is a controversial issue[19]. Metal binding proteins such as metallothionein or ceruloplasmin are included in the family of acute phase proteins. In acute infections, acute phase proteins are increased and consequently metal binding proteins acting as metal transporters or storage proteins for trace elements are also increased. In the first days of acute infection, the metallothionein expression increases in the liver and intestine of experimental animals[10]. The increase of metallothionein in the liver was found to correlate positively with both Zn and Cu in previous studies[10]. Consequently during hepatocyte injury in acute infection, a leak of trace elements to the blood may occur[10]. In the current study, Zn exhibited positive correlation with ALT which is a marker of hepatocyte damage.

According to the above study[10], low or high levels of Zn in acute hepatitis depend on the time elapsing since the onset of infection. Zn levels are elevated in the first days of infection and they are diminished thereafter[10]. Our results showed a variety of alterations above and below normal values in both Cu and Zn concentrations at the clinical onset of acute hepatitis compared to healthy controls. We do

not have sequential sera in order to determine possible alterations of trace elements during the course of the disease. Many factors may account for high and low abnormal trace element values in acute hepatitis, including damage of the hepatocytes - leaking of trace elements and elevated metal binding proteins for the former and reduced intestinal absorption as well as low albumin synthesis for the latter. The controversy between our results and those of Pramoolsinap et al[14], Fota-Markowska et al[13], or Kalkan et al[16], may be attributed to different setting of patients since the above studies included only patients with acute hepatitis B.

Gender-specific concentrations were not found in our study. Zn differences were prominent in both men and women compared to healthy controls while Cu concentrations were practically the same. Gender-specific differences in both Cu and Zn were not found between men and women in the acute hepatitis group but they were evident in the control group. The higher Cu in females of the control group was in agreement with Grungreiff et al[19], but this gender-specific difference was not confirmed in our patient group. Hormonal contraception was not used in patients and controls and expected changes induced by sex hormone use[19] were not apparent in the current study.

Another finding of the current study was that levels of Cu and Zn were similar irrespective of the etiology of acute hepatitis and the frequency of patients with abnormal values of trace elements did not differ among variable etiologies of acute hepatitis. In a previous study on patients with autoimmune hepatitis Zn levels were described as low[24] but the timing of tissue sampling in the above inflammatory conditions was not clear. It was not stated whether Zn and Cu were calculated during acute exacerbations or during a quiescent remission period of autoimmune hepatitis. It is therefore possible that there are elevations and reductions of trace elements concentrations, depending on the phase of the disease. Moreover, we found that in severe cases of acute hepatitis, Cu and Zn exhibited positive correlations with prothrombin time and ALT respectively, reflecting correlations with severity and activity of the disease.

It must be noted that the current study is based on preliminary data. For this reason, no sequential data during the course of the disease are exhibited and the sizes of groups of different etiologies are small.

In conclusion, serum Cu and Zn levels display wide variations in patients with acute hepatitis. Zn abnormalities at the onset of the disease are usually above normal and thus Zn supplementation is not necessary. Cu abnormalities may be above or below normal and more investigation is needed for its role in the severity of the disease.

Conflict of interest

None declared.

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