Serum Zinc Level and Urinary Zinc Excretion in Patient with Liver Cirrhosis

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ABSTRACT

Background: *Zinc deficiency is commonly found in patient with liver cirrhosis, and it is usually caused by excessive urinary excretion that is exaggerated by diuretic agents. The objective of this study is to know the differences of zinc serum concentration according to the Child-Turcotte-Pugh (CTP) score and clinical factors that influence zinc serum level and 24-hour urinary zinc excretion.*

Method: *The design of this study was cross-sectional. In adult patients with liver cirrhosis, blood samples were collected after patients had fasted for at least 8 hours. Zinc levels were measured by the flame atomic absorption spectrophotometry method. Correlation test was performed among numeric variables, as well as Mann-Whitney U test to measure mean differences of zinc serum concentration and of 24-hours urinary zinc excretion according to clinical factors. The level of significance was $p < 0.05$.*

Results: *During the period of May 1st - September 30th 2007, there were 36 eligible patients. The mean value of zinc serum levels was 63.70 ± 24.85 µg/dL. There were 24 (66.67%) patients with hypozincemia. The mean value of 24-hour-urinary zinc excretion was 787.52 ± 570.20 µg. There were 19 (52.8%) patients with urinary zinc excretion > 550 µg/24 hours. The results of mean difference test of zinc serum concentration between CTP score B and C showed no statistical significance ($p = 0.052$). Urinary zinc excretion correlated to urine volume ($r = 0.638$, $p = 0.000$), and it was higher in hospitalized patients compared to outpatients. It also was higher in men compared to women. There were no statistically significant differences in zinc serum level, zinc urinary level, and urinary zinc excretion on the administration of diuretic agents.*

Conclusion: *There were no significant differences of fasting zinc serum concentration in patients with liver cirrhosis between the CTP scores B and C. In patients with liver cirrhosis, urinary zinc excretion positively correlates to urine volume.*

Keywords: *liver cirrhosis, serum zinc level, urinary zinc excretion*

INTRODUCTION

Zinc is the most essential trace element involved in various physiologic functions. Zinc is required for tissue growth and repair, development of sexual organ, and immune function.[1] Zinc affect protective action in the activity of hepatocyte and probably prevent cellular damage caused by oxidative stress.[2]

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The decrease of zinc concentration commonly occurs in patients with advanced stage of cirrhosis. Plasma zinc concentration of low-normal or decreased (53 - 84 µg/dL) in 16 alcoholic cirrhosis or hepatitis C virus (HCV) related subjects was reported by Marchesini et al.[3] Study by Nurdjanah et al, in 82 liver cirrhosis who visited polyclinic of gastroentero-hepatology or treated in inpatient care of internal medi-cine in our hospital, revealed zinc deficiency was found in 55.1% of the subjects.[4] In the previous study, zinc concentration under the normal value was found in 95% of 20 subjects with liver cirrhosis in the company of encephalopathy.[5]

Patients with liver cirrhosis showed decrease blood zinc concentration and increase urinary zinc

excretion that aggravated by the administration of diuretic agents.[6,7] In healthy individual, zinc is secreted mainly through the gastrointestinal tract,[8,9,10] via gastric, pancreatic, and bile juice,[8] while its excretion through urine and perspiration is low.[9,10] Yoshida et al, revealed that fasting zinc serum concentration in 10 patients with decompensate liver cirrhosis (56.3 ± 13.7 µg/dL) is significantly lower ($p < 0.05$) than 10 patients with compensated liver cirrhosis (75.0 ± 15.0 µg/dL). [7]

Zinc serum examination is not an examination that can be routinely done in every laboratory. The zinc examination require instrument preparation and unpractical specimen container because the validity of zinc measurement depend mainly to the successful analysis in avoiding contamination of ambient zinc.[2] It had not been recognized whether zinc serum concentration is different according to the Child-Turcotte-Pugh (CTP) score, and whether certain clinical factors affect serum zinc concentration and 24-hours urinary zinc excretion in liver cirrhosis patients in our hospital.

METHOD

This study is an observational, cross-sectional study conducted in the polyclinic and inpatient care of Department of Internal Medicine Sardjito hospital conducted from May 1st, 2007 to September 30th, 2007.

Inclusion criteria were adult liver cirrhosis patients that the diagnosis had been established clinically and by the use of ultrasonografi (USG), who also gave written informed consent to participate in the study. Patients with shock or suffer from hemodynamic impairment, renal failure (serum creatinine > 2.0 mg/dL), myocardial infarction, malignancy, severe metabolic or electrolyte disturbances, recent active infection, recent massive bleeding and/or receive blood transfusion in the last two days, pregnancy or breastfeed, or using hormonal drugs, were excluded from this study.

The diagnosis of liver cirrhosis was established by clinical examination and laboratory data according to the Soedjono-Subandiri criteria, and the USG findings.[11] Child-Turcotte criteria modified by Pugh (CTP score) was selected to assess the severity of liver cirrhosis.[12] Fasting zinc serum concentration in the morning is considered low if less than 74 µg/dL for men and less than 70 µg/dL for women.[13] Normal urinary zinc excretion from 24-hours urine specimen is 402 ± 150 µg/24 hours. [14] Blood sample for zinc examination was taken in the morning (06:00 – 12:00 AM) after the subject had fasting for minimum 8 hours. Urine sample was taken from 24-hours urine collection using zinc-free plastic container. Blood sample and 24-hours urine collection of the outpatient subjects were obtained when the laboratory examination was conducted before the follow up visit at the polyclinic. All blood examination, except the zinc concentration examination, was conducted in the clinical pathology laboratory of our hospital . The examination of zinc concentration using the flame Atomic Absorption Spectrophotometry (AAS) was conducted at Laboratory of Integrated Testing & Research in University of Gadjah Mada.

Data distribution were tested using normality test of Kolmogorov Smirnov. Pearson or Spearman correlation test (according to the normality of the data) were conducted to evaluate the correlation of numeric data, while Mann-Whitney U test was used to evaluate the difference of mean between groups of clinical factors. The data was analyze using the computer program with the $p < 0.05$.

RESULT

Between the periods of May 1st to September 30th 2007 there are 36 liver cirrhosis patients that meet the criteria of the study. Table 1 shows the baseline char-acteristic of liver cirrhosis patients participated in the study.

Statistically significant correlation was found between the variable of 24-hours zinc urinary excretion and the volume of 24-hours urine ($r = 0.638$, $p = 0.000$), and also between urinary zinc concentration and zinc urinary excretion ($r = 0.526$, $p = 0.001$).

To evaluate the correlation between zinc serum concentration, urinary zinc concentration, and urinary zinc excretion in 24-hours with sex, diabetes mellitus (DM) comorbidity, diuretic use, intake of hepatic diet, treatment status of the patients, and the duration of liver cirrhosis, the data is grouped into those factors (table 2). The difference of mean zinc serum concentration between men and women are not statistically significant. However the difference of mean of urinary zinc concentration are statistically significant ($p = 0.036$) between men group (0.86 ± 0.57 µg/dL) and women group (0.47 ± 0.30 µg/dL), also for the mean of 24-hours urinary zinc excretion (913.66 ± 572.52 µg vs 409.12 ± 377.34 µg, $p = 0.010$). Urinary zinc excretion is also significantly different according to the treatment status ($p = 0.003$). 24-hours urine volume is also different according to the use of diuretics ($p = 0.025$), the hepatic diet ($p = 0.009$) and the treatment status ($p = 0.048$). There are no significant difference for the use of diuretics on the serum zinc concentration, urinary zinc concentration, and urinary zinc excretion.

Table 1. Baseline characteristic of liver cirrhosis patients who meet the study criteria

Variable	Mean ± SD	Median (min - max)	Frequency (%)	95% CI
Age (years)	55.75 ± 12.97	57 (29-80)	-	51.36-60.14
Sex (%)				
Male	-	-	27 (75.0)	
Female			9 (25.0)	-
Comorbidity				
Gastritis/ulcer/GERD			4 (11.1)	
Diabetes mellitus	-	-	8 (22.2)	-
Hypertension			2 (5.6)	
Treatment status				
Outpatient	-	-	17 (47.2)	-
Inpatient			19 (52.8)	
Duration of liver cirrhosis (years)				
< 5			28 (77.8)	
5-10	-	-	7 (19.4)	-
> 10			1 (2.8)	
CTP score	8.83 ± 2.11	8 (5-14)		8.10-9.55
A			2 (5.6)	
B			24 (66.7)	
C			10 (27.8)	
Hepatic diet				
Yes			24 (66.7)	
No	-	-	10 (27.8)	-
Unknown			2 (5.6)	
Acites				
No			11 (30.6)	
Mild	-	-	18 (50.0)	-
Moderate			7 (19.4)	
Diuretic use				
No			9 (25.0)	
Spironolactone	-	-	20 (55.6)	-
Spironolactone & furosemide			7 (19.4)	
Urine volume/24 hours (mL)	1.25 ± 1.11	1.03 (0.06-5.50)		0.88-1.63
< 500			9 (25.0)	
500-2,500			23 (63.9)	
> 2,500			4 (11.1)	
Urine zinc concentration (µg/dL)	0.76 ± 0.54	0.64 (0.08-2.34)	-	0.58-0.94
Urinary zinc excretion (µg/24 hours)	787.52 ± 570.20	694.43(27.92-1960.90)		594.59-980.45
< 250			8 (22.2)	
250-550			9 (25.0)	
> 550			19 (52.8)	
Serum zinc concentration (µg/dL)	63.70 ± 24.85	59.08 (23.25-119.36)		55.29-72.11
Hypozincemia			24 (66.7)	
Normozincemia			12 (33.3)	
Laboratory examination				
Creatinine (mg/dL)	1.09 ± 0.28	1.05 (0.65-1.79)		1.00-1.19
RBG (mg/dL)	117.91 ± 39.64	107.0 (70.0-200.0)	-	103.85-131.96
Albumin (g/dL)	2.74 ± 0.67	2.65 (1.60-4.20)		2.52-2.97

SD: standard deviation, CI: confidence interval, GERD: gastroesophageal reflux disease, CTP: Child-Turcotte-Pugh, RBG: random blood glucose

Table 2. Mean serum zinc concentration and 24-hours urinary zinc excretion of liver cirrhosis subjects according to clinical factors

Variable	Serum zinc concentration (µg/dL)		Urinary zinc concentration (µg/dL)		24-hours urinary zinc excretion (µg)		24-hours urine volume (mL)	
	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p
Sex								
Male (n = 27)	65.55 ± 24.82	0.454	0.86 ± 0.57	0.036	913.7 ± 572.5	0.010	1412.3 ± 1222.6	0.112
Female (n = 9)	58.14 ± 25.58		0.47 ± 0.30		409.1 ± 377.3		773.3 ± 454.5	
DM status								
DM (n = 8)	58.55 ± 18.93	0.594	0.98 ± 0.64	0.223	808.0 ± 420.1	0.819	900.0 ± 402.2	0.530
Non DM (n = 28)	65.17 ± 26.41		0.70 ± 0.50		781.4 ± 612.8		1353.3 ± 1230.2	
Diuretic use								
No (n = 9)	73.67 ± 32.41	0.371	0.89 ± 0.49	0.221	598.16 ± 502.61	0.221	653.9 ± 552.6	0.025
Diuretic (n = 27)	60.37 ± 21.50		0.72 ± 0.56		850.64 ± 586.00		1452.2 ± 1185.3	
Hepatic diet								
Yes (n = 24)	65.28 ± 22.40	0.940	0.77 ± 0.46	0.762	889.5 ± 519.4	0.151	1452.9 ± 1099.4	
No (n = 10)	66.03 ± 29.60		0.84 ± 0.72		636.8 ± 679.7		828.3 ± 1174.4	0.009
Treatment status								
Inpatient (n = 19)	69.20 ± 29.44	0.247	0.92 ± 0.58	0.059	1031.1 ± 495.4	0.003	1523.3 ± 1201.7	0.048
Outpatient (n = 17)	57.54 ± 17.32		0.59 ± 0.43		515.3 ± 534.8		950.0 ± 946.3	
Duration of liver cirrhosis								
< 5 years (n = 27)	63.22 ± 26.76	0.622	0.82 ± 0.59	0.352	893.5 ± 589.3	0.051	1418.3 ± 1216.8	0.089
≥ 5 years (n = 9)	65.13 ± 19.29		0.58 ± 0.30		469.5 ± 377.2		755.6 ± 475.3	

Mann-Whitney U test

DISCUSSION

In this study 66.7% of the liver cirrhosis subjects suffer from hypozincemia. Mean serum zinc concentration in this study is 63.70 ± 24.85 µg/dL that is quite different compared to the previous result (75.15 ± 1 1.40 µg/dL), [4] but is quite similar from study by Yoshida et al, decompensate liver cirrhosis patients 56.3 ± 13.7 µg/dL, while compensated hepatic cirrhosis patients 75.0 ± 15.0 µg/dL). [7] The exact percentage of zinc deficiency in this study may be higher. Some researcher assumed that serum zinc measurement in zinc deficiency is relatively less sensitive because mild zinc deficiency can occur with normal zinc serum concentration. The examination of zinc concentration in granulocyte and lymphocyte give more sensitive diagnostic criteria for marginal zinc deficiency compared to plasma zinc concentration,[9] but can not be done in our laboratory.

The decrease of zinc concentration commonly occur in advance liver cirrhosis patients, and aggravated by the portosystemic shunt.[3,15] Biochemical basis of zinc deficiency has not yet been fully known. Several factors such as the poor diet intake that aggravated by protein restriction, intestinal absorption impairment, and impairment in albumin bound and the excessive loss through the urine could be responsible for the decrease of overall body zinc concentration.[2,7,16] The existence of portosystemic shunt and malabsorption are not evaluated in this study because of the difficulty of assessing those two factors, while food intake is not evaluated and the data of hepatic diet was based on the anamnesis from the patients.

In this study, we do not find statistically significant difference (p = 0.052) in the mean serum zinc concentration of decompensated liver cirrhosis patients with CTP score B (67.68 ± 21.55 µg/dL) and CTP score C (54.04 ± 32.25 µg/dL), with the p approaching to the significance limit. The small sample size is probably the cause of the lack statistical significance.

Zinc deficiency can also occur in DM patients, but in this study there are no significant differences in mean serum zinc concentration based on the existence of DM comorbidity. Hotz et al, revealed that serum zinc concentration of women are about 5 µg/dL lower than men.[13] In this study mean serum zinc concentration of women are 7.6 µg/dL lower than men but this difference do not reach statistical significance.

In this study, the mean 24-hours urinary zinc excretion is higher than normal that is 787.52 ± 570.20 µg with the highest value of 1,960.90 µg. The value of this mean is lower than the result from Yoshida et al (1,440 ± 770 µg). [7] In post-alcoholic cirrhosis, urinary zinc excretion can achieve the value of 5,010 µg. [14] In this study, there are 19 patients (52.8%) with urinary zinc excretion > 550 µg/24 hours. Hiperzincuria in patients with cirrhosis seems related to the impairment of albumin synthesis. The decrease in serum albumin and the increase of free amino acid concentration in the circulation in the condition of cirrhosis cause displacement of zinc bound from the macromolecular ligand that result in the increase of zinc filtration in the renal glomerulus.[6] In this study, there are no statistically significant correlation between albumin concentration and serum zinc concentration and also urinary zinc excretion.

Urinary zinc concentration correlates with urinary zinc excretion (r = 0.526, p = 0.001) and urinary zinc excretion correlates with the urine volume (r = 0.638, p = 0.000) were appropriate with the statements from the literatures that the amount of zinc excreted in the urine correlates with the rate of urine production (or urine volume).[2,8] Urinary zinc excretion in this study also correlates with the sex (p = 0.010) and treatment status of the patients (p = 0.003). Statistically significant correlation between the mean of 24-hours urinary zinc excretion with the use of diuretics is not found (p = 0.221), although mean urinary zinc excretion in the diuretic group is higher than the non-diuretic group (850.6 ± 586.0 mL and 598.2 ± 502.6 mL). In this study, the mean of 24-hours urine excretion in the inpatient group is higher (p = 0.048), and correlates with the use of diuretics (p = 0.025). The use of diuretics and sex is not different according to the treatment status (p = 1.000 and p = 0.706), but the CTP score is higher in the inpatient group (p = 0.001) and the inpatient is higher in patients with duration of cirrhosis < 5 years (p = 0.055). Long-term use of diuretics[8] and excessive loss through the urine[7,16] can cause zinc deficiency. liver cirrhosis patients with diuretics and inpatient status would be better to be given more zinc supplementation to replace the urinary zinc loss.

CONCLUSION

There are no significant difference in fasting zinc serum concentration in CTP score B and C in patients with hepatic cirrhosis. In patients with liver cirrhosis, urinary zinc excretion correlates positively with the urine volume.

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