

SELENIUM IN CHRONIC LIVER DISEASE AND HEPATIC ENCEPHALOPATHYMohamed S. Zaghlol¹, Ahmed Qasem Mohamed², Elawady M. M.², Majed Darraj³ and Dr. Erwa Elmakki*³^{1,2}Department of Clinical Pathology and Tropical Medicine, Al-Azhar Faculty of Medicine.³Department of Internal Medicine, Faculty of Medicine, Jazan University.***Corresponding Author: Dr. Erwa Elmakki**

Department of Internal Medicine, Faculty of Medicine, Jazan University.

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ABSTRACT

Background: Hepatic encephalopathy (HE) describes a spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of unrelated neurologic and/or metabolic abnormalities. **Objectives:** The objectives of this study were to assess the relation between serum selenium concentration and liver diseases, also to determine if there is a role of serum selenium concentration in prediction of minimal hepatic encephalopathy (MHE). **Methodology:** Eighty patients with liver cirrhosis were included in this prospective study. The patients were classified into two groups (**Group, 1**): includes 40 patients with cirrhosis and no overt HE. This group further subdivided into 2 subgroups MHE and non MHE according to the results of the psychometric tests for the detection of MHE (**Group, 2**) includes 40 patients with liver cirrhosis and overt HE. While, 20 healthy volunteers were included as control group (**Group, 3**). The patients were subjected to full history, focusing on history of liver disease, clinical examination and routine laboratory investigations and serum selenium concentration. **Results:** Highly significant ($p < 0.01$) differences were observed between the study groups in selenium levels as following; the highest selenium levels is present in the control group than group 1 (as a whole) than group 2, but no significant difference between non MHE and MHE subgroups. In addition, the results showed that highly significant positive correlation was found between selenium concentration and both albumin and hemoglobin concentrations however, significant inverse correlation was found between selenium concentration and bilirubin, INR, AST and ALT levels. There was a highly significant decrease in selenium levels in ascitic patients than those without ascites and there were no significant differences between patients with and without HCC in selenium concentration. There was a significant decrease in selenium levels with the increase in child score. Also, the results showed that no significant correlation was found between selenium levels and grade of HE. The sensitivity and specificity of selenium in the prediction of MHE was 86.4% and 83.3%, respectively, with AUC of 0.465 but was not significant. **Conclusion:** Serum selenium concentration would have a beneficial effect on some complications of liver cirrhosis and on the progression of cirrhosis, so it is advisable to provide laboratory analysis of trace elements as a routine especially in cirrhotic patients who are refractory to traditional lines of treatment.

KEYWORDS: Selenium, liver diseases, Cirrhosis, Hepatic encephalopathy.**INTRODUCTION**

Hepatic encephalopathy (HE) is defined as “a condition which reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease.”^[8] Symptoms of overt HE are reported in approximately 30–45% of patients with liver cirrhosis and 10–50% of patients.^[26] Minimal hepatic encephalopathy (MHE), the mildest form of HE, is characterized by subtle motor and cognitive deficits, and impairs health-related quality of life (HRQOL),^[7] and those with clinical signs of hepatic encephalopathy, called overt HE.^[2] Overt HE is a syndrome that can be diagnosed by clinical examination and is the familiar “hepatic encephalopathy” that is known to clinicians.^[3]

Selenium levels have also been found to be decreased in patients with chronic liver disease.^[15] Selenium is an essential trace mineral for animals including humans.^[14] It is critical for antioxidant defense, thyroid hormone metabolism,^[17] fertility,^[12] immune response,^[19] muscle development,^[22] and have a protective effect at different stages of carcinogenesis.^[32] Several mechanisms for selenium anti-cancer action have been proposed including antioxidant protection, enhanced carcinogen detoxification, and enhanced immune surveillance, modulation of cell proliferation, and inhibition of tumor cell invasion and inhibition of angiogenesis.^[14] It is speculated that the biosynthesis of selenoproteins in brain is affected in hepatic encephalopathy.^[29] On the other hand, the high priority of the brain for selenium supply and retention at dietary selenium deficiency might ensure that antioxidant selenoproteins could participate

in the protection of astrocytes from oxidative stress associated with this disease. Indeed, elevated mRNA levels of two selenoproteins, Selenoprotein S and Selenate, have been detected recently in the brain of patients with HE but not in the brain of patients suffering from cirrhosis without HE.^[11] As selenoprotein S is also up-regulated in reactive astrocytes upon brain injury,^[9] so it might be worth to examine its role in astrocytes in HE.

PATIENTS AND METHODS

Eighty patients with liver cirrhosis selected from the outpatient clinic and inpatient department of Gastroenterology and Hepatology, Al-Azhar university hospital-Assiut were enrolled in the study from June 2012 to June 2013. The patients were confirmed clinically and/or by abdominal imaging as having liver cirrhosis. Twenty healthy volunteers' age and sex matched with the patients group included in this study as control group.

They were classified into three groups:

Group (1): includes 40 patients with cirrhosis and no overt HE. This group further subdivided into 2 subgroups MHE and non MHE according to the results of the psychometric tests for the detection of MHE.

Group (2) includes 40 patients with liver cirrhosis and overt HE.

Group (3): includes 20 healthy volunteers as control group.

Age and sex matched with the patients groups.

Inclusion criteria

- For Group 1 & 2 included patients with liver cirrhosis confirmed clinically and/or by abdominal imaging without other causes of impaired mental function.
- For Group 2 included patients with overt HE.

Exclusion criteria

- For Group 1 included: absence of CLD (cirrhosis and/or portal hypertension), overt HE and recent G.I.T. bleeding in the last 6 weeks, serum creatinine > 1.5 mg/dl, active infection, patients taking psychotropic drugs, patients with TIPS, severe comorbidities as severe cardiac or pulmonary diseases, blind patients, patients taking selenium containing drugs and the presence of other causes of impaired mental status.
- For Group 2 included: absence of CLD and the presence of other causes of encephalopathy.

All patients and control were subjected to the following:

1- Full history including; name, age, sex, residence, occupation, educational state, any drug use, history of liver disease as regarding stigmata of chronic liver disease e.g. jaundic, flabbing tremors, palmer

erythema, bleeding tendency, lower limb edema, Ascites and encephalopathy.

2- Thorough clinical examination stressing on; jaundice, feter hepaticus, conscious level, nails, palmer erythema, tremors, LL edema, Ascites and splenomegaly.

3- Abdominal US for diagnosis of liver cirrhosis, its complications and any associated diseases.

4- Laboratory investigations

a. Routine laboratory investigations: (CBC, liver function and kidney function).

b. Serum selenium concentration using colorimetric assay.

Statistical analysis

Statistical analysis of the data was performed by using SPSS_16 software package under Windows 7 operating system. Categorical data parameters were presented in the form of frequency and percent. Comparison was performed by Chi-square test for categorical data. Quantitative data were expressed in the form of mean; SD. Analysis of variance (ANOVA) test and T-test were used to test the significance between groups for quantitative data. The differences between means were analyzed by Duncan's Multiple Range Test. Spearman correlation coefficient was used to get the correlation among parameters. Probability level (P-value) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.001. P-value was considered non-significant if greater than or equal to 0.05.

RESULTS

Results of **table (1)** revealed that highly significant differences were noticed between the study groups in selenium levels as following; the highest selenium levels is present in the control group than group 1(as a whole) than group 2, but no significant difference between non MHE and MHE subgroups.

Regarding the correlation between selenium concentration and laboratory data **table (2)**, highly significant positive correlation was found between selenium concentration and both albumin and hemoglobin concentrations however, significant inverse correlation was found between selenium concentration and bilirubin, INR, AST and ALT levels.

Table (3) shows that there was highly significant decrease in selenium levels in ascitic patients than those without Ascites and there were no significant differences between patients with and without HCC in selenium concentration. Also, the results presented in table (3) indicated that there was significant decrease in selenium levels with the increase in child score. Selenium in child A is 106.9 ± 19.6 , child B is 90.4 ± 20.2 and child C is 80 ± 25.1 . Also, the results showed that no significant

correlation was found between selenium levels and grade of HE.

Table (4) shows the results of receiver operating characteristic curves (ROC) for selenium in group 1 for

detection of MHE. The sensitivity and specificity of selenium in the prediction of MHE was 86.4% and 83.3%, respectively, with AUC of 0.465 but was not significant.

Table (1): Selenium concentration between studied groups.

Parameter	Groups			P. value (Sig.)	
	Control (20)	Group 1 (cirr. without enceph.)			Group 2 (cirr. with enceph.) (40)
		Non MHE (18)	MHE (22)		
Selenium (ng/ml)	123.2 ^a ± 27.9	100.8 ^b ± 13.5	98.8 ^b ± 94.8	75.6 ^c ± 25.5	<0.001**

a,b,c Means in the same row with different superscripts are significantly different.

NS Not significant.

*Significant (p<0.05).

**Significant (p<0.01).

Table (2): Correlations between selenium concentration and other laboratory investigations.

Correlations		(r)	P. value (Sig.)
Selenium	Albumin	0.42	<0.001**
	Bilirubin	-0.21	0.049*
	INR	-0.58	<0.001**
	Hb	0.31	<0.001**
	Creatinine	-0.42	<0.001**
	AST	-0.42	<0.001**
	ALT	-0.21	0.044*

*Significant (p<0.05).

**Significant (p<0.01).

Table (3): Selenium concentration in patients with and without Ascites.

Parameter	Selenium (ng/mL) (M ± SD)	P. value (Sig.)
Ascites	With Ascites (n=56)	86.3 ± 28.5
	Without ascites (n=34)	112.4 ± 26.9
Child scores	A (n=17)	106.9 ± 19.6
	B (n=20)	90.4 ± 20.2
	C (n=43)	80 ± 25.1
HCC	With HCC (n=4)	98.6 ± 20.4
	Without HCC (n=76)	100.6 ± 32.5
Grade of HE	G1	88.8 ± 15.2
	G2	83.7 ± 9.1
	G3	76.9 ± 29.9
	G4	71.4 ± 21.1

NS Not significant*

**Significant (p<0.01).

Table (4): Receiver operating characteristic curves ROC curve results.

Parameter	Cut off	AUC	Sensitivity	specificity	P. value (Sig.)
Selenium	78.8	0.465	86.4	83.3	0.70 ^{NS}

DISCUSSION

Hepatic encephalopathy is a complex neuropsychiatric syndrome that may occur in such diverse clinical situations as acute or chronic liver disease, and spontaneous or iatrogenic portosystemic venous shunting, including that following procedures to establish a transjugular intrahepatic portosystemic shunt. The clinical manifestations of this syndrome range from

subtle abnormalities detectable only by psychometric testing to deep coma.^[30] It has been suggested that some of the clinical features of liver cirrhosis, such as testicular atrophy, loss of body hair, night blindness, poor wound healing, poor appetite, decreased taste and smell acuity, susceptibility to infections, enhanced sensitivity to drugs, and decreased neurocognitive

performances, may be related to conditioned zinc deficiency.^[1]

Significant differences were found between the study groups in selenium levels as following; the highest selenium levels is present in the control group, then non MHE, then MHE, and the lowest in group 2, but no significant difference between non MHE and MHE subgroups (table 1). This agrees with,^[20] who found in their study that the lowest serum selenium levels were obtained from alcoholics with decompensated cirrhosis and agree with,^[16,22] who found significant reduction in selenium level in cirrhotic patients than control group.^[25] stated that there is strong inverse relationship between serum Selenium level and the GOT/GPT ratio indicating the strong correlation of serum selenium level with the severity of CLD and decreased levels could already be detected in the early stages of disease. Also,^[13] found that serum selenium levels declined in proportion to the severity of hepatic fibrosis.

We also found significant positive correlation between selenium and albumin levels. This agrees with the results of,^[4,13,25] who found that serum selenium levels positively correlated with serum albumin levels, suggesting that the synthesis of albumin might depend on the serum Se concentration.^[13] Presumed that Selenium deficiency might occur due to the deterioration of the hepatic reserve. On the other hand,^[31] documented that the serum selenium concentration in patients with hypoalbuminemia was within reference range as selenium is likely to be mainly transported in globulin from the small intestine to the liver. Hence, Se deficiency did not result from the depletion of the Se-binding protein in patients with HCV-related CLD. Also,^[24] found that Serum selenium concentrations were not statistically correlated with serum nutritional markers (triglycerides and albumin).

The study also revealed significant inverse correlation between bilirubin and selenium levels (table, 2).^[6] Found significant direct correlation between selenium and Hb in British people aged 65 years and over. Also there is significant inverse correlation between AST and selenium levels in serum. This agrees with,^[25] who found inverse correlation between AST and serum selenium in patients with chronic liver diseases and control but was not significant in the patients group.

There is significant inverse correlation between ALT & serum selenium levels. This may indicate that the more active liver disease is the more decrease in selenium levels or may be due to oxidative stress in selenium deficient patients which lead to increase in necro-inflammatory parameters which include AST and ALT. These results agree with,^[18] who found significant inverse correlation between serum selenium and serum ALT in liver cirrhosis patients. This disagrees with,^[13,25] stated that no significant correlation between serum

Selenium and ALT levels was found in patients with HCV-related CLD.

We also found significant decrease in serum selenium with the increase in child score. These agree with,^[10,27] who found that those with grade C (severe) liver damage had lower concentrations than those in whom liver damage was less severe (grades A and B).

Our study also showed no significant correlation between selenium levels and grades of HE. This agrees with,^[23] Who found that serum selenium level is significantly decreased in patients with HE but not correlated with the grades of HE in a study conducted on 55 patients with acute and CLD with HE.

The receiver operating characteristic curve for the prediction of MHE in our study revealed no statistical significance for selenium in the prediction of MHE.

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