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Original Research Article.

Study of Zinc Level in Egyptian Cirrhotic Patients with Different Stages of Liver Cirrhosis

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ABSTRACT

Background: Liver cirrhosis is a widespread disease differentiated by spread liver fibrosis and formation of nodules. During the last years, concentrations of minerals in patients with chronic hepatic disease have been investigated extensively. In fact, liver is responsible for regulation of the metabolic pathway and trace elements (TE) transport, and their bioavailability, distribution in tissue and consequent toxicity. , for magnesium, manganese, chromium, selenium and zinc in other types of chronic hepatic disease. The alterations of these trace elements were related mostly to malnutrition in hepatic disease. Zinc is one of the most important trace elements in the human body. Zinc is responsible for activation of about 300 different metallo-enzymes and metal-activated enzymes in vivo and is essential for the metabolism of nucleic acids and proteins.

Methods: The work was carried out on a cluster of (60) patients with liver cirrhosis attending outpatient clinic and those admitted at the internal medicine inpatients wards. They were calcified into three groups A, B & C according to child calcification, 20 patients in each group. Full history, clinical examination and investigation were done, estimation of serum Zinc level.

Results: Serum zinc level decreases with cirrhosis especially with advanced cases and have direct relation with the degree of severity of liver disease and its complications as hepatic encephalopathy, ascites, hypoalbuminemia and malnutrition.

Conclusion: Zinc, is a helping element of the urea cycle enzymes, can be decreased in patients with cirrhosis, particularly if joined with malnutrition.

Key Words: Serum Zinc, Liver Cirrhosis, Trace Elements.

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INTRODUCTION

Liver cirrhosis is a widespread disease differentiated by spread liver fibrosis and formation of nodules. It happens at different ages, has considerable morbidity and is leading cause of early death. The most common causes of cirrhosis are chronic viral hepatitis and excessive alcohol consumption. The most common cause of portal hypertension and its related complications is cirrhosis.[1]

During the last years, concentrations of minerals in patients with chronic hepatic disease have been investigated extensively.[2]

In fact, liver is responsible for regulation of the metabolic pathway and trace elements (TE) transport, and their bioavailability, distribution in tissue and consequent toxicity. Abnormalities of blood levels were found for copper in primary biliary cirrhosis for iron in primary or secondary hemochromatosis and in HCV-associated chronic hepatitis.[3] for magnesium, manganese, chromium, selenium and zinc in other types of chronic hepatic disease. The alterations of these trace elements were related mostly to malnutrition in hepatic disease.[4]

Zinc is one of the most important trace elements in the human body. The daily requirement of zinc in adults is 10–15 mg and is absorbed from the upper gastrointestinal tract, mostly the small intestine. Zinc is responsible for activation of about 300 different metallo-enzymes and metal-activated enzymes in vivo and is essential for the metabolism of nucleic acids and proteins.[5]

Therefore, it has been established that zinc deficiency can cause different pathological conditions in humans. Among these, in patients with chronic viral hepatitis C liver disease, the serum zinc concentration decreases with progression of the disease from

chronic hepatitis (CH) to Compensated liver cirrhosis (LC), to decompensated LC, to hepatocellular carcinoma (HCC).[6]

Patients with liver cell failure or HCC is known to have a sever state of zinc deficiency and zinc supplementation may improve liver damage.[7]

It was reported that the hepatitis C virus (HCV) NS5A protein is a zinc metalloprotein and that zinc is involved in the activation of the NS5A protein. Also, it has been reported that the eradication rate of HCV is higher when interferon (IFN) therapy for Virus-C CH is combined with zinc supplementation, compared to IFN therapy alone.[8]

Thus, zinc supplementation has a clear effect on the clinical profile of chronic hepatitis C and liver cirrhosis.

AIM OF THE WORK

Screening for the state of zinc level in hepatic patients with different stages of cirrhosis and correlate zinc levels with grade and complications of cirrhosis.

Primary Objective

Screen for presence of zinc deficiency in patients with liver cirrhosis and the level of deficiency with the severity of the disease and complication of cirrhosis in patients attending the outpatient and inpatient of Suez Canal University.

Secondary Objective

To evaluate the degree of zinc deficiency with different stages of liver cirrhosis and the complications of liver cirrhosis will increase with increase in the level of zinc deficiency. Zinc levels should be screened in patients with liver cirrhosis as the severity of the disease increases.

PATIENTS AND METHODS

The work was carried out on a cluster of patients with liver cirrhosis attending outpatient clinic and those admitted at the internal medicine inpatients wards.

Type of Study

Cross section study for HCV patients complicated by liver cirrhosis.

Inclusion Criteria

1. Include all HCV patients with cirrhosis as confirmed by history, clinical examination, laboratory results and abdominal U/S.
2. Patients of both sexes above 18 years old.

Exclusion Criteria

1. Patients with cirrhosis due to other causes.
2. Refusal to participation in the study.
3. Patients who receive zinc supplementation.

Data Collection

All patients included in the study submitted to the following scheme: -

1. History Taking

Data was collected by personal interview. According to Items:

1. Basic demographic data.
2. History suggestive of etiology (blood transfusion).
3. Presence of other chronic diseases (e.g. DM, HTN).
4. History of jaundice or encephalopathy.
5. Presence of ascites.

2. Clinical Examination

Including: -

2.1: General Examination: with special emphasis on vital signs and the presence of signs of chronic liver disease such as darking of the face, wasting of temporalis and maseter muscles & prominent zygomatic bone, bilateral parotid enlargement, jaundice, fetor hepaticus, palmar erythema, spider nevi, lower limb edema, flapping tremors and impaired level of consciousness.

2.2: Local examination: with special emphasis on liver examination and detection of ascites.

2.3: Investigations

The following investigations will be done:

A) Laboratory Investigations:

1. Complete blood count.
2. AST, ALT, Alkaline phosphatase.
3. Tests for hepatitis B (HBs Ag) and hepatitis C (HCV Ab).
4. INR, PT.
5. Serum Albumin.
6. Serum Bilirubin (total, direct).
7. Zinc levels.

Measurement of Zinc Levels:

Zinc Colorimetric Assay Kit was provided by BioVision Incorporated. (California, USA).

Normal serum zinc is 66 to 110µg/dl

B) Imaging Investigations:

Abdominal U/S to detect:

- Liver cirrhosis
- Ascites will be assessed (absent, mild, moderate or severe)

Ultrasonic criteria of cirrhosis are:

- Diffuse coarse texture,
- Irregular surface,
- Attenuated intra-hepatic veins,
- Usually shrunken size,
- Prominent caudate lobe,
- With or without splenomegaly and dilated portal vein.

Data Management

- All collected data was cleaned and filtered.
- Each variable was coded to facilitate the transfer of data.
- These codes were entered into computer through Statistical Package for Social Science (SPSS) version 22 where all statistical analyses were performed.
- the process of data analysis which consisted of:

- Descriptive statistics which was applied in numerical form; mean (standard deviation) for quantitative data and number (%) for qualitative data, or whatever suitable.
- Associations between the outcome measures and different variables were tested for significance by using both Fisher's exact test and Chi-square test for categorical variables and the student t- test and ANOVA test for numerical variables with normally distributed data. Then, we studied the relations between continuous variables using Pearson correlation test.
- Statistical significance was pre-determined at 95% level of confidence (i.e. differences will be considered significant if $P < 0.05$)
- Data was presented as required according to the type of variables; graphs and tables will be used when appropriate.

Table 1: General characteristics of the studied patients (n=60).

General characteristics		Group A (n=20)	Group B (n=20)	Group C (n=20)	*P-value*
Age	**Mean± SD**	56±9	59±10	61±9	*0.233**
(years)	**Range**	(36-70)	(40-83)	(42-78)	
Gender	**Male**	12(60)	12(60)	12(60)	*1***
Frequency (%)	**Female**	8(40)	8(40)	8(40)	

Table 2: Laboratory investigations of the studied patients (n=60).

Laboratory investigations	Group A (n=20)	Group B (n=20)	Group C (n=20)	*F*	*P-value*
ALT (u/ml)	37±35	45±25	71±105	*1.493*	*0.074**
AST (u/ml)	37±28	50±21	76±105	*2.724*	*0.233**
Albumin (g/dl)	4.2±0.3	3.3±0.3	2.4±0.2	*230.505*	*0.0001***
Bilirubin (mg /dl)	0.7±0.3	1.4±0.5	3.9±1.3	*78.949*	*0.0001***
INR	1±0.04	1.1±0.08	1.3±0.3	*14.568*	*0.0001***
Zinc (µg/dl)	56±19	38±24	32±21	*7.023*	*0.002***

Table 3: Levels of Albumin and Zinc of the studied patients (n=60).

Laboratory investigations		Group A (n=20)	Group B (n=20)	Group C (n=20)	Total	*P-value*
Albumin (g/dl)	**Normal**	20	11	0	31	*0.0001**
	Abnormal	0	9	20	29	
Zinc	**Normal**	12	5	1	18	*0.001**
(µg/dl)	**Abnormal**	8	15	19	42	

Table 4: Presence of encephalopathy among the studied patients (n=60).

Hepatic encepehalopathy	Group A (n=20)	Group B (n=20)	Group C (n=20)	Total	*P-value*
No	20	1	0	21	*0.0001**
Grade I	0	1	0	1	
Grade II	0	18	3	21	
Grade III	0	0	17	17	

Table 5: Child's score among the studied patients (n=60).

Child's score	Group A (n=20)	Group B (n=20)	Group C (n=20)	*P-value*
Mean± SD	5.1±0.3	8.2±0.5	12.3±0.8	*0.0001**
Range	(5-6)	(7-9)	(11-14)	

Table 6: Correlations of Zinc among the studied patients (n=60).

Correlations of Zinc								
		Age	**AST**	**ALT**	**Albumin**	**Bilirubin**	**INR**	**Child**
Zinc	**Pearson**	0.041	-0.281	-0.243	0.435	-0.406	-0.291	-0.410
(µg/dl)	**Correlation (r)**							
	P-value	*0.758****	*0.029**	*0.062****	*0.001***	*0.001***	*0.024**	*0.001***

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

*** Correlation is not significant.

Figure 1: Correlations of Zinc with AST among the studied patients (n=60).

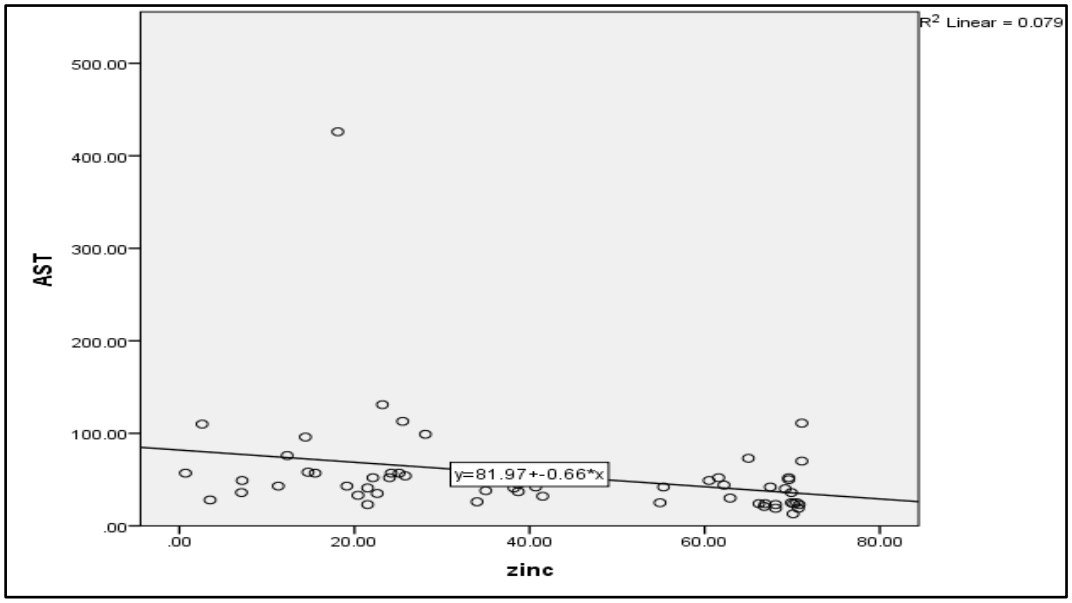

Figure 2: Correlations of Zinc with Albumin among the studied patients (n=60).

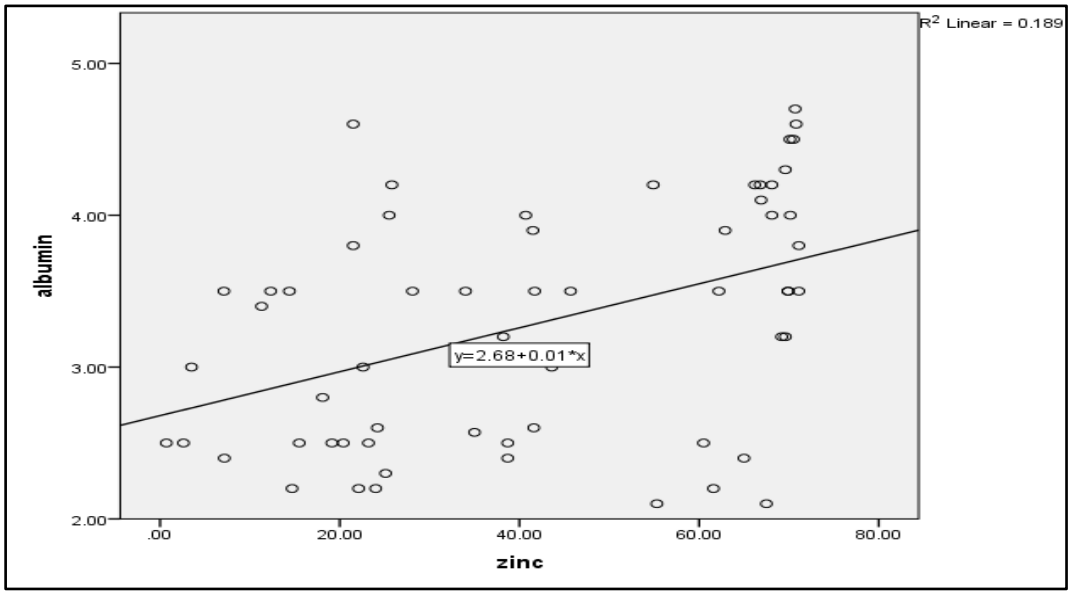

Figure 3: Correlations of Zinc with Bilirubin among the studied patients (n=60).

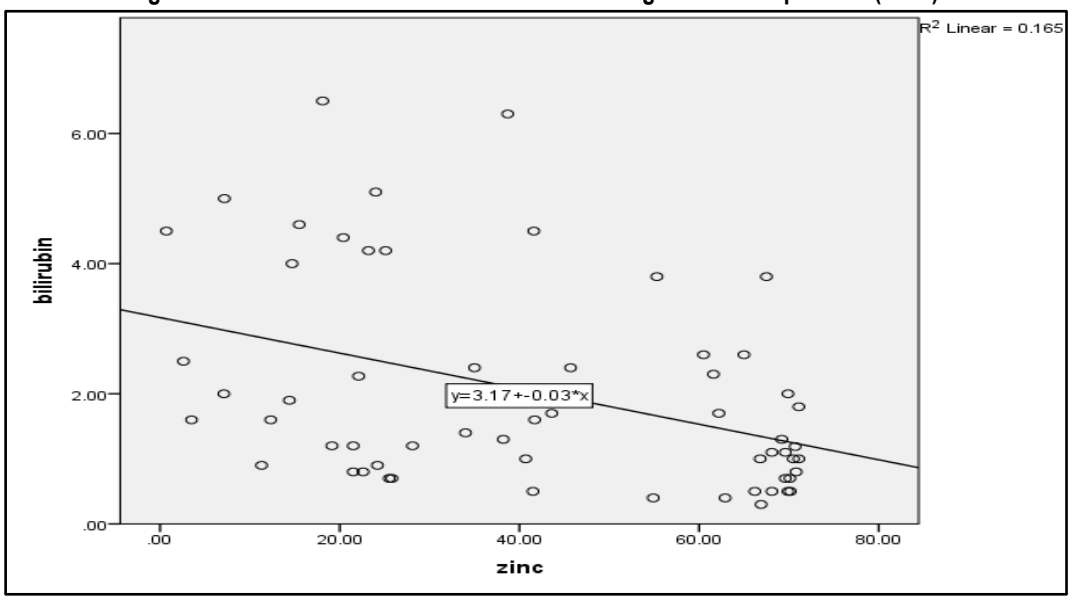

Figure 4: Correlations of Zinc with INR among the studied patients (n=60).

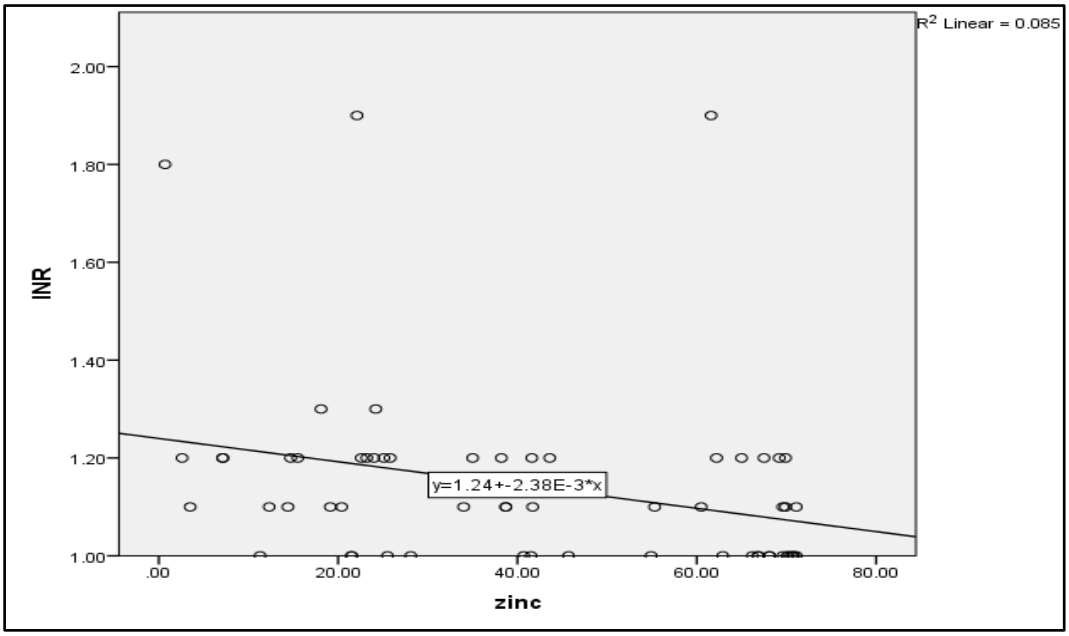

Figure 5: Correlations of Zinc with Child score among the studied patients (n=60).

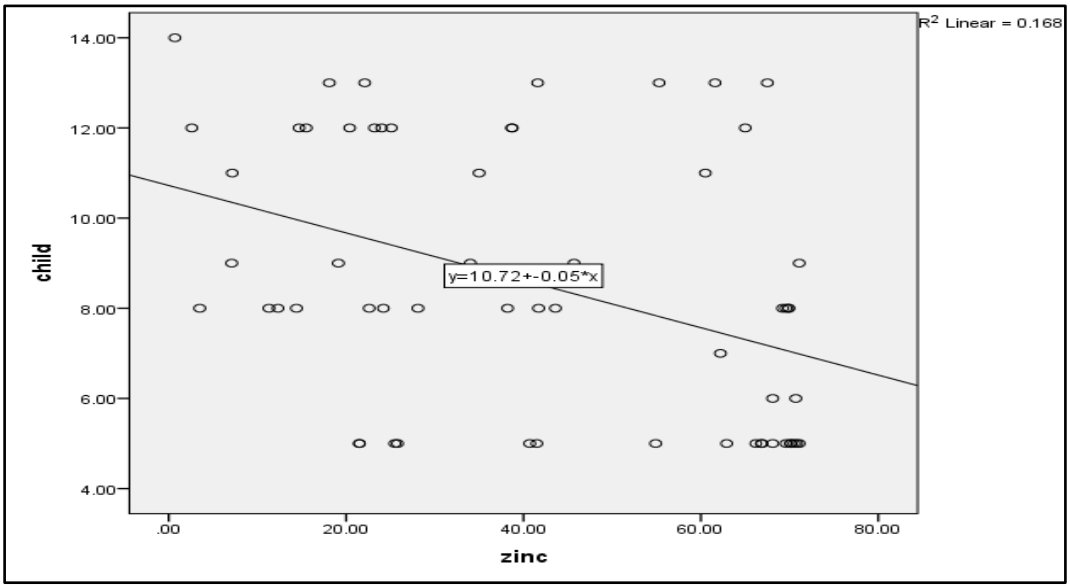

Table 7: Correlations of Zinc among the class A patients (n=20).

Correlations of Zinc								
		Age	**AST**	**ALT**	**Albumin**	**Bilirubin**	**INR**	**Child**
Zinc (µg/dl)	**Pearson Correlation (r)**	-0.003	-0.32	-0.167	0.227	-0.103	-0.378	0.239
	P-value	*0.991**	*0.169**	*0.481**	*0.337**	*0.001**	*0.101**	*0.31**

** Correlation is not significant.*

Table 8: Correlations of Zinc among the class B patients (n=20).

Correlations of Zinc								
		Age	**AST**	**ALT**	**Albumin**	**Bilirubin**	**INR**	**Child**
Zinc (µg/dl)	**Pearson Correlation (r)**	0.196	-0.159	-0.088	0.259	0.007	0.135	-0.155
	P-value	*0.408**	*0.503**	*0.712**	*0.271**	*0.978**	*0.572**	*0.514**

** Correlation is not significant.*

Table 9: Correlations of Zinc among the class C patients (n=20).

Correlations of Zinc								
		Age	**AST**	**ALT**	**Albumin**	**Bilirubin**	**INR**	**Child**
Zinc (µg/dl)	**Pearson Correlation (r)**	0.254	-0.227	-0.275	-0.341	-0.535	-0.111	0.018
	P-value	*0.28**	*0.337**	*0.24**	*0.141**	*0.126**	*0.64**	*0.941**

** Correlation is not significant.*

Table 10: Relation of Zinc with gender, Albumin and hepatic encephalopathy among the studied patients (n=60).

Variables		**Zinc (µg/dl)**		***P-value***
		Normal (n=18)	**Abnormal (n=42)**	
Gender	**Male**	11	25	*1**
	Female	7	17	
Albumin (g/dl)	**Normal**	15	16	*0.001***
	Abnormal	3	26	
Hepatic encephalopathy	**No**	12	9	*0.003****
	Grade I	0	1	
	Grade II	5	16	
	Grade III	1	16	

Table 11: Relation of Zinc with gender of the Class A patients (n=20).

Variables		**Zinc (µg/dl)**		**F**	***P-value***
		Normal (n=12)	**Abnormal (n=8)**		
Gender	**Male**	6	6	0.816	*0.373**
	Female	6	2		

Table 12: Relation of Zinc with gender, Albumin and hepatic encephalopathy of the Class B patients (n=20).

Variables		**Zinc (µg/dl)**		**F**	***P-value***
		Normal (n=5)	**Abnormal (n=15)**		
Gender	**Male**	5	7	0.816	*0.06**
	Female	0	8		
Albumin (g/dl)	**Normal**	3	8	0.905	*1**
	Abnormal	2	7		
Hepatic encephalopathy	**No**	0	1	-0.314	*1**
	Grade I	0	1		
	Grade II	5	13		

Table 13: Relation of Zinc with gender and hepatic encephalopathy of the Class C patients (n=20).

Variables		**Zinc (µg/dl)**		**F**	***P-value***
		Normal (n=1)	**Abnormal (n=19)**		
Gender	**Male**	0	12	0.816	*0.4**
	Female	1	7		
Hepatic encephalopathy	**Grade I**	0	3	-0.314	*1**
	Grade II	1	16		

Table 14: Relation of Zinc with age and laboratory investigations among the studied patients (n=60).

Variables	**Zinc (µg/dl)**		***t***	***P-value***
	Normal (n=18)	**Abnormal (n=42)**		
Age (years)	±856	±1059	1.228	.225**
ALT (u/ml)	±3134	±7557	1.221	.227**
AST (u/ml)	±2435	±6262	1.747	.086**
Albumin (g/dl)	±0.64	±0.73	-4.559	.000*
Bilirubin (mg /dl)	±0.81	±1.72	3.195	.002**
INR	±0.081.05	±0.21.17	2.485	.016**

Table 15: Relation of Zinc with age and laboratory investigations of the Class A patients (n=20).

Variables	Zinc (µg/dl)		*t*	*P-value*
	Normal (n=8)	Abnormal (n=12)		
Age (years)	±855	±1057	.441	.665*
ALT (u/ml)	±3834	±3341	.427	.674*
AST (u/ml)	±2731	±2945	1.066	.301*
Albumin (g/dl)	±0.274.2	±0.254	-1.516	.147*
Bilirubin (mg /dl)	±0.30.8	±0.30.7	-.474	.641*
INR	±0.01	±0.071.02	1.242	.230*

Table 16: Relation of Zinc with age and laboratory investigations of the Class B patients (n=20).

Variables	Zinc (µg/dl)		*t*	*P-value*
	Normal (n=5)	Abnormal (n=15)		
Age (years)	±756	±1159	.543	.594*
ALT (u/ml)	±1038	±2847	.693	.497*
AST (u/ml)	±1744	±2252	.720	.481*
Albumin (g/dl)	±0.23.3	±0.33.2	-.815	.426*
Bilirubin (mg /dl)	±0.61.3	±0.41.5	.563	.580*
INR	±0.051.1	±0.091.1	-.314	.757*

DISCUSSION

Many studies proposed the importance of zinc deficiency in pathogenesis of HE.[9] Zinc, is a helping element of the urea cycle enzymes, can be decreased in patients with cirrhosis, particularly if joined with malnutrition.[10]

We are trying to prove the relation between state of zinc level in hepatic patients with different stages of cirrhosis and correlate zinc levels with grade and complications of cirrhosis such as hepatic encephalopathy.

In this work we studied 60 patients with liver cirrhosis caused by hepatitis C virus as confirmed by history, clinical examination, laboratory results and abdominal U/S the studied patients were classified according to Child classification A, B and C, 20 patients in each. Their general characteristics were studied and compared. There was no statistically significant difference regarding age and gender among the 3 groups (P-value >0.05).

Malnourishment and an inadequate protein diet is proposed to be a causes of zinc deficiency in cirrhotic patients with HE.[11]

All the studied patients of class A had normal Albumin level, 55% of class B and no one in class C. These differences were statistically significant (P-value <0.05).

Hepatic encephalopathy was absent in all class A Patients, although that, it was reported in as grade I in only 5% of Class B patients, grade II as 80% and 15% in classes B and C respectively, and finally grade III in 85% of class C patients. These differences were statistically significant (P-value <0.05).

Our results agreed with.12 report in prevalence of minimal hepatic encephalopathy varying between 22% to 74% depending on the time and the number of tests and the severity of the liver disease.

Regarding Zinc level, it was normal in 60% and 25% of classes A and B respectively, while all the studied patients of class C had abnormal Zinc level except in one patient. These differences were statistically significant (P-value <0.05).

Zinc deficiency is prevalent in cirrhotic patients. There are many causes for zinc deficiency in hepatic disease patients, such as decrease zinc in diet, change in amino acids and protein metabolism, decrease liver excretion, portosystemic shunts, decrease absorption due to alcohol consumption, and the effect of cytokines, primarily interleukin-6 (IL-6), well-known to change zinc metabolism.[7]

Increase urinary zinc excretion in patients with cirrhosis seems to be associated with impairment of albumin synthesis. The decrease in serum albumin and the increase of free amino acid concentration in cirrhosis cause displacement of zinc bound from the macromolecular ligand that result in the increase of zinc filtration in the renal glomerulus. [13]

Serum zinc was significantly low in cirrhotic cases with grade 2 and 3 HE then that without HE. This confirmed results of Yang who studied only 20 nonalcoholic cirrhotics.[9]

Our results have indicated that cirrhotic patients with overt HE had significant lower serum zinc level than non-HE, these results confirm the studies suggesting that zinc deficiency is more prevalent in cirrhotic patients complicated by HE.

Correlations of Zinc with age, laboratory investigations and child score were studied for all the studied patients. It was significant for AST, Albumin, Bilirubin, INR and Child score, and not significant for age and ALT. All these significant correlations were negative; which means when these variables increase, Zinc level decreases, except for Albumin, it was a positive correlation; which means when Albumin decreases, Zinc level decreases, as shown in table (10) and figures (5-9).

Our results showed that zinc deficiency is significantly widespread in cirrhotic patients and correlates with disease severity. This confirmed results of S.Sengupata which showed 56 % of studied patients in class A were zinc deficient and 91% and 94 % deficient among class B and C respectively.

Also confirmed by the results indicate that the diminshed liver function, rather than the liver injury, is related to a serious reduction of two key trace elements, as Zn and Se.[4]

SUMMARY & CONCLUSION

Zinc is an essential trace element and is a part of several metalloenzymes and metal–binding proteins such as metallothionine to prove the relation between zinc deficiency and

the progression of liver disease and cirrhosis and its complications. The study included 60 patients classified into three groups, according to child classification, Divided equally into three classes A, B and C with 20 patients in each class. Serum zinc was found to be lower in cirrhotic in general and significantly lower in patients in class B and C with more cirrhosis and more complications of liver disease. Serum zinc level decreases with cirrhosis especially with advanced cases and have direct relation with the degree of severity of liver disease and its complications as hepatic encephalopathy, ascites, hypoalbuminemia and malnutrition.

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