ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com
Journal DOI: 10.21474/IJAR01

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

REALATIONSHIP OF SERUM LEVEL AND EFFECT OF LOW DOSE ZINC SUPPLEMENTATION ON SEVERITY OF LIVER CELL FAILURE IN PATIENTS WITH LIVER CIRRHOSIS.

Mohamed yehia seddek[1],Mohamedshawky el-sayed[1],Mohamed el-hadidi[2] , ayman el-badawy[1] Mohamed shebleemara.

1. Internal medicine department,faculty of medicine,benhauniversity,qalyubia,Egypt.
2. Internal medicine department,faculty of medicine,Mansourauniversity,daqahlia,Egypt.

Manuscript Info

Manuscript History:

Received: 15 March 2016
Final Accepted: 12 May 2016
Published Online: May 2016

Key words:
serum zinc level, liver biobsy, colorimetricassay, serum albumin.

Corresponding Author

Mohamed yehia seddek.

Abstract

Aim: the study aimed to determine the relationship between serum zinc level and severity of liver cell failure and the effect of low dose zinc supplementation on the severity of liver cell failure.

Patients/methods: the present study was conducted in the period extending from June 2014 to June2015 at BenhaUniversity Hospitals. the study included 60 patients with chronic liver disease in addition to 30 healthy volunteers who served as controls. On all patients were done complete blood count, biochemical liver function tests (ALT, AST, ALP, serum bilirubin, serum albumin, INR) using spectrophotometric assays, blood urea and serum creatinine using spectrophotometric assays, serum zinc level using colorimetric assay and liver biopsy according to the guidelines recommendations. Every patient received 30mg of Zinc/day for one month and all patients were followed up for one month after Zinc supplementation using the same laboratory parameters mentioned above. The mean age of the patients was 51.0+5.6, while mean age of controls was 49.4+6.4.

Results*:* patients had significantly impaired liver functions (ALT, AST, ALP, albumin, bilirubin and INR) when compared with controls. In addition patients had lower WBCs count, RBCs count, platelet count and lower hemoglobin level when compared with controls. Furthermore, zinc levels are significantly lower in patients when compared with controls.

Zinc supplementation resulted in significant improvement of serum ALT, AST, albumin, total bilirubin, direct bilirubin, INR and Child Pugh Score.

Conclusion*:* reduction in Zinc level was observed in patient with liver disease

Zinc supplementation resulted in raised serum Zinc level and improvement of liver functions.

Introduction:-

The liver plays a central role in nutritional homeostasis. Malnutrition is an early aspect of liver cirrhosis which may be an important factor in the development and production of cirrhosis ***(Johnson et al 2013).***

Malnutrition accounts for more than 60 % of patients with severe liver failure and negatively affects clinical outcomes in terms of survival and complications ***(Juakiem et al., 2014).***

A consequence of impaired liver function , particularly in patients with cirrhosis , is the change in contents of several trace elements in the serum and liver , such as iron, zinc and copper. The alteration in metabolism of trace elements may be a factor for ongoing liver fibrogencsis and consequently hepatic cirrhosis or hepatocellular

carcinoma ***(Toshikuni et al., 2014).***The results of some studies suggest that serum zinc levels in patients with liver cirrhosis and hepatocellular carcinoma are significantly lower than healthy controls ***(Mohammad et al., 2012).***

Zinc deficiency has been implicated in the progression of liver cirrhosis to higher stages . A number of observations have reported significantly higher serum Cu in cirrhotic patients than healthy controls . According to many authors, a decrease in serum Zn concentration and increase in serum Cu levels could be associated with liver carcinogenesis ***(Maxwell and Kowdley, 20***

Subjects and Methods:-

Subjects:-

The study included 60 patients with chronic liver disease. They were selected according to the following criteria:

Inclusion criteria:-

1. Adult cirrhotic patients
2. 18 years or older.

Exclusion criteria:-

1. Patients with Child Pugh scores above 12 (due to unstable conditions, overt ascites or necessity for admission) .
2. Hepatocellular carcinoma
3. Age less than 18 years.
4. Use of anabolic steroids.
5. Diuretics or albumin use in the last one month
6. Severe respiratory or renal disorders.

In addition, there was age and sex matched healthy controls.

Methods:-

All subjects were submitted to the following:

A) Complete history taking and physical examination with stress on :
   1) A etiology of liver disease.
   2) Clinical manifestations of liver cell failure.
   3) The current and past medications.

B) Lab investigation :
   1) CBC.
   2) Biochemical liver function tests (ALT, AST, ALP, serum bilirubin , serum albumin , INR) using spectrophotometric assays ***(Knight, 2005).***
   3) Blood urea and serum creatinine using spectrophotometric assays ***(Prigent, 2008).***
   4) Serum Zinc level using colorimetric assay ***(Makino, 1991).***

C) Liver biopsy according to the guidelines recommendations ***(Grant and Neuberger, 1999).***

D) Child Pugh score assessment.

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, μmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Interpretations:-
Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.[1]

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

E. Assessment of zinc levels before and after supplementation.
1. Zinc supplementation: Every patient received 30 mg of Zinc/day for one month given as an daily oral tablet.
2. Follow up: Patients were followed up for one month after zinc supplementation using the same clinical and laboratory parameters mentioned above.

Results:-
Results of the present study are shown in the following tables

Table-1 Comparison between patients and controls regarding the laboratory data before zinc supplementation.

	Patients n=60	Controls n=30	Student t test	
			t	p
WBCs	4.4 ± 1.4	6.5 ± 1.2	-6.9	**0.0001***
RBCs	3.9 ± 0.4	4.2 ± 0.8	-0.14	**0.001***
Hb	11.0 ± 1.1	12.0 ± 1.0	-3.9	**0.0001***
Platelets	114.1 ± 43.6	261.4 ± 55.9	-12.6	**0.0001***
Creatinine	0.8 ± 0.1	0.9 ± 0.1	-0.92	0.35
Urea	25.7 ± 3.9	24.2 ± 2.6	1.9	0.057
ALT	82.8 ± 51.6	36.0 ± 4.8	6.9	**0.0001***
AST	85.0 ± 49.6	38.5 ± 4.4	7.1	**0.0001***
ALP	199.8 ± 20.5	176.6 ± 10.3	7.1	**0.0001***
Albumin	3.1 ± 0.4	4.0 ± 0.2	-12.0	**0.0001***
Total bilirubin	1.9 ± 1.0	1.0 ± 0.1	5.1	**0.0001***
Direct bilirubin	0.48 ± 0.27	0.23 ± 0.04	5.0	**0.0001***
INR	1.36 ± 0.26	1.06 ± 0.07	5.9	**0.0001***

Table-2 Comparison between patients and controls regarding the zinc levels before zinc supplementation

		Patients n=60	Controls n=30	Student t test	
				t	p
Zn levels		60.1 ± 10.1	93.8 ± 14.9	-11.0	**0.0001***
				Fisher exact test	
				X2	P
Zn status	Normal	14	30	47.0	**0.0001***
	Low	46	-		

Table-3 Correlation between zinc level and the demographic and laboratory data inthe studied patients before zinc supplementation

	Pearson's correlation	
	r	**p**
Age	0.07	0.54
BMI	-0.01	0.93
WBCs	0.16	0.19
RBCs	0.23	0.07
Hb	0.17	0.14
Platelets	0.4	**0.001***
Creatinine	-0.24	0.055
Urea	-0.17	0.21
ALT	-0.26	**-0.0061***
AST	-0.24	**0.027***
ALP	-0.13	**0.18**
Albumin	0.6	**0.0001***
Total bilirubin	-0.67	**0.0001***
Direct bilirubin	-0.48	**0.0001***
INR	-0.58	**0.0001***
Child pugh score	-0.72	**0.0001***

Table-4 Comparison between the laboratory data in the studied patients before and after zinc supplementation

	Before supplementation	**After supplementation**	**Student t test**	
			t	**p**
WBCs	4.4 ± 1.4	4.2 ± 1.4	0.51	0.6
RBCs	3.9 ± 0.4	3.8 ± 0.4	1.38	0.16
Hb	11.2 ± 1.1	11.0 ± 1.1	0.73	0.46
Platelets	122.4 ± 43.8	114.1 ± 43.6	0.7	0.18
Creatinine	0.8 ± 0.1	0.7 ± 0.1	1.9	0.13
Urea	25.7 ± 3.9	28.6 ± 3.2	1.2	0.18
ALT	82.8 ± 51.6	70.6 ± 44.8	1.37	**0.017***
AST	85.0 ± 49.6	62.8 ± 44.3	2.4	**0.014***
ALP	199.8 ± 20.5	186.2 ± 19.6	1.99	0.13
Albumin	3.1 ± 0.4	3.4 ± 0.4	-2.2	**0.021***
Total bilirubin	1.9 ± 1.0	1.2 ± 1.0	-1.42	**0.019***
Direct bilirubin	0.48 ± 0.27	0.3 ± 0.2	-2.23	**0.048***
INR	1.36 ± 0.26	1.18 ± 0.2	-2.6	**0.044***

Table-5 Comparison between zinc level in the studied patients before and after zinc supplementation

		Before supplementation	**After supplementation**	Student t test	
				t	p
Zinc levels		60.1 ± 10.1	70.5 ± 9.3	-5.8	**0.0001***
				Fisher Exact test	
				X2	P
Zinc status	**Normal**	14	34	14.0	**0.0001***
	Low	46	26		

Table-6 Comparison between Child Pugh score before and after zinc supplementation

		Before supplementation	After supplementation	Student t test	
				t	p
Child Pugh (Points)		7.2 ± 2.1	5.8 ± 1.1	2.46	**0.044***
				Chi-square test	
				X2	**P**
Child Pugh (Categories)	**A**	31	43	6.29	**0.043***
	B	17	7		
	C	12	10		

Discussion:-

Zinc is an essential trace element required for normal cell growth, development, and differentiation. It is involved in DNA synthesis, RNA transcription, and cell division and activation. It is a critical component in many zinc protein/enzymes, including critical zinc transcription factors ***(Mohammad et al., 2012).***

The liver is important for the regulation of zinc homeostasis, while zinc is necessary for proper liver function. Decreased zinc levels have been implicated in both acute and chronic liver disease states, and zinc deficiency has been implicated in the pathogenesis of liver diseases ***(Stamoulis et al., 2007).***

Zinc deficiency/altered metabolism is observed in many types of liver disease, including alcoholic liver disease (ALD) and viral liver disease ***(Mohammad et al., 2012).***

Moreover, it was found that a low zinc level is associated with lower survival rates in patients with chronic hepatitis and liver cirrhosis ***(Moriyama et al., 2006).***

Some studies suggested that zinc supplementation can improve the long-term outcome in viral chronic hepatitis and liver cell failure patients ***(Matsuoka et al., 2009).***

The present study aimed to evaluate the relationship between the serum zinc level and severity of liver cell failure and to study the effect of low dose zinc supplementation on the Severity of liver cell failure.

This study was conducted on 60 patients with histologically documented liver cirrhosis, as well as age and sex matched healthy volunteers who served as controls.

Patients were subjected to thorough history taking, thorough clinical examination and routine laboratory investigations. serum zinc level was measured in every subject every patient received 30mg of zinc/day for one month.Then, all patients were reevaluated regarding the clinical, laboratory and pathological data.

In the present study, patients had significantly impaired liver functions (ALT, AST, ALP, albumin, bilirubin and INR) when compared with controls. In addition patients had lower WBCs count , RBCs count, platelet count, and lower hemoglobin levels when compared with controls.

Zinc levels are significantly lower in patients when compared with controls(table-3), This is in agreement with the study of ***Rahelić et al., (2006)*** who studied serum concentrations of zinc, copper, manganese and magnesium in 105 patients with alcoholic liver cirrhosis and 50 healthy subjects by means of plasma sequential spectrophotometer. In their study, serum concentrations of zinc were significantly lower (median 0.82 vs. 11.22 micromol/L, $p < 0.001$) in patients with liver cirrhosis in comparison to controls. This is explained by the fact that liver is the main organ responsible for the zinc metabolism which can be affected by liver diseases ***(Grüngreiff et al., 2016).***

In addition, our study found that there was a statistically significant direct correlation between zinc level and both platelets count and albumin levels. In addition, there was a statistically significant inverse correlation between zinc level and ALT, AST, total bilirubin, direct bilirubin, INR level and Child Pugh score before Zinc supplementation. This is in accordance with the study of ***Shaposhnikova et al., (2007)***who investigated 15 patients with liver cirrhoses of different etiology for zinc levels. They found that with the rising of class of liver impairment and developing liver encephalopathy, level of zinc in blood drops.

In addition, the study of ***Friedrich et al., (2015)*** assessed the impact of zinc deficiency in patients with end-stage liver disease awaiting liver transplantation. They found that serum zinc levels are tightly associated with liver function as patients with low zinc levels had a higher Model for End-Stage Liver Disease (MELD) score than patients with normal zinc levels. Furthermore, multivariate analysis demonstrated that serum zinc levels function as an independent predictor of hepatic decompensation.

In the present study, zinc supplementation resulted in significant improvement of serum AST, ALT, albumin, total bilirubin, direct bilirubin, INR and child pugh score after zinc supplementation (table-5, 8).

This is in agreement with ***Matsuoka et al., (2009)****who* treated 62 patients with C-viral chronic hepatitis (CH) and liver cirrhosis (LC) with polaprezinc and determined.

Prospectively the effect on long-term outcome. Thirty two patients were given 1.0 g polaprezinc. Results showed that changes of liver functions in the polaprezinc administration group were significantly lower than those of the untreated group. The decrease in platelet count was clearly less than that of the untreated group. Zinc treated patients were divided into two groups, whose zinc concentration increased (zinc responders) and those who zinc concentration remained stable or decreased (zinc non-responders).The zinc responders had a clearly lower cumulative incidence of HCC than the zinc non-responders

Conclusion:-

- Zinc deficiency is common in patients with liver disease.
- Zinc supplementation resulted in raised serum zinc level and improvement of liver functions

Reference:-

1. Friedrich K, Baumann C, Brune M, Wannhoff A, Rupp C, Scholl SG, Antoni C, Dollinger M, Neumann-Haefelin C, Weiss KH, Stremmel W, Schemmer P, Gotthardt DN. Association of serum zinc levels with liver function and survival in patients awaiting liver transplantation. Langenbecks Arch Surg. 2015 Aug 26.
2. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. British Society of Gastroenterology. Gut. 1999 Oct;45Suppl 4:IV1-IV11.
3. Grüngreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. Ann Hepatol. 2016 Jan-Feb;15(1):7-16.
4. Johnson TM, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. NutrClinPract. 2013 Feb;28(1):15-29.
5. Juakiem W, Torres DM, Harrison SA. Nutrition in cirrhosis and chronic liver disease. Clin Liver Dis. 2014 Feb;18(1):179-90.
6. Knight JA. Liver function tests: their role in the diagnosis of hepatobiliary diseases. J InfusNurs. 2005 Mar-Apr; 28(2):108-17.
7. Makino T. A sensitive, direct colorimetric assay of serum zinc using nitro-PAPS and microwell plates. ClinChimActa. 1991 Mar 29; 197(3):209-20.
8. Matsuoka S, Matsumura H, Nakamura H, Oshiro S, Arakawa Y, Hayashi J, Sekine N, Nirei K, Yamagami H, Ogawa M, Nakajima N, Amaki S, Tanaka N, Moriyama M. Zinc supplementation improves the outcome of chronic hepatitis C and liver cirrhosis. J Clin Biochem Nutr. 2009 Nov;45(3):292-303.
9. Maxwell KL, Kowdley KV. Metals and the liver. CurrOpinGastroenterol. 2012 May;28(3):217-22
10. Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. NutrClinPract. 2012 Feb;27(1):8-20.
11. Moriyama M, Matsumura H, Fukushima A, Ohkido K, Arakawa Y, Nirei K, Yamagami H, Kaneko M, Tanaka N, Arakawa Y. Clinical significance of evaluation of serum zinc concentrations in C-viral chronic liver disease. Dig Dis Sci. 2006 Nov;51(11):1967-77.
12. Prigent A. Monitoring renal function and limitations of renal function tests. SeminNucl Med. 2008 Jan;38(1):32-46
13. Rahelić D, Kujundzić M, Romić Z, Brkić K, Petrovecki M. Serum concentration of zinc, copper, manganese and magnesium in patients with liver cirrhosis. CollAntropol. 2006 Sep;30(3):523-8
14. Shaposhnikova NA, Drozdov VN, Petrakov AV, Sil'vestrova SIu. [Effect of zinc deficiency on effectiveness of the treatment of liver encephalopathy in patients with liver cirrhoses]. Eksp Klin Gastroenterol. 2007;(5):46-50, 164.
15. Stamoulis I, Kouraklis G, Theocharis S. Zinc and the liver: an active interaction. Dig Dis Sci. 2007 Jul;52(7):1595-612. Epub 2007 Apr 6. Review. PubMed PMID: 17415640
16. Toshikuni N, Arisawa T, Tsutsumi M. Nutrition and exercise in the management of liver cirrhosis. World J Gastroenterol. 2014 Jun 21;20(23):7286-97.