

SERUM ZINC LEVEL IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Objective: To determine the serum zinc level in patients with liver cirrhosis.

Methodology: This descriptive cross sectional study was conducted at Liaquat University Hospital Hyderabad Sindh, Pakistan. All patients above 12 years of age, of either gender and known (diagnosed) cases of liver cirrhosis were further evaluated for their serum zinc level. The data was analyzed in statistical software (SPSS) and the p value <0.05 was considered as statistically significant.

Result: One hundred twenty seven cirrhotic patients with means age 42.7559 ± 15.8894 were evaluated and assessed. The serum zinc was low in 69% patients. According to Child-Pugh classification 72% zinc deficient cirrhotic subjects were in class C, 16% in class B & 12% in class A. 94% subjects had hepatitis C virus infection, 4% had hepatitis B virus infection and 2% had history of alcoholism.

Conclusion: The serum zinc level was low in patients with liver cirrhosis.

KEY WORDS: Liver cirrhosis, Zinc, Trace elements.

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INTRODUCTION

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrous scar leading to progressive loss of liver function. It is most commonly caused by alcoholism and hepatitis B or C but has many other possible causes.¹ Epidemiology of liver cirrhosis varies between gender, ethnic groups and geographical distribution. In 2000 liver cirrhosis was the fifth leading cause of death in

Mexico² where as it was 12th most common cause of death in the United States.³

Majority of patients remain symptom free until the advance stage called decompensated cirrhosis, characterized by ascites, spontaneous bacterial peritonitis, hepatic coma or variceal bleeding from portal hypertension. The physical examination of patients with cirrhosis may reveal variety of findings that necessitate a hepatic or a gastrointestinal based work-up to determine the aetiology. There is correlation observed between persistently disturbed liver function tests and biopsy-proven underlying hepatic disease so to diagnose the cirrhosis liver biopsy should be considered when all initial and specific measures have failed to confirm.⁴ The treatment strategy is usually against the underlying complication i.e. bleeding esophageal varices managed by endoscopic sclerotherapy or rubber band ligation. Ascites and edema are often

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responsive to low sodium, diuretic therapy and peritoneal paracentesis.⁵ A low protein diet and agents such as lactulose are used to manage hepatic encephalopathy. Infections such as spontaneous bacterial peritonitis must be aggressively rapidly treated with appropriate antibiotics. Coagulation disorders will sometimes respond to vitamin K and fresh frozen plasma. However liver transplantation is highly effective for the treatment of end-stage cirrhosis.⁶

The Zinc (Zn, also called spelter) is a metallic element, symbol Zn, atomic number 30 and it is a transition metal in group 12 of the periodic table.⁷ The Recommended Dietary Allowance (RDA) is 8 mg/day for women and 11 mg/day for men. Red meats, especially beef, lamb and liver have some of the highest concentrations of zinc in food.⁸ Nearly two billion people in the developing world are deficient in zinc.⁹ The low serum zinc level is common in patient with liver cirrhosis due to decreased intake, decrease absorption, decreased bioavailability, and increased losses (because of malabsorption). There is also reduced liver protein synthesis in patients with liver cirrhosis, the metallothionein (MT) is an important zinc-binding protein (formed by liver) and is involved in zinc metabolism, homeostasis and its release in number of oxidants, the released zinc will inhibit the activity of the enzymes involved in fibrogenesis (fibrosis) in the liver, all these are yet known pathophysiological mechanisms.¹⁰⁻¹¹ Zinc is also essential for some of the neutrophil functions and it appears that zinc has a role in the maintenance of human immunity. Recent evidence suggests that thymic-dependent lymphocytes (T cells are zinc dependent. T-helper and suppressor cells, T-effector cells and T-natural killer cells appear to be zinc dependent.¹² In a study of Stamoulis et al published by Digestive Diseases and Sciences in 2007 the prevalence of low serum zinc level in cirrhotic patients was 65.3%.¹³

Therefore keeping all such important points and views in mind the present study was conducted in medical department of Liaquat university hospital - a tertiary care 1500 bedded

teaching hospital located in the center of Hyderabad city of province Sindh, Pakistan. The hospital covers both the urban and rural population of province and provides all necessary emergency facilities to the patient. The focus and aim of this study was to evaluate and assess the serum zinc level in patients with liver cirrhosis. So far no study has been conducted on this topic in Pakistan. As such this study will fill the gap, open new forum of discussion and will provide knowledge and information regarding the medical workup of patients with liver cirrhosis. Moreover such parameters and protocol will add some weight in the management of cirrhotic patients.

METHODOLOGY

This descriptive cross sectional study was conducted in the department of Medicine at Liaquat University Hospital (a tertiary care teaching hospital) Hyderabad from August 2008 to January 2009. All patients above 12 years of age, of either gender and were known cases (already diagnosed) of liver cirrhosis who came through outdoor patient department (OPD) for follow up visit were evaluated and enrolled in the study. However the diagnostic parameters and tools of liver cirrhosis were also kept in mind i.e. on the basis of clinical (reduced liver span <8 cm on clinical exam with ascites and splenomegaly), biochemical (prolonged prothrombin time >12 seconds and reduced level of serum albumin <3.5 g/dl), radiological (increased liver echopattern, shrunken liver <8cm in mid-clavicular line, portal vein diameter >1.3 cm and spleen size >13 cm longitudinally) and prior biopsy (presence of widespread fibrosis, obliteration of central vein and regenerating nodules). The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed.

The sample size was calculated by assessing the prevalence of low serum zinc level in liver cirrhosis (65.3%) with 5% margin of error.¹³ The severity of liver cirrhosis was assessed by Child-Pugh score¹⁴ and viral hepatitis B and C

infection was detected by Enzyme-linked immunosorbent assay (ELISA) method. All patients were then advised for fasting serum zinc level whereas the cirrhotic patients who were not vitally stable were admitted and then their serum zinc level was assessed by taking 2cc venous blood sample on next morning. The normal range of serum zinc level is 11-19 mmol/L and the value < 11 mmol/L was considered as low.¹⁵The informed consent was taken from every patient or from attendant of patients after full explanation of procedure regarding the study, and all such maneuvers was performed under medical ethics and through the cooperation of whole research team. The serum zinc status was reviewed by panel of expert consultant physicians of the ward and labeled as “low” when the serum level was below the normal range.¹⁵

The exclusion criteria of the study were; (a)The patients who were already on zinc therapy. (b) The non-cooperative patients or who refused to give consequent or did not have interest to participate in the study. (c) The patients who were known cases of any autoimmune disease, immunodeficiency disorder (CD4+ count < 200, granulocytopenia < 500/mm³) or already on cancer chemotherapy. (d) The patients already on hormonal therapy. (e) Patients with acute or chronic diarrhea. (f) The patients with history of pregnancy. Regarding ethical justification all the expenses of this study was paid by cooperation of whole research team.

The data were evaluated in statistical program SPSS version 16.0. The variable of serum zinc deficiency was recoded from numeric to categorical i.e. normal and low level. Qualitative data (frequency and percentage) like gender and

serum zinc level presented as n (%) and Fisher’s exact (2x2) test of X² was applied to compare the proportions. The mean + standard deviation (SD) was calculated among the numerical variables and student t-test was applied to compare the means (2 tailed) among the gender and serum zinc level. All the data was calculated on 95% confidence interval. The P value <0.05 was considered as statistically significant level for all the comparisons.

RESULTS

One hundred twenty seven (127) cirrhotic patients were evaluated and assessed with mean age 42.7559 ± 15.8894 (SD). In 107(84%) patients serum zinc level was observed through follow up visit while 20 (16%) patients were not vitally stable so they were hospitalized and assessed for their serum zinc status. The serum zinc level was low in 88 (69%) patients while remaining 39(31%) patients had normal serum zinc level. The gender distribution in relation to serum zinc status, mean and standard deviation of serum zinc level in all cirrhotic patients and in relation to gender is given in Table I-III.

According to Child-Pugh score system 92(72%) zinc deficient subjects were in class C, 20 (16%) were in class B and 15 (12%) were in class A. The 119 (94%) patients had history and evidence for hepatitis C virus infection, 05(4%) had hepatitis B virus infection while 03 (2%) had history of alcoholism. However; fulminant liver failure with low serum zinc level was observed in one patient. The majority of subjects belonged to the periphery of the province Sindh, Pakistan i.e. rural population 104 (82%), whereas remaining 23(18%) was urban population.

Table-I: Gender distribution of cirrhotic patients in relation to serum zinc status

	Low n = 88	Normal n = 39	Total n = 127	P value
Gender:				
Male	49(55.7%)	12(30.8%)	61(48.0%)	0.01*
Female	39(44.3%)	27(69.2%)	66(52.0%)	

* P value is statistically significant calculated by Fisher’s exact test
X² value = 6.719 df = 1

Table-II: Mean serum zinc level in patients with liver cirrhosis

	<i>Low</i> <i>n = 88</i>	<i>Normal</i> <i>n = 39</i>	<i>P value</i>
Serum zinc level	8.034 + 1.14	13.025 + 0.76	< 0.001*

Results are expressed as Mean + Standard deviation
* P value is statistically highly significant

DISCUSSION

The liver plays an important role in Zn homeostasis and different Zn compartments have been recognized to explain Zn kinetics in humans; the liver represents a fast-exchangeable Zn pool with an important role in the metabolism of Zn and other trace elements.¹⁶In our study the serum zinc level was low in patient with liver cirrhosis, however such observation resembled with two different studies conducted by Go et al and Sullivan et al.¹⁷⁻¹⁸ Where as Kalkan et al also identified zinc deficiency in patients with liver disease in his study published in 2002.¹⁹It has long been speculated that Zn has a protective effect against liver fibrosis and Zn intake in cirrhosis are based mostly on observations of reduced Zn levels in cirrhotic patients and on the beneficial effects of Zn supplementation on liver metabolism.²⁰⁻²¹

In the present study the 94% subjects had viral hepatitis C induced liver cirrhosis, the viral infection induced cirrhosis causes oxidative stress and secondary cellular damage, Low plasma Zn concentrations contribute to oxidative stress and its replenishment by high doses has been considered mandatory.²²It has also been thought that Zn could directly affect Hepatitis C viral (HCV) replication, thus supporting structural and functional stability of certain HCV proteins like NS5A and NS3. In our study three patients had alcohol induced liver cirrhosis and we identified and observed that their serum zinc level was low, where as a study on "Hepatic zinc content in patients with various stages of alcoholic liver disease and in patients with chronic active and chronic persistent hepatitis" shown similar finding.²³Animal model studies have shown that Zn supplementation

Table-III: Mean serum zinc level in relation to gender distribution

	<i>Male</i> <i>n = 61</i>	<i>Female</i> <i>n = 66</i>	<i>P value</i>
Serum zinc level	9.024 + 2.3388	10.068 + 2.6251	0.02*

Results are expressed as Mean + Standard deviation
* P value is statistically significant

prevented ethanol-induced liver injury under both acute and chronic exposure conditions. Zn supplementations decreases ethanol-induced hepatic Zn depletion, suppressed the elevated cytochrome P450 2E1 activity, and enhances the activity of enzyme alcohol dehydrogenase which will responsible for the suppression of ethanol-induced oxidative stress. Zn administration also enhanced hepatic glutathione (GSH) and Zn related antioxidant capacity.²⁴

In our study the mean age of cirrhotic patients was 42.75 ± 15.88 however such age distribution resembled with the study of Bhise et al.²⁵ In the present study, majority of zinc deficient cirrhotic patients one belonged to rural population and it is similar to the study of Ma et al on "assessment of intake inadequacy and food sources of zinc of people in China" published in 2007.²⁶ In our study, there was male predominance in relation to zinc disturbance with liver cirrhosis however there were no differences in the concentrations of zinc between male and female patients with liver cirrhosis in the study by Dario et al.²⁷

In this series one patient was in fulminant failure and had low serum zinc level however similar finding was also detected by Chetri et al.²⁸In fulminant hepatic failure and hepatic encephalopathy, biochemical parameters suggesting liver dysfunction presenting inverse correlation with serum Zn levels. The present study identified 4% had hepatitis B virus induced liver cirrhosis and their zinc level was also low where as Gur et al²⁹ states that serum and hepatic Zn levels were reduced in hepatitis B virus (HBV) infected patients with cirrhosis. The Zn depletion in cirrhosis has been attributed to decreased intestinal Zn absorption, increased urinary loss, malnutrition, hypoalbuminemia, portosystemic

shunts, and diminished hepatic Zn extraction. Majority of the published studies have suggested that Zn absorption was reduced in cirrhotic patients. Two mechanisms were proposed for Zn malabsorption in liver cirrhosis (1) damage of the small bowel mucosa (2) impairment of pancreatic exocrine function accompanied by reduced synthesis of ligands such as picolinic acid in the liver.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 Zn deficiency. In some cases Zn supplementation was beneficial to these patients.³¹The zinc supplementation also reduces the inflammation and contributes to faster inflammation resolution, therefore further advance, modified and related studies are needed to update the data, knowledge and information regarding medical workup of patients with liver cirrhosis.

CONCLUSION

We have identified the lower level of serum zinc level in patients with liver cirrhosis. Therefore a routine biochemical assessment of zinc status in patients with liver cirrhosis is an important step in the management protocol and to reduce progression of the disease.

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