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ORIGINAL RESEARCH

Serum zinc levels in decompensated chronic liver disease and its correlation with the stages of hepatic encephalopathy

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Abstract

Introduction: The low serum zinc levels in patients with liver cirrhosis are due to decreased intake, decreased absorption, decreased bioavailability, and increased losses. There is also reduced liver protein synthesis in patients with liver cirrhosis. Decreased zinc levels may be a precipitating factor for hepatic encephalopathy.

Aims and Objectives: To study the level of zinc in decompensated chronic liver disease and to study correlation of serum zinc levels with various stages of hepatic encephalopathy in decompensated chronic liver disease.

Materials and Methods: This cross-sectional study was conducted in 50 patients of decompensated chronic liver disease admitted or attending the Medicine Emergency or Outpatient Department (OPD) of General Medicine in Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. The study was carried out after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. Detailed history and physical examination and biochemical tests were done. Written informed consent was obtained from the patients.

Conclusion: The present study concluded that mean serum zinc levels were low in DCLD patients and it decreased significantly with worsening of hepatic encephalopathy grades. The study found out that there was a significant association between serum zinc levels and grades of hepatic encephalopathy. The study raises a possibility that decrease in serum zinc levels can have a role in the development of hepatic encephalopathy and zinc supplementation may have a beneficial role in the treatment of hepatic encephalopathy.

Introduction

Cirrhosis is a chronic progressive disease of liver characterized byextensive degeneration and destruction of the liver parenchymal cells and inan attempt to regenerate, normal liver architecture is replaced by abnormalnodules that lack normal lobular organization.[1] The low serum zinc levels in patients with liver cirrhosis are due to decreased intake, decreased 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 pathways. The released zinc will inhibit the activity of the enzymes involved in fibrogenesis (fibrosis) in the liver, all these are yet known pathophysiological mechanisms.[2,3] The excess use of diuretics also increases the urinary secretion of Zn. Frequent bowel wash and lactulose also increase GI loss of zinc.

Zn increases the natural defense against reactive oxygen radicals, Zn also acts as an anti-apoptotic agent, co-factor for deoxyribonucleic acid (DNA) synthesis and an anti-inflammatory agent. Zinc also plays pivotal

roles in cellular integrity and biological functions related to cell division, growth and development.[4,5]
Decreased zinc levels may be a precipitating factor for hepatic encephalopathy. The aim of the study is to study the levels of serum zinc in decompensated chronic liver disease patients and to study correlation of serum zinc levels with various stages of hepatic encephalopathy in decompensated chronic liver disease.

Aims and objectives:
1. To study the level of zinc in decompensated chronic liver disease
2. To study correlation of serum zinc levels with various stages of hepatic encephalopathy in decompensated chronic liver disease.

Materials and Methods:
This cross-sectional study was conducted in 50 patients of decompensated chronic liver disease admitted or attending the Medicine Emergency or Outpatient Department (OPD) of General Medicine in Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. The study was carried out after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. Written informed consent was obtained from the patients.

Criteria for Decompensated Cirrhosis:
The criteria for decompensated cirrhosis was presence of cirrhosisof liver along with any of these features of decompensation of liverfunction manifesting as presence of: -

- Portal hypertension in the form of ascites or variceal bleed
- Hepatic insufficiency in the form of hepatic encephalopathy
- Patients classified as Child Pugh score class B and above
- Radiological evidence of liver cirrhosis

Hepatic encephalopathy was diagnosed on the basis of history taken according to a questionnaire. A detailed clinical history of patients was taken regarding present and past illness. Questions asked about altered sleep pattern anxiety, depression, altered sensorium, disorientation and confusion, history about precipitating factors was taken like upper gastrointestinal bleeding, fever, diarrhea, abdominal pain, abdominal distension, constipation, jaundice, malnutrition and high protein diet etc.

Inclusion criteria:

- Patient diagnosed as decompensated chronic liver disease presenting with
- Hepatic encephalopathy
- Age more than 20 years
- Written informed consent

Exclusion criteria:

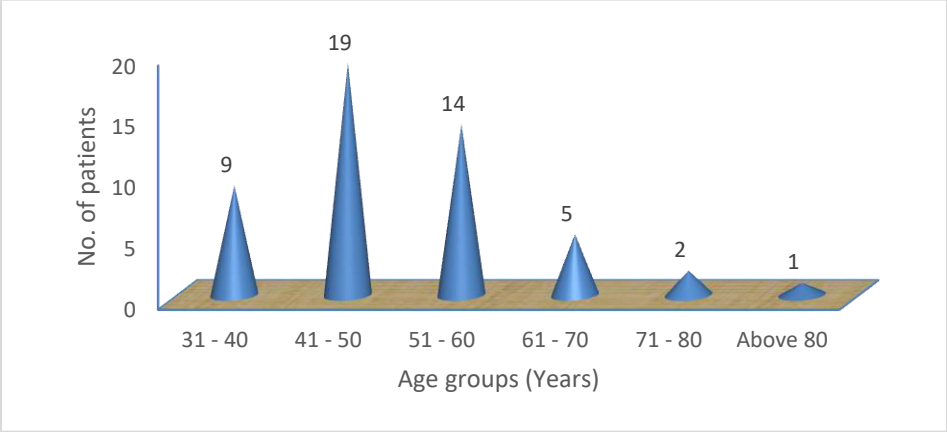
- Other Metabolic causes of encephalopathy
- Altered sensorium due to head injury and stroke
- Psychiatric disorders
- Patients not giving informed consent

Methods of collection of data
Study included patients of both genders above 20 years of age with decompensated chronic liver disease, admitted with complications of hepatic encephalopathy. Detailed clinical examination for sign of liver failure like icterus, pallor, spider nevi, palmar erythema, clubbing, ascites and pitting edema, was done. Personal history for alcohol intake and duration of alcohol abuse, drugs abuse and smoking were taken. Grading of hepatic encephalopathy was done on the basis of West Haven Classification. Patients were divided into 5 groups according to hepatic encephalopathy grading. For each group patients, serum zinc levels were measured individually. Average of each group was calculated.
The following investigations were performed:

1. Serum zinc levels (Dithizone Reagent Method).
2. CBC, blood urea, serum creatinine, serum electrolytes (Na^+/k^+)
3. LFT (OT, PT, Bilirubin total and direct, ALP, LDH, TSP, DSP)
4. Fasting blood glucose and post prandial blood glucose.
5. 12 lead ECG.
6. Urine analysis if necessary.
7. PTI/INR.
8. SFOB (Stool for occult blood).
9. USG whole abdomen
10. Fibro scan if necessary
11. Chest X-ray PA view if necessary
12. Viral markers (HIV, HBsAg, HCV)

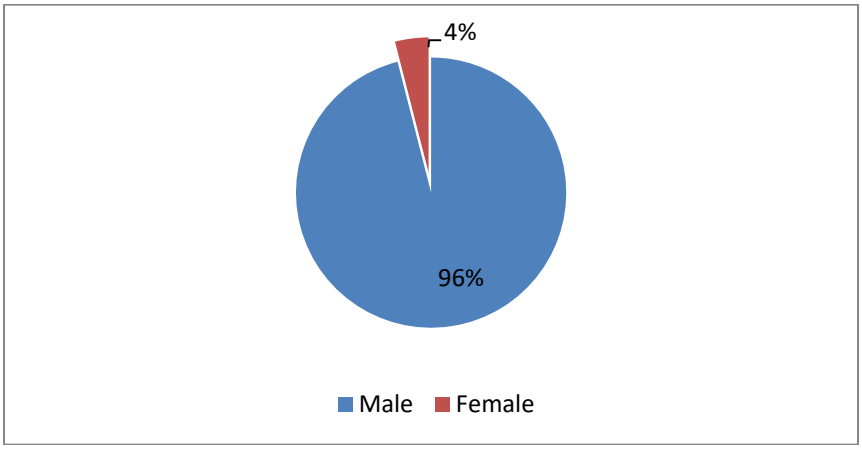
The data was collected systematically and edited after collection. The data was then entered into computer and statistical analysis of the results was obtained by using windows-based computer software devised with Statistical Packages for Social. The results were presented in tables and figures. Statistical significance was set at $p<0.05$ and confidence interval set at 95% level. Continuous variables were expressed as mean with standard deviation and categorical variables as count with percentage. Mean serum zinc levels were calculated for each CTP (Child-Turcotte-Pugh score) class, HE grades, serum albumin, serum and other baseline biochemical parameters. One way ANOVA test was used for data analysis. The correlation between mean serum zinc levels and hepatic encephalopathy grades was evaluated by means of Pearson's correlation test.

Observations and results



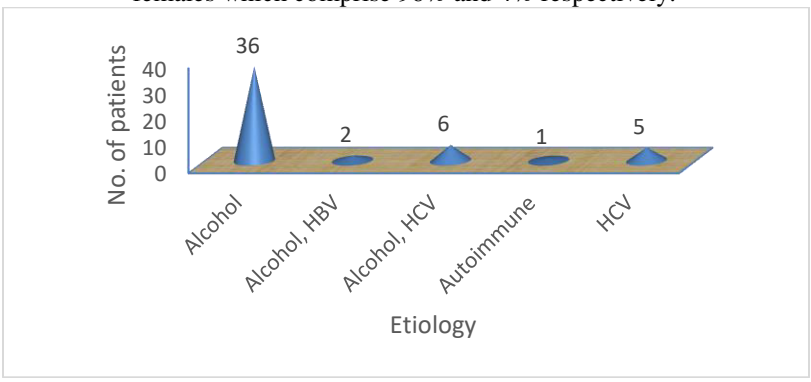
Age wise distribution of patients

Graph show the distribution of total patients according to age in the population. The age groups were divided as (31-40), (41-50), (51-60), (61-70) and (71-80) and above 80. The maximum number of patients were in the group of (41-50). The mean age of study population was found to be 51.02 yrs. with a standard deviation SD of 11.43yrs.



Gender wise distribution of patients

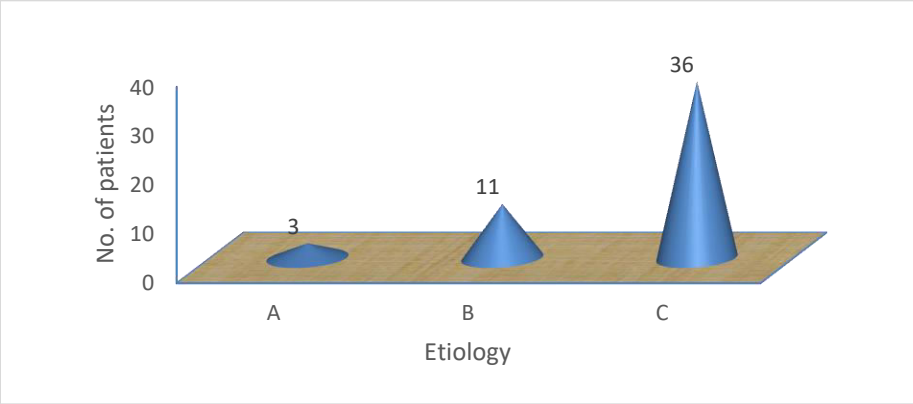
Pie Chart show distribution of patients according to gender. Out of total 50 patients, 48 were male and 2 were females which comprise 96% and 4% respectively.



Etiology wise distribution of patients

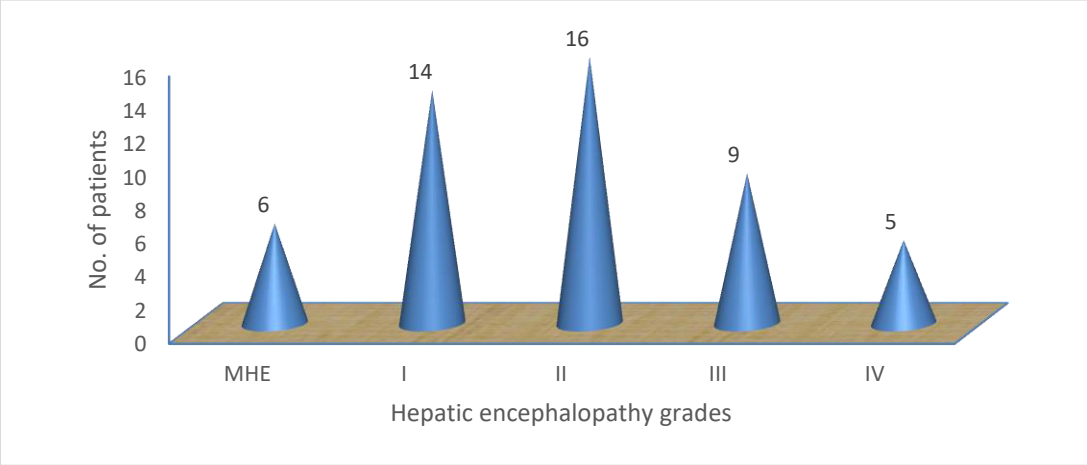
Graph show etiology wise distribution of patients. Out of 50 patients, 72 percent (36) were suffering from alcohol related liver disease and 10 percent (5) patients had HCV as the cause of their liver disease. 4% (2) patients had both

alcohol and HBV as the etiology of their disease. 12% (6) patients had both alcohol and HCV as their etiology. 2% (1) patients had autoimmune etiology.



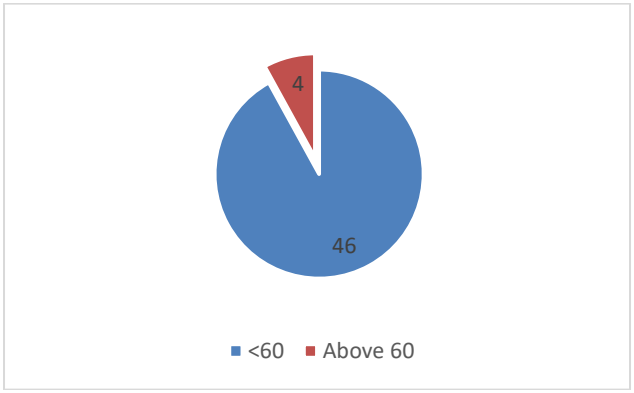
CTP class distribution among patients

Graph show that out of 50 patients, CTP class A included 3(6%) patients, CTP class B included 11(22%) patients and CTP class C included 36(72%) patients.



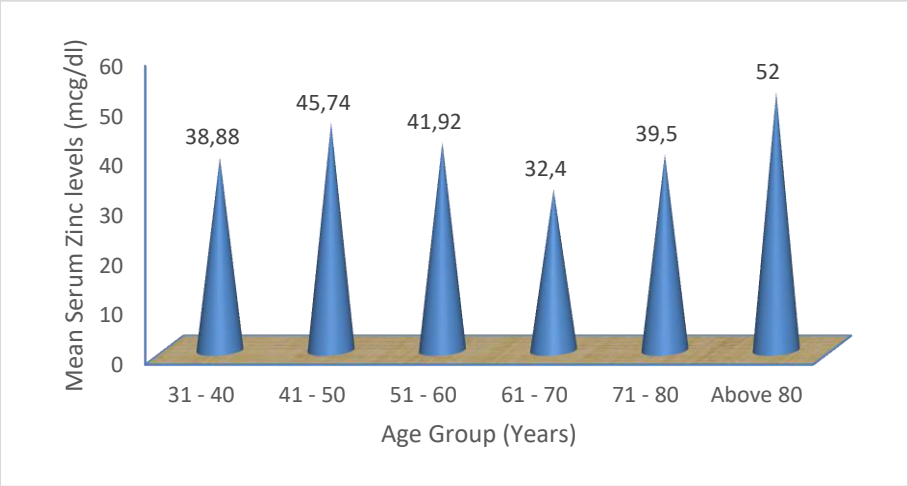
Hepatic encephalopathy grades among patients

Graph show that out of total 50 patients, 6 patients had MHE, 14 patients had Grade I hepatic encephalopathy, 16 patients had Grade II hepatic encephalopathy, 09 patients had Grade III hepatic encephalopathy, 05 patients had Grade IV hepatic encephalopathy.



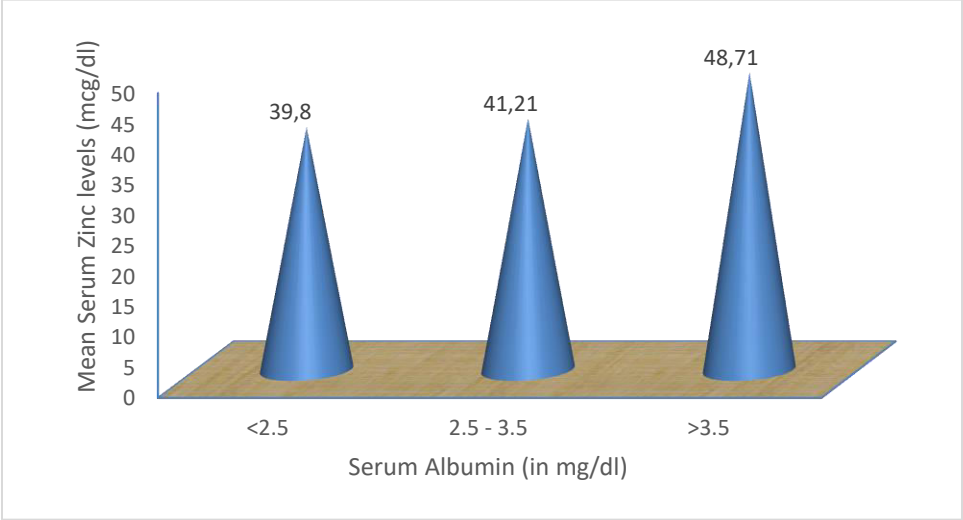
Serum zinc levels among patients

Pie Chart show distribution of mean serum zinc levels among patients. 46(92%) patients had serum zinc less than 60 mcg/dl. 4(8%) patients had serum zinc above 60 mcg/dl. Mean serum zinc levels of all the patients were 41.98 mcg/dl.



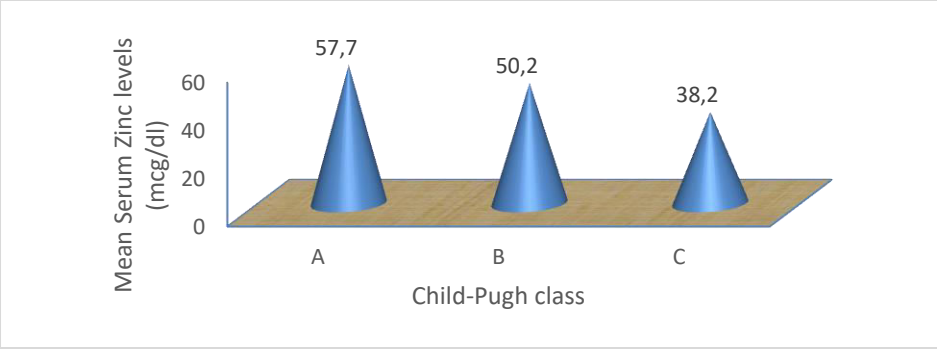
Age wise distribution of serum zinc levels among patients

Graph show mean serum zinc levels among different age groups. Mean zinc levels were 38.8±7.71 mcg/dl in age group (31-40), 45.74±13.86 mcg/dl in (41-50) years, 41.92±9.80 mcg/dl in (51-60) years, 32.4±5.57 mcg/dl in (61-70) years, 39.5±5.50 mcg/dl in (71-80) years, 52±0 mcg/dl in people above 80 yrs. age group. The p value calculated is 0.54 which is non-significant.



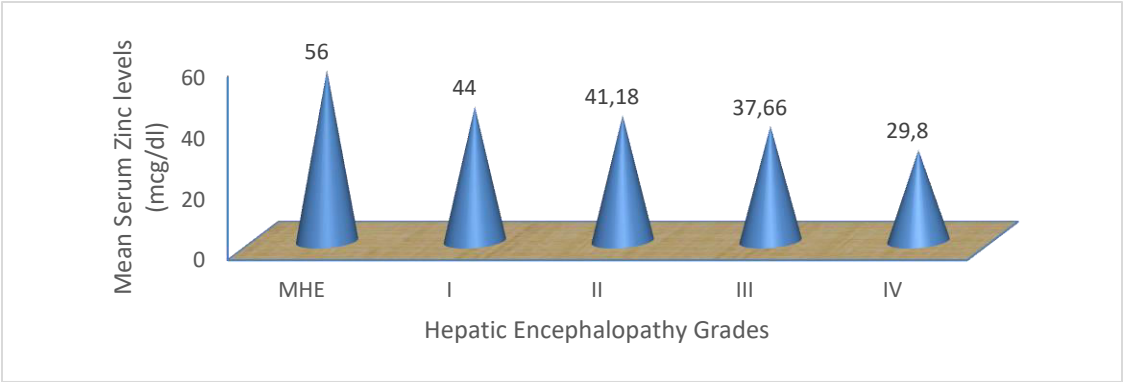
Mean serum zinc levels according to serum albumin levels among patients

Graph show that mean serum Zinc levels in patients with serum albumin<2.5 mg/dl were 39.8±12.03mcg/dl. Mean serum Zinc levels in patients with serum albumin (2.5-3.5) mg/dl were 41.21±11.35mcg/dl. Mean serum Zinc levels in patients with serum albumin>3.5 mg/dl were 48.71±9.16mcg/dl. In this study, serum zinc levels decreased with decrease in serum albumin levels. The p value came out to be 0.036 which is highly significant.



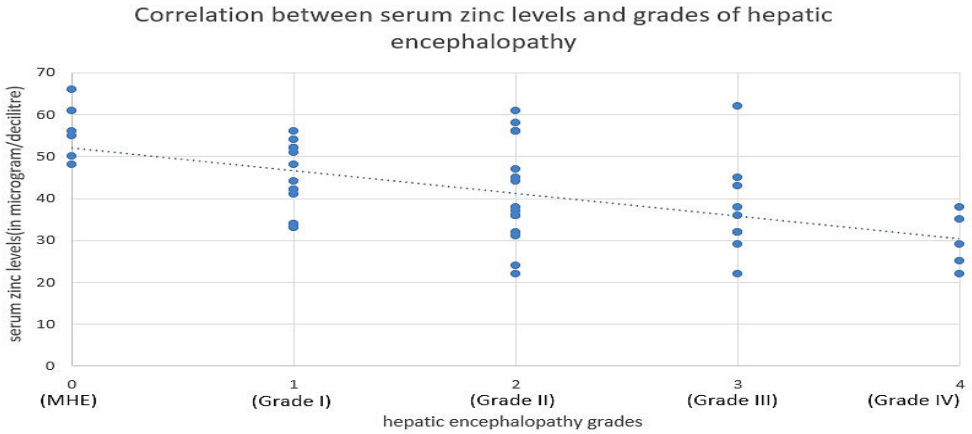
Mean serum zinc levels according to CTP class among patients

Graph show mean serum zinc level is highest in CTP class A (57.7mcg/dl±4.19) followed by Class B (50.2 mcg/dl±11.62) and followed by Class C (38.2mcg/dl±9.39). The result is significant with p value of 0.0002.



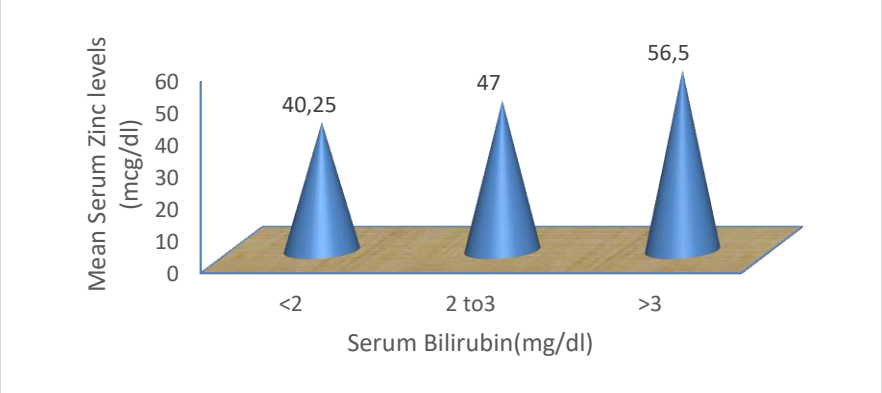
Mean serum zinc levels according to hepatic encephalopathy grades among patients

Graph show mean serum zinc levels in different hepatic encephalopathy grades. Mean serum zinc levels in patients with MHE is 55.5±5.82mcg/dl. Mean serum zinc levels in patients with Grade I hepatic encephalopathy is 44±8.0mcg/dl. Mean serum zinc levels in patients with Grade II hepatic encephalopathy is 41.18±11.54mcg/dl. Mean serum zinc levels in patients with Grade III hepatic encephalopathy is 37.66±11.62mcg/dl. Mean serum zinc levels in patients with Grade IV hepatic encephalopathy is 29.8±5.98mcg/dl. Mean serum zinc levels decreased progressively with increase in hepatic encephalopathy grades and the p value of the study is 0.001 which is highly significant.



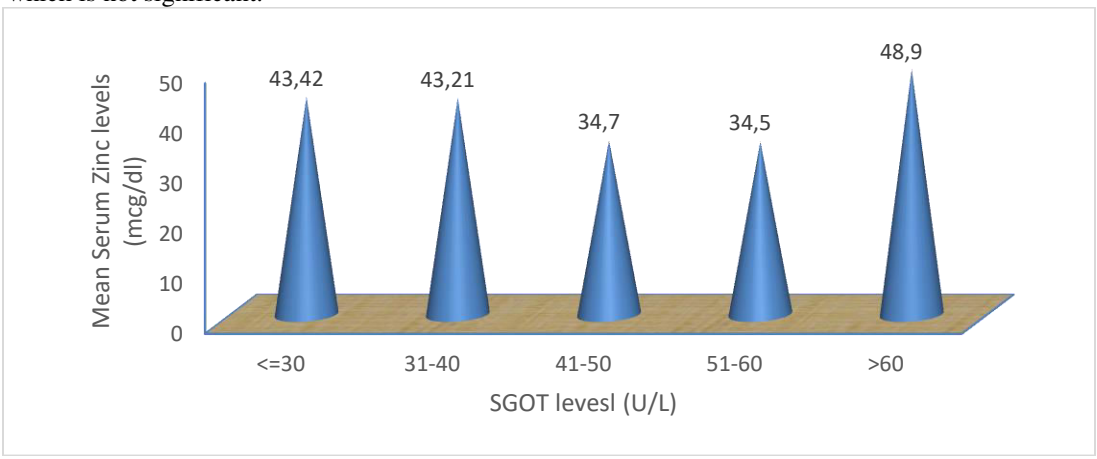
Correlation between serum zinc levels and grades of hepatic encephalopathy

Graph shows correlation between serum zinc levels and grades of hepatic encephalopathy among patients. Pearson's correlation coefficient was used to assess the relationship between serum zinc levels and HE. There was a negative correlation between two variables with r value of -0.2906.



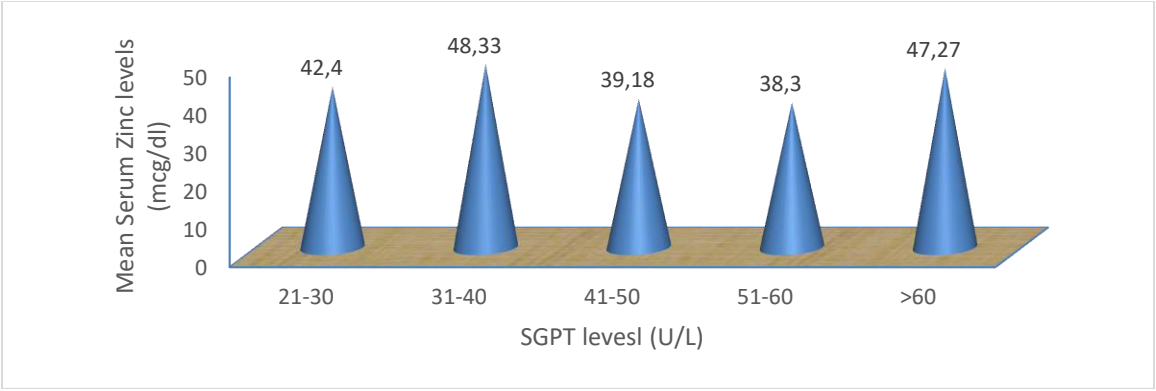
Mean serum zinc levels according to serum bilirubin levels among patients

Graph show mean serum zinc levels among different serum bilirubin groups. Patients with bilirubin <2 mg/dl had mean serum zinc of 40.25±10.71 mcg/dl. Patients with bilirubin 2-3 mg/dl had mean serum zinc of 47±12.73 mcg/dl. Patients with bilirubin >3 mg/dl had mean serum zinc of 56.5±4.5 mcg/dl. The p value calculated came out as 0.39 which is not significant.



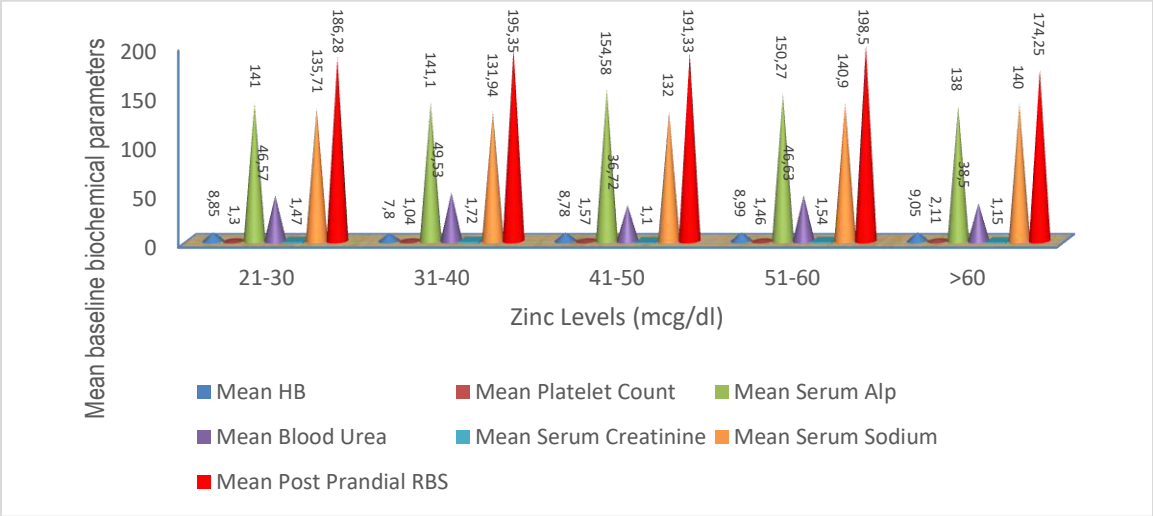
Mean serum zinc levels according to SGOT levels

Graph show mean serum zinc levels according to SGOT levels. The p value calculated in this study came out as 0.22 which is statistically non-significant.



Mean serum zinc levels according to sgpt levels

Graph show mean serum zinc levels according to sgpt levels. The p value calculated in this study came out as 0.22 which is non-significant.



Mean baseline biochemical parameters according to serum zinc levels

Graph show mean of baseline biochemical parameters among different serum zinc groups. Difference was non-significant for all parameters (p>0.05).

DISCUSSION

In our study involving 50 DCLD patients, the severity of cirrhosis was assessed with CTP score. CTP class A had 3(6%) cases while class B and C had 11(22%) and 36(72%) patients respectively. Grading of HE was done by West Haven criteria. Out of all patients, 6 patients had MHE, 14 patients had grade 1 HE, 16 patients had grade 2 HE, 09 patients had grade 3 HE, 5 patients had grade 4 HE.

The present study had maximum number of patients in the age group of 41-50. The mean age of the present study population was found to be 51.02 years with a standard deviation of 11.43 years. Similar age groups were considered in many studies (Yuwono B et al,[6] Rahelic D et al[7]). Yuwono B et al reported the mean age of patients as 53.81 years. In another study, Rahelic D et alreported that the mean age of patients was 55 years.

The present study had gender distribution in the form of 96% males and 4% females. In a study by Meena RK et al,[8] in which total 100 patients were studied, out of which 72(96%) were males and 3(4%) were females.

In the present study, alcohol abuse and viral hepatitis were the two most common causes of cirrhosis. Alcohol abuse alone as an etiological agent was seen in 36(72%) patients while 5(10%) patients suffered from HCV etiology. Hepatitis C was most common among viral etiologies. 6(12%) patients had both alcohol and HCV) as etiology. 2 (4%) patients had both alcohol and HBV as etiology. In a study on etiological trends in cirrhosis by Mishra D et al,[9] it was found that alcohol (63.3%) was the most common etiological agent of cirrhosis followed by viral etiology (19.8%).

In the present study, it was found that most of the patients were zinc deficient (<60 mcg/dl). Out of total 50 patients, zinc deficiency was seen in 46(92%) patients with only 4(8%) patients having zinc levels above 60 mcg/dl. Mean serum zinc of study population was 41.98 mcg/dl. Various studies have confirmed zinc deficiency in cirrhotic patients, attributing this to many causes. This is in agreement with study done by Yuwono B et al[9] which calculated mean serum zinc levels in their patients as 39.28 ± 15.33 mcg/dl. The lowest was 18 mcg/ dl and the highest was 87 mcg/dl. The normal level of Zn serum was taken as 60-120 mcg/dl. Four patients (9.3%) had normal serum zinc levels, while 39 patients (90.7%) had less than normal serum zinc levels.

In a study by Ozeki I et al[10] in 1973 CLD cases in Japan, 89.5% of cirrhotic patients had serum zinc levels of less than 80 µg/dL. In addition, zinc deficiency (serum zinc level < 60 µg/dL) was observed in about 90% of patients with serum albumin levels < 3.5 g/dL, and in about half of the patients with serum albumin levels between 3.5 g/dL and 4.0 g/dL.

This is also in agreement with McClain CJ et al,[11] Rahelić D et al[7] and Ramzy I et al.[12]This also has been previously documented by Yang SS et al,[40] who concluded that cirrhotic patients suffering from

subclinical portosystemic encephalopathy had lower serum zinc levels than control subjects.

In present study, mean zinc levels in patients of CTP class A were 57.7 ±4.19 mcg/dl. Mean zinc levels were 50.2±11.62mcg/dl in class B and 38.2±9.39mcg/dl in class C. p value calculated came out to be 0.0002 which is highly significant. Similar study done by Yuwono B et al,[6] showed that CTP class A had mean zinc levels 58 mcg/dl, class B had mean zinc levels 43.4, class C had zinc levels 31.6 mcg/dl with p value of 0.0001 which was highly significant indicating that worst the CTP score, lower the zinc levels.

The same thing was reported by Somi MH et al[13] and Maher M et al[14] which stated that more the severity of liver cirrhosis, lower were the serum zinc levels. Somi MH et al,[13] Maher M et al.[14]Triwikatmani C et al[15] showed different results on the correlation between the degree of liver cirrhosis severity based on CTP scores with serum Zn levels. The results showed that there was no significant difference with p = 0.052 between the patients with CTP B score (67.68 ± 21.55 µg/dl) and patients with CTP C score (54.04 ± 32.25 µg/dl).

In the present study, mean serum zinc levels were calculated for patients falling in groups based on different grades of hepatic encephalopathy. Mean serum zinc levels of patients with MHE were 56±5.82 mcg/dl. Similarly, patients with grade 1 HE had 44±8 mcg/dl mean serum zinc levels. Mean serum zinc levels in patients with grade 2 HE were 41.18±11.54 mcg/dl. Mean serum zinc levels in patients with grade 3 HE were 37.66 ±11.62mcg/dl and 29.8±5.98 mcg/dl in grade 4. Serum zinc levels were higher in patients with MHE and it decreased progressively as grades of hepatic encephalopathy worsened. The result was highly significant with p value of 0.001 and r value of -0.29 suggesting negative correlation between serum zinc levels and grades of HE.

Similarly, in the study by Galal GM et al[16] serum zinc levels were variable with different grades of hepatic encephalopathy. It was significantly lower in higher grades of hepatic encephalopathy (P = 0.001) thus serum zinc deficiency may play a role in hepatic encephalopathy if not well corrected.

A cross sectional study done by Meena RK et al[8], involving 75 patients with DCLD, also found out that serum zinc levels were significantly low with worsening grades of HE with p value of 0.001.

In a study by Rahelic D et al,[7] they reported that significantly lower zinc levels were found in cirrhotic patients with hepatic encephalopathy (median 0.54 micromol/L in patients with encephalopathy and 0.96 micromol/L in patients without encephalopathy, p= 0.002).

Various studies were done which showed reversal of grades of hepatic encephalopathy have occured after zinc supplementation (Grungreiff K et al,[17] Riggio O et al.[18]

In the present study, the patients with serum albumin <2.5 had mean zinc levels of 39.8±12.03 mcg/dl. Those with albumin levels between 2.5-3.5 had mean zinc values of 41.21±11.35 mcg/dl. Patients with albumin levels >3.5 had mean zinc values of 48.71±9.16 mcg/dl. p value calculated was 0.036 which is highly significant. So, as there was decrease in serum albumin levels, the zinc levels also fell. Similar findings were seen in other studies like Loomba V et al[19] and Ramzy I et al[12] showing that there was a positive correlation between serum zinc levels and serum albumin levels. There was significant positive correlation between serum albumin and serum zinc levels (r=0.71 and p value <0.01) in study by Yoshida Y et al.[22] Vatsalya V et al[20] also reported similar results.

In the present study, no significant association was seen between serum bilirubin and serum zinc levels. The p value of serum bilirubin and serum zinc levels came out to be 0.41 which is non-significant. Mean serum zinc level of patients with bilirubin <2mg/dl was 40.2± 10.71mcg/dl and of patients with bilirubin 2-3 was 47±12.73mcg/dl. Similarly, mean serum zinc levels of patients with bilirubin >3 was 56.5±4.5 mcg/dl. This was in agreement with study done by Galal GM et al,[16] which calculated a p value of 0.277 between serum zinc and bilirubin levels. However, findings of our study were not comparable with similar study done by Loomba V et al,[19] which studied 55 patients (age 17-65 years, 35 men), out of which 30 had acute, 5 subacute and 20 chronic liver disease. Loomba V et al[19] showed that high serum bilirubin levels showed inverse relationship with serum zinc levels.

In the present study, patients were divided into age groups of (21-30), (31-40), (41-50), (51-60) and >60. For each age group mean serum zinc levels were calculated. To see significance, p value was calculated which was 0.54, which is highly insignificant. Hence, the study showed that there is no age related variation in the serum zinc levels in study age groups. Similar results were seen in study by Meena RK et al.[72]In a study done by Rafiei R et al,[21] 80 cirrhotic patients with any etiology were chosen and divided in two groups with and without hepatic encephalopathy. They were examined for plasma zinc concentration. The mean (±standard deviation) plasma zinc concentrations in patients with and without hepatic encephalopathy were 75.10±23.9 and 104±23/10 µg/dL, respectively and there was statistical difference related to plasma zinc concentrations between with and without hepatic encephalopathy (P<0.05) patients. Butno associations were found between age, gender, and serum zinc concentration (P>0.05).

In our study, no significant association was found between serum zinc levels and AST, ALT p value for

serum zinc with SGOT (Serum glutamic oxaloacetic transaminase) and sgpt (Serum glutamic oxaloacetic transaminase) came out to be 0.22 and 0.23 respectively. This is in agreement with study done by Vatsalya V et al,[20] which showed ast, alt levels were numerically greater in the low zinc group than in the normal zinc group, but this did not reach the statistical significance.

Mean hemoglobin, mean platelet counts, mean serum alp, mean blood urea, mean serum creatinine, mean serum sodium, mean post prandial RBS (random blood sugar) values were calculated for each group of patients divided on the basis of zinc. The p value calculated for each of the above biochemical parameters was statistically insignificant.

It can be seen that serum zinc levels were very low in patients of decompensated chronic liver disease. Serum zinc level was significantly lower in higher grades of hepatic encephalopathy. A negative correlation was found between serum zinc levels and grades of hepatic encephalopathy. There was a positive correlation between serum zinc levels and serum albumin levels. So, supplementation of zinc can help in the treatment of HE. However, larger studies are required to confirm all of these.

Summary and conclusion

The present study tested serum zinc levels in patients of decompensated chronic liver disease and correlated serum zinc levels with grades of hepatic encephalopathy. The present study concluded that mean serum zinc levels were low in DCLD patients and it decreased significantly with worsening of hepaticencephalopathy grades. The study found out that there was a significant association between serum zinc levels and grades of hepatic encephalopathy. The study raises a possibility that decrease in serum zinc levels can have a role in the development of hepatic encephalopathy and zinc supplementation may have a beneficial role in the treatment of hepatic encephalopathy. Hepatic encephalopathy is a major cause of mortality in DCLD patients. Hence, finding other precipitating factors of hepatic encephalopathy like zinc deficiency, is of utmost importance.

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