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A STUDY ON SERUM LEVEL OF COPPER AND ZINC IN DECOMPENSATED LIVER CIRRHOSIS PATIENTS

Hossain M. S.*[1], Malek M. A.[2] and Mannan M. B.[3]

[1]Assistant Professor, Department of Biochemistry, Community Based Medical College Bangladesh, Mymensingh, Bangladesh.
[2]Assistant Professor, Department of Biochemistry, North Bengal Medical College, Sirajganj, Bangladesh.
[3]Assistant Professor, Department of Biochemistry, Ashiyan Medical College, Dhaka, Bangladesh.

***Corresponding Author: Hossain M. S.**

Assistant Professor, Department of Biochemistry, Community Based Medical College Bangladesh, Mymensingh, Bangladesh.

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ABSTRACT

Introduction: Liver cirrhosis is an end stage condition of liver disease and the leading cause of death for both men and women all over the world. It causes death due to acute or chronic gastrointestinal blood loss & multi organ failure. The aim of the study is to evaluate the serum copper and zinc levels in patients with liver cirrhosis. **Methods:** A total 120 subjects were included in this study. Among them, 60 diagnosed decompensated liver cirrhosis patients denoted as case group (n=60) and 60 were normal healthy individuals denoted as control group (n=60), both the case and control groups were male because liver cirrhosis occurs rarely female in Bangladesh. The subjects were briefed and written consents were taken. Under all aseptic precaution 5 ml of venous blood was collected from median cubital vein, analysis was carried out in the Department of Biochemistry, Mymensingh Medical College, Mymensingh, over a period of one year from July 2015 to June 2016. All statistical analysis was performed by SPSS windows package, version 20. Significance of the difference between two groups were evaluated by using student's unpaired 't' test. All the values were expressed as mean ± SD and P value 0.05 was taken as the level of significance. **Results:** After careful evaluation, in the present study we found significant increase in the serum copper levels and significant decreases in the serum zinc levels in liver cirrhosis patients when compared with that of control group. **Conclusion:** It can be concluded that to overcome fatal consequences of decompensated liver cirrhosis patients we should avoid high Copper containing food and Zinc supplementation may be beneficial.

KEYWORDS: Liver cirrhosis, Copper, Zinc.

INTRODUCTION

Liver cirrhosis is the end-stage condition of liver disease. Cirrhosis results from persistent and progressive necrosis of hepatocytes, followed by fibrosis and abnormal nodule formation. So, entire liver is involved, loss of architecture, necrosis of hepatocyte, fibrosis, nodules are formed by regeneration of hepatocytes.[1]

The exact prevalence of cirrhosis worldwide is unknown. Cirrhosis prevalence was estimated at 0.15% or 400000 in the USA. This may be on underestimation as we recognize the high prevalence of undiagnosed cirrhosis in both nonalcoholic steato hepatitis (NASH) and hepatitis C. Similar number have been reported from Europe and numbers are even higher in most Asian and African countries when chronic viral hepatitis B or C are frequent. Since compensated cirrhosis often goes undetected for prolonged periods of time, a reasonable estimate is that up to 1% of population may have histological cirrhosis.[2]

In hepatic cirrhosis, the presence of any one or more of jaundice, ascites, portal hypertensive gastrointestinal bleeding, and/or, encephalopathy is considered as decompensation. Decompensation, per se, is a significant risk for mortality. One-year mortality in compensated cirrhosis is 1- 3.4%, but in decompensation it is elevated to 20- 57%. The above manifestations appear when the disease process overwhelms the compensatory mechanisms, either by disease progression or a superimposed acute insult or some other contributing factors like micronutrient deficiency.[3]

Many elements, although present in minute quantities, are essential nutrients for humans. Their presence was long overlooked and it has only been found in recent years that these elements perform functions indispensable for maintenance of life, growth and reproduction. Inadequate levels of some elements may impair cellular and physiological functions causing illness. Considering the vital role, those trace elements in

enzymatic reactions they have been examined critically as potential key factors in varied diseases like liver cirrhosis. Although trace elements are only a part of total picture, they contribute significantly to nutrition and maintenance of health as well as prevention of several diseases like liver cirrhosis.[4]

Copper (Cu) is an important trace element which is widely distributed in all human tissues, with high concentration in liver, heart, brain and kidney. The majority (96%) of serum Cu is firmly bound with α2 globulin that is called ceruloplasmin. Remaining 4% is loosely bound to albumin that is metabolically active. Some study reported that the fraction of copper loosely bound to protein (nonceruloplasmin fraction) was increased in cirrhosis. They suggested that hypercupremia might be produced by decreased capacity of liver to inactivate the circulating oestrogen which leads to excessive circulating oestrogen resulting in hypercupremia.[5] Cu is highly toxic in excess and results in cellular damage and hepatocellular carcinoma.[6]

Zinc (Zn) is an essential trace element. It is an essential component of more than 300 enzymes, which participate in metabolism of carbohydrate, protein, fat and nucleic acid. Protein metabolism impairment in cirrhotic patients would appear to affect the plasma transport of Zn rather than its overall availability in the organ.[7] Zn is transported in plasma mostly by albumin (60-70%) and by α_2 macroglobulin (30-40%). Low serum Zn level in liver cirrhosis patients might be the result of decreased liver albumin content, decreased α_2 macroglobulin synthesis, poor dietary intake, or protein restriction.[8]

There has been a growing awareness of possible alteration of serum Zn level in patients with liver cirrhosis. Various studies of serum Zn level in patients with liver cirrhosis were undertaken and significant decreases in serum zinc levels were found in these patients. Symptoms of acute Zn deficiency like anorexia, dysfunction of smell and taste, mental and cerebellar disturbance as well as symptoms of chronic Zn deficiency like growth retardation, anaemia, testicular atrophy, and impaired wound healing are common in cirrhotic patients. So, micronutrient deficiency may contribute to the features of cirrhosis or to the development of decompensated cirrhosis as a continuum. Despite this controversy persists regarding the importance of serum Zn & Cu level in the patients of liver cirrhosis, the merits of routine screening of these elements continue to be debated.

Table 1: Child-pugh classification of prognosis in cirrhosis.

SCORE	**1**	**2**	**3**
Encephalopathy	**None**	**mild**	**Marked**
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (G/L)	>35	28-35	<28
Prothrombin time Prolonged in sec.	<4	4-6	>6
Ascites	None	mild	Marked

Add the individual score <7=child's A, 7-9= child's B, >9= child's C. To convert bilirubin in µmole/L to mg/dl, divide by 17.1.

Table 2: Survival in cirrhosis.

Child Pugh	**Survival (%)**			
Grade	1 year	5 Years	10Years	*Hepatic death (%)
A	82	45	25	43
B	62	20	7	72
C	42	20	0	85

[9]

MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry, Mymensingh Medical College, Mymensingh from over a period of one year from July 2015 to June 2016. A total of 60 patients of decompensated liver cirrhosis (all are child's Pugh B & C) ranging from 20-60 years were selected. 60 age matched, healthy subjects (from students and hospital employees) were selected in the control group. All participants were recruited after obtaining their written consents. All study subjects were from the same geographical area with no significant difference in their food habits and drinking water quality. Cases were selected from indoor ward of the same hospital. Liver cirrhosis patients were diagnosed provisionally from detailed history, positive findings on clinical examination. Final diagnostic criteria were fulfilled by ultrasonographic examination of the abdomen and relevant biochemical tests. Liver cirrhosis patients associated with concomitant pathology like diabetes mellitus, hyper tension, chronic diarrhoea, renal failure or taking drugs causing alteration of trace elements status

were excluded from this study. Blood was obtained from patients and controls after an overnight fast. The blood was drawn into plastic syringes fitted with stainless steel needles, immediately transferred to metal free tube, allowed to clot, centrifuged and serum removed to another metal free tube for storage -20 degree centigrade until assayed.

Serum Copper and Zinc in µgm/dl were measured spectrophotometrically. All data were recorded systematically in a preformed data collection sheet. The collected data were processed and analyzed by computer software SPSS (Statistical package for social science) version 20. Students unpaired 't' test was used to analyze the data between groups. For analytical test, 95% confidence limit P<0.05 was taken as the level of significance.

RESULT ANALYSIS

In the present study, a total number of 120 subjects were participated. Among them, 60 were decompensated liver cirrhosis patients denoted as case group and 60 were normal healthy individuals denoted as control group. Different variables of the subjects were being analyzed in this section. Serum Copper & Zinc levels were estimated from blood samples collected from 120 human subjects. Data were expressed in Mean ±SD and statistical significance of difference among the groups were calculated by unpaired student's 't' test. If p value is less than 5% (p <0.05) it indicates statistically significant result. If p value is less than 1% (p<0.01) it indicates statistically highly significant result. If p value is more than 5% (p>0.05) it indicates statistically not significant result.

The results were expressed as serum copper in µgm/dl, serum zinc in µgm/dl. The study revealed that mean serum copper level was higher in case group as compared to control group. The mean values of copper were 104.69 ± 9.15 and 149.17 ± 5.72 in control and case group respectively. The analysis showed that, the difference in mean serum copper levels between two groups was highly significant. Analysis of mean serum copper levels of study population were presented in figure I. The study revealed that mean serum zinc level was lower in case group as compared to control group. The mean values of zinc were 91.08 ± 6.16 and 45.89 ± 14.10 in control and case group respectively. The analysis showed that, the difference in mean serum zinc levels between two groups was highly significant. Analysis of mean serum zinc levels of study population were presented in figure II.

Table: Serum Copper and Zinc levels in the study population.

Variables	Mean± SD Control group	Mean± SD Case group	t value	p value
Serum Copper (µgm/dl)	104.69±9.15	149.17±5.72	32	P< 0.001
Serum Zinc (µgm/dl)	91.08±6.16	45.89±14.10	22.82	P<0.001

Unpaired student's 't' test, Significant

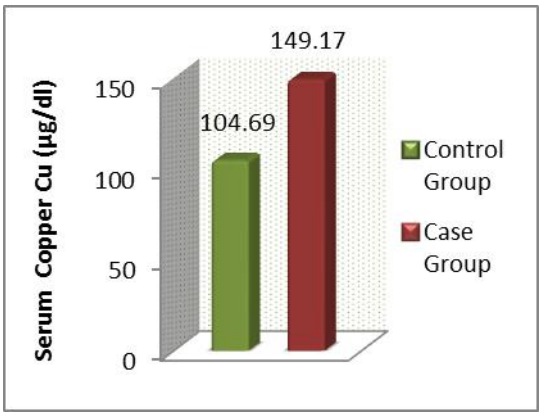

Fig. I Mean serum Copper levels in study group.

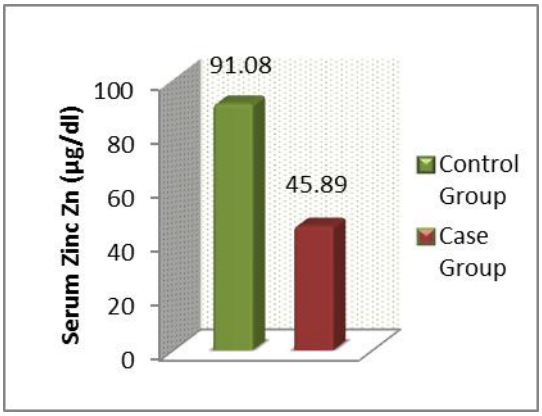

Fig. II Mean serum Zinc levels in study group.

DISCUSSION

This present work was carried out to evaluate the serum Copper & Zinc status in liver cirrhosis patients. In statistical analysis mean of the different characteristics for each group were compared and student's unpaired 't' test were done. The results were calculated and analyzed by using SPSS windows package, version 20 (statistical package for social science). In the present study, the results showed a significant (p<0.001) increase in serum Copper and significant (p<0.001) decreases in serum Zinc levels in liver cirrhosis patients when compared with that of control group. **Copper** (Cu) is an essential trace element that is involved in the function of several cuproenzymes. It also shows anti-oxidant activity. As a cofactor it is involved in metabolic reactions angiogenesis, oxygen transport, and anti-oxidant protection.[10] Cu and Zn are involved in several reactions in the protection from free radical damage.

They are component of several metallo enzyme with redox capacity. This redox capacity converse then an antioxidizing and anti-reactive oxygen radical action.[11] In the present study, the mean values of serum Cu levels were 104.69 ± 9.15 and 149.17 ± 5.72 in control and case group respectively. The analysis showed the significant increase level of serum Cu in liver cirrhosis patient when compared with that of control group. This finding is in agreement with the result of Gubbler et al[5], kar et al.[12] and Lin et al.[8] The possible role of estrogens in the pathogenesis of the hypercupremia associated cirrhosis of the liver is worthy of comment. Gubbler et al.[5] suggested that hypercupremia may be produced in human subjects by estrogen administration and is present in pregnant women in whom there is a high level of estrogen in subject with cirrhosis of the liver, there are many manifestations of excessive estrogenic stimulation because of the diminished capacity of the liver to "inactivate" the circulating estrogens. Several studies have also shown that plasma copper concentrations are increased in various cancers.[13] Zowczak et al.[14] demonstrated significant increase in mean serum total copper levels and serum copper: zinc ratio in all cancer patients group relative to a control group. Pramoolsinsap et al.[15] suggested that serum Zn levels decreased significantly in patients with chronic active hepatitis, cirrhosis and hepatocellular carcinoma and Cu levels increased significantly only in patients with hepatocellular carcinoma. In agreement with most of the previous studies, we found that higher copper concentration in blood were associated with the degree of severity of the disease in liver cirrhosis. Hence, we observed and suggested that high copper levels in decompensated cirrhosis might lead to a more severe outcome and low copper diet might be necessary for decompensated patients to prevent the fatal outcome.

Zinc (Zn) is an essential trace element. It is second to iron as the most abundant trace element in the body and it is the only metal which appears in all energy classes, which participate in metabolism of carbohydrate, Protein, fat and nucleic acid.[16] Variation in trace element can occur in several pathological conditions.

In the present study, the mean values of serum Zn levels were 45.89 ± 14.10 and 91.08± 6.16 in case and control group respectively. The analysis showed a significant lower level of serum Zn in liver cirrhosis patients when compared with that of control group. This finding is in agreement with the study of Soomro et al.[17] Triwikatmani et al.[18] and Atia et al.[19] Prasad and Pandey[20] revieSwed association between Zn and liver cirrhosis patients. The protein synthesis is reduced in the liver cirrhosis patients. The important element in the Zn binding to protein is "metallothionein". This protein is involved in Zn metabolism, homeostasis and its release in number of oxidants. The released Zn then inhibit the activity of the enzymes involved in fibro genesis in the liver. Impaired synthesis of this protein may decrease the availability of Zn. However, kar et al.[12] have been suggested that Zn is transported in plasma mostly by albumin (60-70%) and by α_2 macroglobulin. Low serum Zn level in liver cirrhosis patient might be the result of decreased liver albumin content, decreased α_2 macroglobulin synthesis, poor dietary intake or protein restriction.

CONCLUSION

The findings of this study revealed significant changes in the studied parameters in liver cirrhosis patients. Here serum Copper levels increased and serum Zinc levels decreased in significant.

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