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Serum zinc and copper levels in chronic hepatitis B and hepatitis B virus induced cirrhosis

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ABSTRACT

The study aims to compare the serum zinc and copper levels in chronic hepatitis B and HBV induced cirrhosis, and whether these parameters can be used as markers of conversion from chronic hepatitis to cirrhosis, and if their supplementation would delay the course of the disease.

50 chronic hepatitis B and 80 HBV induced Cirrhosis patients were included in the study. Serum zinc and copper levels were estimated in 1800 UV spectrophotometer.

Statistically significant decrease in serum zinc levels and a statistically significant increase in serum copper levels were observed in cirrhosis when compared to chronic hepatitis B ($P < 0.001$). Decreased serum zinc and increased serum copper levels indicate the conversion of chronic hepatitis B to cirrhosis. Supplementation of zinc and reduction of copper intake will delay the progression of chronic hepatitis B to cirrhosis and improve survival.

1. Introduction

Chronic hepatitis B is the inflammation of the liver that is caused by the Hepatitis B virus for more than 6 months. Cirrhosis following viral hepatitis B is post necrotic. The cardinal pathologic features reflect irreversible chronic injury of the hepatic parenchyma and include extensive fibrosis in association with the formation of regenerative nodules. These features result from hepatocyte necrosis, the collapse of the supporting reticulin network with subsequent connective tissue deposition, distortion of the vascular bed, and nodular regeneration of remaining liver parenchyma.

The central event leading to hepatic fibrosis is the activation of the hepatic stellate cell. Upon activation by factors released by hepatocytes and kupffer cells, the stellate cells assume a myofibroblast-like conformation and, under the influence of cytokines such as transforming growth factor-beta (TGF – beta), produces fibril forming type I collagen. The result of this continuous process is a small scarred coarsely nodular liver. Loss of functioning hepatocellular mass may lead to jaundice, edema, coagulopathy, and a variety of metabolic abnormalities; fibrosis and distorted vasculature lead to portal hypertension and its sequelae, including gastroesophageal varices and splenomegaly.Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension. India is a country with intermediate endemicity (2-7%) based on the prevalence of Hepatitis B surface antigen (HBsAg). Every year over the world, there are 4 million acute clinical cases of HBV, and about 1 million die from chronic active hepatitis, cirrhosis or primary liver cancer.

In untreated patients with predominantly HBeAg positive chronic hepatitis B, the incidence of cirrhosis ranges from 2 to 5.4 per 100 person-years with a 5-year cumulative incidence of cirrhosis of 8–20%.[1–3] Chronic hepatitis B progresses to cirrhosis over some time.

Zinc deficiency has been involved in the pathogenesis of many clinical findings in chronic liver disease. Identifying a serum marker that could be used to assess the liver function in HBV patients early is of importance for the possibility

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of delaying the development of cirrhosis. So that corrective measures could be adapted to delay the progression of chronic hepatitis B to cirrhosis.

The study aims to compare serum copper, zinc in chronic hepatitis B and HBV Cirrhosis with controls to evaluate the value of these trace elements in the assessment of liver dysfunction at a point of time when intervention can be instituted and progression of cirrhosis can be delayed.

2. Materials and Methods

The study was conducted in the Department of Biochemistry of the central laboratory, KIMS & RF, Amalapuram. 50 Chronic hepatitis B and 80 HBV cirrhosis patients from the department of General medicine, KIMS&RF and 40 age and sex-matched controls were included in the study. Prior permission was taken from the Institutional Ethics Committee of KIMS&RF, Amalapuram, to conduct the study. All of the subjects provided their informed consent as approved by the ethics committee.

Chronic hepatitis B patients, diagnosed to be hepatitis B positive since 2 $\pm$ 0.2 years, serologically HBsAg and anti-HBc positive by immunological assays, with the age of 46.76 $\pm$ 4.02years and Cirrhosis patients diagnosed based on history, clinical signs, abnormal ultrasonogram of the abdomen and positive serology for HBsAg since 3 $\pm$ 0.5years, with the age of 57.03 $\pm$ 2.12 years were included in the study.

Patients with positive serological tests for Hepatitis C virus / Human immunodeficiency virus (HIV), liver diseases due to drug toxicity, Wilson's disease, autoimmune disorders, acute or chronic diarrhea, or on any mineral supplements, malnutrition, other causes of cirrhosis, on drugs affecting mineral metabolism, diabetics and hypertensives were excluded from the study.

5 ml of the random venous blood sample was drawn. The sample was centrifuged and serum separated. All samples were immediately analyzed by kit methods using UV 1800 spectrophotometer.

Serum zinc and copper was estimated by using the spectrophotometric method with Nitro-PAPS and Di- Br-PAESA (dibromo pyridylazo –N- ethyl- N- sulfopropyl aniline) respectively.

2.1. Statistical analysis

Results are shown as Mean $\pm$ S.D. (standard deviation). To analyze statistically significant differences in means of continuous variables between 2 groups of patients, a student t-test was used. $P \leq 0.05$ was considered statistically significant.

3. Results and Discussion

It has long been speculated that Zinc has a protective effect against liver fibrosis and Zinc intake in cirrhosis is based mostly on observations of reduced zinc levels in cirrhotic patients and on the beneficial effects of Zinc supplementation on liver metabolism.[4]

The mechanisms contributing to zinc deficiency are poor dietary intake, reduced intestinal absorption, reduced hepato-intestinal extraction, portal-systemic shunting, altered protein, and amino acid metabolism, protein restriction and increased clearance of zinc in pancreatic or intestinal fluids, which leads to loss of zinc in the stool which is the main route of zinc excretion. Two mechanisms were proposed for zinc 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.[5] 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 zinc deficiency. In some cases, zinc supplementation was beneficial to these patients.[6] There is also reduced liver protein synthesis in patients with liver cirrhosis, the metallothionein (MT) is an important zinc-binding protein (formed by the liver) and is involved in zinc metabolism, homeostasis and its release in many oxidants, the released zinc will inhibit the activity of the enzymes involved in fibrogenesis (fibrosis) in the liver, all these are yet known pathophysiological mechanism.[7,8] Decrease in serum zinc in Chronic hepatitis B and cirrhosis is due to decreased serum albumin, poor dietary intake, and increased clearance of zinc.

The elevated levels of serum copper are due to cholestasis as a result of either a functional defect in bile formation at the level of the hepatocytes or from impairment in bile secretion and flow at the bile ducts level, which causes impaired biliary excretion of Copper and excess Copper absorption, as bile ducts are the main way to excrete copper from the body. Copper being oxidative, and hepatotoxic causes the progression of chronic liver diseases. Copper binds to sulfhydryl groups of enzymes, as glutathione reductase, thus interfering with their protection of cells from free radical damage. Redox cycling between cupric and cuprous ions can catalyze the production of toxic hydroxyl radicals.

The interaction between zinc and copper in their intestinal absorption and their competition for binding sites on the carrier proteins and cellular uptake may be the regulators of their homeostasis. Maybe this can explain the inverse concentration of zinc and copper.

Zinc administration has been shown to inhibit the accumulation of hepatic collagen in experimentally produced hepatic necrosis and to significantly improve neurological signs in hepatic encephalopathy in humans.

Table 1: Comparison of Mean± S.D. of serum copper and zinc in Chronic hepatitis B and controls.

Parameter	Chronic Hepatitis B(50)	Controls (40)	P value
Copper(μg/dl)	148.21 ± 4.5	110.24 ± 8.9	< 0.001
Zinc (μg/dl)	55.9 ± 7.2	88.17 ± 7.04	< 0.001

Table 1 shows a statistically significant increase in copper and a statistically significant decrease in Zinc in Chronic active hepatitis B when compared to controls.

Table 2: Comparison of Mean ± S.D. of copper and zinc in cirrhosis and controls.

Parameter	Cirrhosis (80)	Controls (40)	P value
Copper(μg/dl)	156.23 ± 7.2	110.24 ± 8.9	< 0.001
Zinc (μg/dl)	50.2 ± 13.88	88.17 ± 7.04	< 0.001

Table 2 shows a statistically significant increase in copper and a statistically significant decrease in Zinc in Cirrhosis when compared to controls.

Table 3: Comparison of Mean± S.D. of copper and zinc in chronic hepatitis B and cirrhosis.

Parameter	Cirrhosis (80)	Chronic Hepatitis B(50)	P value
Copper(μg/dl)	156.23 ± 7.2	148.21±4.5	< 0.001
Zinc (μg/dl)	50.2 ± 13.88	55.9 ± 7.2	< 0.001

Table 3 shows a statistically significant increase in serum copper and a statistically significant decrease in Zinc in Cirrhosis when compared to chronic Hepatitis B.

Also, dietary zinc supplementation could improve liver regeneration by increasing the expression of genes involved in hepatic cellular proliferation. As the severity of the disease worsened, zinc levels decreased, so zinc may be used as a prognostic indicator of chronic liver diseases. Serum zinc, copper could be included in the routine assessment of patients with chronic liver diseases as chronic hepatitis B and HBV cirrhosis. Zinc supplementation may be encouraged in patients with chronic hepatitis and HBV cirrhosis as it is an antioxidant. Caution regarding Copper intake either dietary or medicinal should be taken in patients with chronic hepatitis B and HBV cirrhosis. The 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.

4. Conclusion

Low levels of serum zinc and high levels of copper are identified in patients with Chronic hepatitis B and HBV cirrhosis. Therefore a routine biochemical assessment of zinc status in patients with Chronic Hepatitis B and HBV cirrhosis is an important step in the management protocol and to reduce the progression of the disease.

5. Source of Funding

None.

6. Conflict of Interest

None.

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