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Medical Sciences

THE ROLE OF ZINC IN CHRONIC LIVER DISEASE

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ABSTRACT:
ONE OF THE FUNDAMENTAL MICRONUTRIENTS NECESSARY IN THE MECHANISM OF CELLULAR METABOLISM, PRODUCTION AND DIFFERENTIATION ARE ZINC. DUE TO ITS FINGER TRANSCRIPTION FACTORS, IT ALSO PLAYS AN IMPORTANT ROLE IN DNA SYNTHESIS, RNA PACKAGING AND CELL RENEWAL. THIS SPECIFIC TRACE ELEMENT IS METABOLIZED IN THE LIVER, SO ANY DISORDER THAT OCCURS AT THIS LEVEL CAN MODIFY THE ASSIMILATION OF ZINC. ALSO, AN INSUFFICIENT LEVEL OF ZINC CAN LEAD TO CHRONIC LIVER DISEASE. LIVER CIRRHOSIS REPRESENTS THE FINAL PATHOLOGICAL PATHWAY IN THE DEVELOPMENT OF MANY CHRONIC LIVER DISEASES REGARDLESS OF ETIOLOGY, THEREFORE ZINC MAY PLAY A ROLE IN ITS PROGRESSION AND OUTCOME. THIS REVIEW WILL ANALYZE THE LATEST FINDINGS ON THE IMPORTANCE OF ZINC IN CHRONIC LIVER DISEASE GENESIS AND PROGRESSION.

KEY WORDS: ZINC, CHRONIC LIVER DISEASE, LIVER CIRRHOSIS.

INTRODUCTION

Appropriate nutrition of all tissues and cells is mandatory for preserving the health of the body as a whole. The elements which compose the human body can be divided into abundant elements and trace elements. Essential trace elements account for only 0.02% of the total body weight and are represented by zinc (Zn), copper (Cu), iodine (I), chromium (Cr),

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selenium (Se), manganese (Mn), cobalt (Co) and molybdenum (Mo)[8]. Micronutrients, which include vitamins, antioxidants and trace elements play a vital role in reducing the oxidative stress in tissues, sustaining the immunity against pathogens and continuously occurring processes of renewal, restoration and tissue growth[9].

The liver plays an indispensable role in the maintenance of essential trace elements homeostasis. Zinc is the second most abundant trace element in the body after iron. It represents a primary nutrient in the process of cell development and is strongly associated with the metabolism of proteins and lipids[10], being also a strong anti-inflammatory agent. The essential role of zinc in humans was established in 1961 following the first discovery of zinc deficiency in an Iranian farmer. Zinc participates at the molecular level in the metabolism of biological proteins, thus influencing cell reproduction, differentiation and death[11].

A normal concentration of serum zinc is essential for the proper functioning of the immune system, intestinal tract and nervous system. The human body cannot produce or store zinc, so it must be constantly supplied with food. The body assimilates zinc from food, whether of plant or animal origin (animal meat, seafood, vegetables, nuts, cereals and various types of dairy products) and from food supplements[12]. A diet poor in these aliments or malabsorption leads to zinc deficiency with anorexia, immune system depression, alopecia, skin lesions, depressed mental function, hypogonadism, poor wound healing, symptoms extremely similar to those encountered in liver cirrhosis[13].

Liver tissue is responsible for many actions like detoxifying the body, it participates in the metabolism of carbohydrates and proteins, the synthesis of cholesterol, phospholipids, lipoproteins, lipids, some elements of the blood, such as albumin, globulin and antithrombin. It is also involved in the production of glycogen, bile and cholesterol. Any condition that alters the normal structure of the liver parenchyma by replacing it with fibrotic tissue will also alter liver function[14]. Europe has the largest burden of liver disease in the world, with the burden expected to grow across many countries.

Cirrhosis is the latest stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions. Liver fibrosis results from chronic damage to the liver in conjunction with the accumulation of extracellular matrix proteins. Clinically, this leads to portal hypertension and end-stage liver disease. The most notable complications of liver cirrhosis are hepatic encephalopathy, esophageal varices, cancer of the liver, and susceptibility to infections[15].

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In this review, we will analyze the implications of zinc deficiency in the occurrence and evolution of the chronic liver disease and its associated complications.

ZINC METABOLISM AND FUNCTIONS

Zinc is an essential trace element and its presence is vital in many processes that take place in the human body. It is found in all types of human tissues, the body of an adult weighing 70 kg contains a total of 2–3 g of zinc[16]. The majority of the body's store zinc is in muscle and bone (approximately 85%), followed by skin and liver, which together make up an additional 11%[17].

Currently, the recommended daily dose of zinc is 8 mg daily for a woman over 19 years of age and 11 mg for a man over 15 years of age. The most substantial sources of zinc are red meat (100 g of meat contains 4.8 mg of zinc), seafood (100 g of fish contains about 7 mg of zinc), vegetables, nuts, dairy products (200 ml of milk - 9% of the daily dose), eggs (1 egg - 1% daily intake) and cereals[18].

Fig. 1 Essential roles of Zn for the human body

Approximately 20% to 80% of zinc from food is absorbed in the duodenum and upper small intestine by a carrier-mediated mechanism. Unabsorbed zinc, as well as zinc secreted into the gastrointestinal tract, is excreted in the feces. Approximately 2% of ingested zinc is excreted in the urine. The majority of zinc in the blood binds to albumin and part of it binds to alpha 2-macroglobulin or aminoacids. In hypoalbuminemia due to liver disease, zinc in the blood that is unbound to albumin binds instead of amino acids, making it likely to be excreted in the urine[19]. Zinc acts as a synergist to over 200 enzymes[20]. These metalloenzymes show a

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significant decline in their actions in the absence of zinc. Different cells in the human body have specific transporters for this trace element like the zinc transporter (ZnT) or solute carrier 30 (SLC 30) family. These transporters can increase zinc from the cytoplasm out of the cell and from the cytoplasm into vesicles[21]. There is another category of transporters known as the zinc importer, Zrt- and Irt-like protein (ZIP), or solute carrier 39A (SLC39A) family which control the influx of zinc into the cytoplasm from outside the cell and from vesicles[22]. These families of transporters are antagonistic to each other. Because of its signaling capacity, zinc can influence the production and signaling of numerous inflammatory cytokines in a variety of cell types[23].

Zinc also carries a unique type of small (~20–100-residue) domains that coordinate one or more zinc ions, usually through cysteine and histidine sidechains, to stabilize their fold

named finger proteins (ZNFs). They are considered one of the most abundant groups of proteins in the human body. Proteins that contain zinc fingers (zinc finger proteins) are classified into several different structural families.

The Cys2His2-like fold group (C2H2) is by far the best well-known and characterized class of zinc fingers. The zinc finger protein 217 (ZNF217) can attach specialized sequences of deoxyribonucleic acid to regulate target gene expression and have been reported in various tumors and linked to poor outcomes in some studies[24].

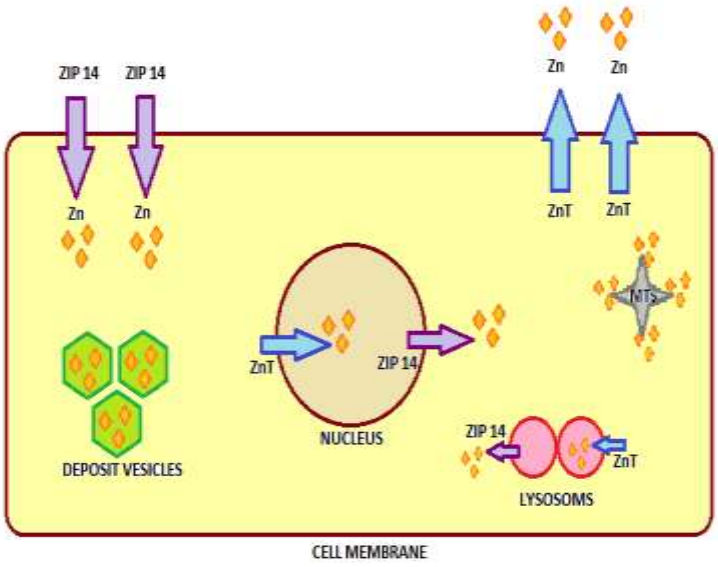

Fig. 2 The role of zinc in genomic stability

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ZINC AND LIVER CIRRHOSIS

The liver is the main organ responsible for maintaining the stability of zinc. Given the importance of this organ, any deficiency or excess of this trace element can affect its function and vice versa[25].

The term "cirrhosis" comes from the Greek word "khirros" meaning yellow-orange, the name of the disease being thus determined by the light brown color of the liver and not by its increased consistency. René Laënnec who gave cirrhosis its name, says in his treatise that he was impressed with the color of the cirrhotic liver. Over time, the term cirrhosis has been identified with liver sclerosis, almost forgetting its significance in color.

Liver cirrhosis is the end-stage of several chronic liver diseases and accounts for more than one million deaths each year worldwide. In 2017, cirrhosis caused more than 1,32 million deaths (440.000 in females and 883.000 in males) globally, compared with less than 899.000 deaths in 1990. Deaths due to cirrhosis constituted 2,4% of total deaths globally in 2017 compared with 1,9% in 1990[26].

Nutritional deficiency, decreased zinc absorption in the gastrointestinal tract, decreased hepatic extraction, increased zinc excretion in the urine, hypoalbuminemia and portosystemic shunt have been reported as the reasons for zinc deficiency in liver cirrhosis.

Zinc deficiency is accompanied by a severe impairment of the immune system, causing a high risk for infections and autoimmune diseases due to the altered functionality of B- and T- cells. Infection and inflammation produce systemic responses that include hypozincemia and hypoferremia. ZIP14 (slc39A14) is a zinc transporter produced in the liver and induced in response to pro-inflammatory stimuli. ZIP14 induction accompanies the reduction in serum zinc (hypozincemia) of acute inflammation[27]. The use of diuretics in decompensated cirrhosis is also known to increase zinc excretion in the urine by a mechanism in which diuretics inhibit renal tubular reabsorption of zinc. Diuretics also decrease albumin levels and increases zinc loss due to lack of binding[28].

Most of the symptoms of liver cirrhosis are similar to those of zinc deficiency: night blindness, taste and smell impairment, sensorineural hearing loss, thickening of the skin, immune dysfunction, iron deficiency, neurological manifestation, gonadal dysfunction, increased risk for malignant neoplasms, coagulation disorders and amino acid imbalance[29].

EFFECTS OF ZINC IN PATIENTS WITH ALCOHOLIC LIVER DISEASE (ALD)

After smoking and hypertension, alcohol is the commonest preventable cause of death. Worldwide, ALD per se accounts for 4% of mortality and 5% of DALYs with Europe being the worst affected. The gut is the first site of injury upon alcohol intoxication, alcohol-induced gut hyperpermeability has been well documented in both experimental and clinical studies. Translocation of gut-derived toxins, including endotoxin, typically activate toll-like

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receptors on Kupffer cells and induce inflammatory cytokine production, such as tumor necrosis factor (TNF), with subsequent hepatic inflammation/injury.

Zinc deficiency in patients diagnosed with ALD was first reported in a study conducted by Vallee, et al.[30]. Hypozincemia in these patients is mainly caused by unbalanced dietary intake[31], malabsorption[32] and inactivation of the critical zinc-finger proteins.

Godde, et al. conducted a study in which were enrolled 17 healthy patients and 13 patients previously diagnosed with alcoholic cirrhosis. The serum zinc concentration of the patients with alcoholic liver cirrhosis was much lower than in healthy ones (7,52 µmol/L vs 12,69 µmol/L). They continued the study on mice that were fed with alcohol and lipopolysaccharides, which were later detected in the blood. This proved that the ingestion of alcohol affects gut permeability and in the aftermath promoting endotoxemia through the destruction of Zn equilibrium[33]. Zhong W, et al. conducted a similar study which showed that supplementation of the diet with zinc at heavy drinkers didn't cause endotoxemia[34].

Another study showed that a daily dose of 200 mg for three months in patients with alcoholic liver disease improved liver function and nutritional status[35].

EFFECTS OF ZINC IN PATIENTS WITH CHRONIC VIRAL HEPATITIS

Chronic viral hepatitis is a syndrome of persisting hepatotropic viral infection usually associated with chronic inflammation, hepatocyte injury and progressive fibrosis. By convention, infection for more than 6 months is considered evidence that spontaneous resolution of infection is unlikely and hepatitis is chronic. In particular, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis, cancer and viral hepatitis-related deaths. An estimated 325 million people worldwide live with hepatitis B and/or C and for most, testing and treatment remain beyond reach.

Many studies have proven over the years that patients diagnosed with chronic viral hepatitis have hypozincemia[36]. In one study the patients with chronic hepatitis C and liver cirrhosis were given zinc supplements for six months, which improved liver inflammation and lowers the alanine aminotransferase and aspartate aminotransferase levels[37]. Patients with

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chronic hepatitis B have also hypozincemia[38] and a diet rich in zinc improves the outcome and the response to the treatment with interferon-alpha (IFN-alpha) and lamivudine.

THE RELATIONSHIP BETWEEN ZN AND MAJOR COMPLICATIONS OF LIVER CIRRHOSIS

Cirrhosis results from progressive fibrosis and is the outcome of all chronic liver disease. The major complications of cirrhosis include varices, ascites, hepatic encephalopathy (HE), coagulation disorders, hepatorenal syndrome, portopulmonary hypertension, spontaneous bacterial peritonitis and hepatocellular carcinoma. These can occur secondary to abnormal synthetic function, portal hypertension, or a combination of both.

HEPATIC ENCEPHALOPATHY AND ZINC

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of brain disease or intoxication. Among the symptoms experienced we find reduced alertness, sleep problems, anxiety or irritability, difficulty concentrating or short attention span, cognitive impairment (confused thinking or judgment), coordination or balance problems, flapping hand motion (asterixis), mood or personality changes, muscle twitches (myoclonus), slurred speech and finally coma.

Takuma, et. al. conducted a study in which were enrolled 79 subjects with liver cirrhosis and hepatic encephalopathy. The patients received a daily dose of 225 mg of zinc for six months. The study concluded that these supplements increase the quality of life[39]. Katayama, et al. came to a similar conclusion with blood ammonia levels significantly decreased[40].

ASCITES AND ZINC

The progression of chronic liver disease results in diminished hepatic glycogen stores due to a catabolic state that requires a higher protein intake than usual. The negative nitrogen balance is exaggerated, especially in advanced liver disease, due to disease-associated factors including low protein intake and anorexia[41]. Albumin is a protein of 585 amino acids and molecular weight 66 kDa encoded by a gene on chromosome 4 and is exclusively synthesized by liver cells, which release it directly into the bloodstream without storage[42]. It constitutes approximately one-half of the proteins in the plasma (3.5-5 g/l) and plays a prominent role in the pathogenesis of ascites because of the alteration of the balance between the forces of Starling in the intrahepatic microcirculation. Taking all of this information into consideration

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scientists have established that the addition of zinc causes a lowering in branched-chain amino acids which causes hyperalbuminemia and a diminishing in the quantity of ascites fluid.

HEPATOCELLULAR CARCINOMA AND ZINC

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. The incidence of liver cancer (hepatocellular carcinoma/HCC) continues to increase worldwide. It is the fifth most common cancer in men worldwide and seventh among women, being the second leading cause of cancer-related mortality in the world[43]. Chronic liver disease due to hepatitis B virus (HBV) or hepatitis C virus (HCV) accounts for the majority of HCC cases.

Poo et all showed that the serum levels of zinc (μg/dl) in patients with hepatocellular carcinoma were significantly lower (71.6 ± 30.5; $P < 0.05$) than those in patients with the benign digestive disease (81.7 ± 17.7 μg/dl) and were similar to those in cirrhotic patients[44].

Metallothionein (MT) is a family of cysteine-rich, low molecular weight (MW ranging from 500 to 14.000 Da) proteins that can bind zinc through their thiol group. It was initially discovered from a horse kidney in 1957 as a protein that contained cadmium. These proteins seem to play a primordial role in understanding zinc deficiency in patients with hepatocellular carcinoma. The study conducted by Kubo et al. enrolled 23 patients with hepatocellular carcinoma who underwent liver resection and 13 patients without liver disease. The Cu, Zn-MT level was significantly greater than Zn-MT in the non-cancerous, but diseased hepatic parenchyma than in the normal hepatic tissue. In comparison with non-cancerous hepatic parenchyma, the Cu-MT in the cancerous section was significantly greater than the Cu, Zn-MT[45] (Fig. 3)

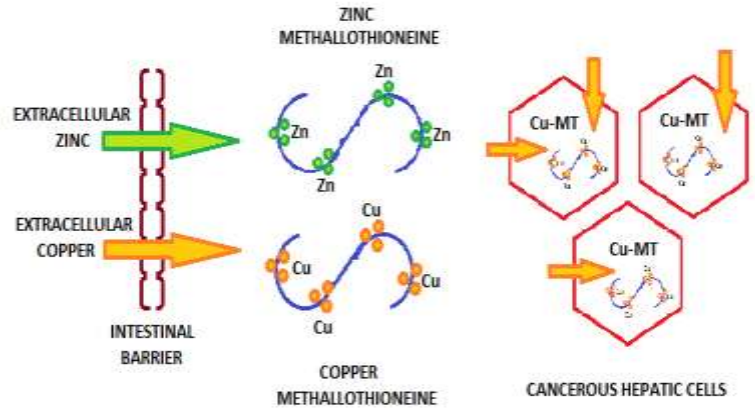

Fig. 3 Displacement of Zn-MT and Cu-MT in malignant liver cells

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Fraklin et al. were able to further investigate the possible association of zinc uptake transporters with the depletion of zinc and concluded in their study that the hypozincemia in malignant liver cells was a repercussion of ZIP 14 transporter absence in malignant cells proving the importance of zinc in the progression to hepatocellular carcinoma[46].

CONCLUSIONS

Cirrhosis is histologically defined as the development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end-stage liver disease. Zinc plays an indispensable role in various zinc enzymes, which are crucial in the maintenance of liver function. Patients with chronic liver diseases usually have lower concentrations of zinc, which decreases further as liver fibrosis progresses. A decrease in this trace element serum concentration leads to rapidly progressive disease and has been associated with a poor prognosis. Taking supplements with zinc to correct this deficiency slows the progression of the disease. These supplements are also beneficial in preventing complications such as hepatic encephalopathy, ascites, and hepatocellular carcinoma. The recommended daily dose of zinc is 50 mg, administered for more than 3 months. The combination of zinc and lactulose is useful in the treatment of encephalopathy. Administration of this trace element has been shown to slow down fibrogenesis.

It is essential to understand the importance of zinc in the occurrence, treatment, and prevention of the complications of chronic liver disease. Recognition of this association may have important implications in zinc supplementation usage as an adjuvant agent in the treatment. To determine the long term outcome, further studies are needed.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors equally contributed to this article and share the first authorship.

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