

Zinc Deficiency and Liver Diseases-
General Observations

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Article Information

Received date: Jun 21, 2016

Accepted date: Jun 22, 2016

Published date: Jun 22, 2016

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Article DOI 10.36876/smjhr.1008

Editorial

Zinc is an essential trace element playing fundamental roles in the cellular metabolism and can be found in all tissues. It acts mostly by binding a wide range of proteins, thus affecting a broad spectrum of biological processes, which include cell division, growth and differentiation [1]. Zinc is critical to a large number of structural proteins, enzymatic processes, and transcription factors. Influencing the molecular functions of many proteins in cell metabolism and signal transduction, zinc is involved in proliferation, differentiation and apoptosis of cells with profound implications for healthy growth, renewal, and repair of cells [2]. Zinc binding proteins represent about 10% of the human proteome, with more than 300 enzymes having zinc ions within their catalytic domains [1]. In addition, zinc has extensive roles in both the innate (non-specific) and adaptive (specific) immune response at multiple levels, including differentiation and development of immune cells [3].

As a component of intracellular signal molecules, zinc is able to mimic the effects of hormones, growth factors and cytokines [4]. Moreover, zinc serves as a remarkable intracellular second messenger, similar to calcium. The stability of the homeostatic mechanisms of free zinc ions in the cell thus exerts a decisive effect on the development and progression of many diseases [5] (Table 1).

Intracellular zinc homeostasis is subject of the control of numerous proteins, which underscore the crucial importance of zinc [7]. Metalloproteins and zinc transporters are the main components in this regulatory process. Metalloproteins are important for the absorption and storage of zinc. Zinc transporters facilitate the influx (Zip) and the efflux (ZnT) through the cell membrane [8]. Both transporter types have a specific tissue expression with different responsibilities in the regulation of nutritionally-induced zinc deficiency or oversupply and in the regulation of physiological stimuli, such as hormones or cytokines. Moreover, zinc transporters coordinate the subcellular, cellular and organelle-based translocation of zinc ions [9]. Abnormalities of zinc metabolism adversely affect the immune system and the function of mitochondria. They result in damage to DNA, birth defects and developmental disorders. An oxidative environment heightens the cellular ability of zinc ions while a reductive milieu reduces this ability [7]. According to Ho [10], it is conceivable that disturbance of zinc's antioxidant function in persons with zinc deficiency may increase their sensitivity to factors that damage the DNA and, in turn, reduce the protective mechanisms of DNA against the development of carcinomas. The implications of zinc biology for human health are enormous about half of the world's population is believed to be at risk for zinc deficiency [11]. The World Health Organization (WHO) has identified zinc deficiency as the fifth most important risk factor for morbidity and mortality in developing countries [12].

As the main organ involved in zinc metabolism, the liver plays an important role in maintaining systemic zinc homeostasis. Subsequently, liver diseases can alter zinc levels, and in turn may be influenced by zinc deficiency [13]. Zinc release from hepatocytes is differentially regulated. Turnover studies using $^{65}\text{Zn}^{++}$ showed that complete exchange of zinc in hepatocytes requires less than two days [14]. The regulatory processes depend almost completely on hormonal control by insulin, glucagon, and the glucocorticoids [15]. Depending on the metabolic situation, these substances trigger a transient dysregulation of zinc metabolism with subsequent plasma zinc deficiency. Stress or mediator substances, like proinflammatory cytokines or lipopolysaccharides, can have a similar effect. Changes in zinc status directly affect gene expression (for details see 6). Zinc deficiency or an altered zinc metabolism in patients with liver disease is caused by a variety of factors, such as inadequate intake, changes in the protein and amino acid metabolism, diminished hepatic extraction, portosystemic shunts; alcohol induced impaired absorption, and the effects of cytokines, mainly IL-6 and endotoxins [6]. Severe muscle catabolism can lead to a substantial loss of zinc in the urine [16]. Cirrhotic patients with ascites are catabolic and show massive reduction of muscle. Diuretic therapy in patients with cirrhosis and ascites results not only in an increased renal zinc excretion, but also to reduced serum albumin and reduced capacity of albumin to bind zinc [17]. Many of the clinical features of liver cirrhosis have been linked to zinc deficiency, including loss body hair, testicular atrophy, cerebral dysfunction, altered taste and smell, reduced vitamin A and thyroid hormone metabolism, delayed wound healing, and diminished drug elimination capacity [18].

OPEN ACCESS**ISSN: 2573-3672**

Table 1: Zinc's functions in the body.

There is a wide range of possible pathomechanisms of zinc deficiency in liver cirrhosis. Zinc deficiency can lead to oxidative stress tissue damage and/or modulation of selected signaling cascades in the liver [19]. Zinc deficiency may also induce oxidative stress and subsequent conditions such as vulnerability to hepatitis, loss of acute-phase response protection against hepatitis and lipid oxidation. In liver disease, stress may occur through increased gut permeability with endotoxemia, infections such as spontaneous peritonitis, or release of stress hormones [20]. By altering redox state, zinc deficiency compromises the functioning of oxidative sensitive transcription factors that can affect cell function, proliferation and survival (for details see 6, 20). Zinc deficiency can impact many functions of the liver and, in particular the liver's capacity for regeneration. Liver cirrhosis is associated with a profound immune dysfunction [21].

Zinc deficiency occurs in many types of liver diseases, especially in more advanced/decompensated disease, and its complications, ascites, hepatic encephalopathy, and hepatocellular carcinoma. Zinc supplementation may be useful as adjunctive treatment in these complications. Zinc supplementation could be highly inexpensive and, within well-described daily dosage limits, quite safer, improve patients with liver cirrhosis [6].

More research is needed to further elucidate the different roles of zinc in both normal and liver disease state.

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