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Review
Derleme

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The relationship between zinc and hepatic steatosis

Çinko ve hepatik steatoz arasındaki ilişki

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most commonly diagnosed liver disease in the recent years, with a prevalence of 15-20% among normal population. Liver steatosis is also a complication of obesity and affects 22-52% of obese children. In this aspect, it is an important public health problem. Increases in the amount of fatty acids entering the liver, increase in fatty acid synthesis and disorders in its secretion are included in its pathogenesis. The relationship between zinc, which is the second most abundant trace element found in the body after iron and necessary for many enzymes to function properly, and fatty liver disease has been shown in previous studies. The aim of this review is to discuss the relationship between zinc and liver steatosis in the light of current studies and contribute to the literature.

Keywords: Zinc, Trace element, Hepatic steatosis

Öz

Non-alkolik yağlı karaciğer hastalığı (NAFLD), prevalansı normal popülasyonda %15-20'lere ulaşan, son yıllarda en sık görülen karaciğer hastalığıdır. Karaciğer yağlanması, obezitenin bir komplikasyonu olarak da karşımıza çıkmakta ve obez çocukların %22-52'ini etkilemektedir. Bu yönüyle önemli bir halk sağlığı sorunudur. Karaciğere gelen yağ asid miktarında artış, yağ asidi sentezinin artışı ve sekresyonundaki bozukluklar, karaciğer yağlanmasının patogenezindeki mekanizmalardan bazılarıdır. Ayrıca, vücutta demirden sonra en bol bulunan ikinci eser element olan ve pek çok enzimin fonksiyon göstermesi için gerekli olan çinko ile karaciğer yağlanması arasında bir ilişki olduğu yapılan çalışmalarda gösterilmiştir. Bu derlemeyi hazırlamaktaki amacımız, vücuttaki çinko miktarının karaciğer yağlanması ile ilişkisini açıklamak ve güncel araştırma sonuçlarını içeren bir veri hazırlamaktır. Bu yönüyle çalışmamızın literatüre katkı sağlayacağı kanaatindeyiz.

Anahtar kelimeler: Çinko, Eser element, Hepatik steatoz

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of fat, particularly triglycerides, in more than 5% of the liver by weight or the existence of fat vacuoles in more than 5% of the hepatocytes [1,2]. NAFLD is commonly seen as a complication of obesity and affects 22% to 52% of obese children [3]. Fatty liver disease is the most commonly diagnosed liver disease in recent years, especially in Western societies, and its prevalence reaches 15-20% in the normal population. Nonalcoholic fatty liver disease, together with macro-vesicular steatosis, represents a spectrum of liver diseases histopathologically characterized by alterations ranging from 'simple steatosis' to 'nonalcoholic steatohepatitis'. Histological findings suggest a transition from fat infiltration to an inflammatory / fibrotic disease that can progress to cirrhosis [4].

Increased amounts of fatty acids entering the liver in cases of obesity or starvation, excessive carbohydrate intake by diet or total parenteral nutrition and increased fatty acid synthesis in the liver, decreased beta-oxidation of fatty acids as a result of carnitine deficiency and mitochondrial dysfunction, and disturbances in the synthesis or release of very low density lipoprotein (VLDL-Cholesterol) due to disruption of apoprotein synthesis or protein malnutrition are the main causes of fatty infiltration in the liver (5). The relationship between liver steatosis and trace elements has been investigated in various studies.

Zinc (Zn) is an important trace element that plays a key role in biological functions such as cellular integrity and cell division, growth, and development [6,7]. Zn acts as a cofactor for many enzymes and proteins involved in regulatory, catalytic, antioxidant, anti-inflammatory and apoptotic processes [8]. Zn-binding proteins represent about 10% of human proteomes, including more than 300 enzymes with Zn ions in their catalytic domains. Zn plays a significant role in the regulation of gene expression through metal-binding transcription factors and metal response elements in the promoter regions of the regulated genes [9].

Zinc deficiency and metabolism

Zn deficiency is quite common in developing countries and may be caused by insufficient Zn intake, increased Zn loss or consumption in the body [10]. Some dietary fiber / phytates may reduce Zn absorption, which is concentration-dependent and occurs throughout the small intestine (mainly jejunum). In cirrhosis, Zn absorption may be defected, and its secretion typically increases. Zn deficiency has clinical manifestations such as skin lesions, depressed cognition, encephalopathy, impaired night vision due to changes in vitamin A metabolism, anorexia (possible changes in taste and odor acuity), hypogonadism, faulty wound healing, and altered immune functions [11]. Zn homeostasis is mainly regulated in the liver; its disruption has been associated with various diseases, such as cancer, diabetes, cardiovascular disease, and Alzheimer's disease [10].

Studies have shown that Zn deficiency is common in NAFLD [12]. The pathogenesis of NAFLD is not accurately known. Endotoxins / cytokines, oxidative stress and hyperinsulinemia are associated with NAFLD development [13]. Zn is associated with hepatosteatosis because it is an important trace element for many enzymes in the synthesis, storage, release, and effects of insulin [12]. The relationship between Zn intake and chronic fatty liver disease is complex, for Zn affects the normal homeostasis of the liver, and the liver plays a central role in Zn hemostasis. Accordingly, deficiencies of this mineral impair liver functions and endanger the recovery and restoration of liver tissues [14].

The effects of Zn co-supplementation on NAFLD before and/or after disease progression are not clear enough [12]. In a previous study, it was shown that the combination of Zn and selenium supplementation had better effects on serum glucose, lipid profile and hepatic fat accumulation after the progression of fatty liver disease as compared to before. These results may be due to depletion of Zn and selenium in fatty liver disease [12]. Increasing evidence suggests that Zn plays a critical role in regulating hepatic lipid metabolism [15].

Stress hormones and pro-inflammatory markers such as tumor necrosis factor-α cause changes in Zn metabolism [16]. NAFLD causes a low degree of inflammation [17]. In this respect, it is highly possible that Zn levels are changed in NAFLD patients due to inflammation.

Zn deficiency, glucose intolerance and insulin resistance may be predisposing to diabetes mellitus and coronary artery disease [18,19]. Several studies have shown that Zn has beneficial effects on insulin resistance, glucose and lipid profiles in patients with diabetes or metabolic syndrome [15,20,21].

Many studies have reported low plasma Zn levels in obese subjects [22,23]. Liver steatosis is considered a complication of obesity [2]. It has been reported that approximately 50% of obese adolescents are also obese in their adulthood [24]. Childhood obesity affects approximately 25-30% of children [25]. For this reason, the relationship between Zn, liver steatosis and obesity is extremely important starting from childhood.

In an experimental study, Zn levels were reported lower in the fatty liver group compared to the rats in the control group in a NAFLD model, which was formed with an excess fatty diet [26]. This data is scientific proof that NAFLD causes Zn deficiency.

Pathogenesis of nonalcoholic fatty liver disease

The mechanism underlying the formation and progression of NAFLD is not fully understood. NAFLD patients are more prone to cardiovascular diseases. NAFLD and cardiovascular diseases are two commonly distinguished diseases in the general population. It has been reported that Zn supplementation reduces the risk factors of cardiovascular disease by causing changes in relevant laboratory tests in patients with NAFLD after disease progression [26].

Oxidative stress plays a key role in the development of NAFLD, particularly in its progression from steatosis to steatohepatitis [27]. The hypothesis emerging in the pathogenesis of non-alcoholic steatohepatitis is a "two-hit theory' including fat accumulation as the first hit and oxidative stress as the second hit [28]. Zn has also been shown to have potential effects on the attenuation of lipid peroxidation in an experimental animal model [29,30]. Since Zn is important for many oxidative and antioxidant molecules in the body [8], it should be kept in mind

that Zn deficiency may be related to liver fattening through the oxidative and antioxidant system.

In a study conducted on patients with HCV-related chronic liver disease, Zn deficiency was reported to increase hepatic iron overload in the liver, increase insulin resistance and trigger hepatic steatosis by facilitating lipid peroxidation [31].

Mikhail et al. [32] demonstrated a close association between Zn deficiency and hepatic steatosis in an experimental fatty liver animal model induced by tetracycline. In this study, the authors concluded that Zn deficiency and a decrease in high-density lipoprotein cholesterol (HDL-Cholesterol) synthesis lead to an exacerbation of hepatic steatosis in experimental animals.

Zn deficiency usually results in impaired liver function or regeneration in patients with chronic liver disease [33]. Indeed, Zn supplementation has been shown to protect against liver damage in an experimental animal model of hepatic fibrosis [34]. An increase in hepatic Zn content with Zn supplementation has been shown to defend the liver from damage [35].

Conclusion

NAFLD is an inflammatory disease with abnormal lipid deposition in the liver. Studies have shown that Zn deficiency is present in these patients and that Zn supplementation is effective against this disease. However, the available data suggest that Zn may be more effective in restraining the progression of the disease rather than preventing its formation in the first place. Given the small number of studies on the subject, further research will clarify the relationship between the formation, progression and treatment of hepatic steatosis and body Zn levels.

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