Magnesium and liver disease

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Abstract: Magnesium is a vital cation that takes part in many cellular processes. Magnesium balance can be disturbed in multiple conditions, and differences in magnesium concentration can be responsible for numerous physiological and pathological processes. Magnesium deficiency is commonly associated with liver diseases, and may result from low nutrient uptake, greater urinary secretion, low serum albumin concentration, or hormone inactivation. In turn, low magnesium content in serum and liver tissue can lead to the progression of these diseases, due to a disruption in mitochondrial function, defective protein kinase C (PKC) translocation, inflammatory responses, oxidative stress, or metabolic disorders. Furthermore, magnesium supplementation can improve liver function in certain liver diseases. This paper comprehensively reviews the changes in magnesium concentrations associated with liver cirrhosis, alcoholic liver disease (ALD), liver cancer, and viral hepatitis, and explains how such changes may in turn impact these disease processes.

Keywords: Magnesium; liver cirrhosis; alcoholic liver disease (ALD); viral hepatitis; inflammatory response

Introduction

Magnesium is the second most abundant intracellular ion and the fourth most abundant cation in the body (1). It is widely distributed in almost all parts of the body and is highly compartmentalized, being present within the nucleus, cytoplasm, mitochondria, and endoplasmic reticulum (2,3). Magnesium plays an important role in lots of cellular processes, including DNA replication and repair, intermediary metabolism, ion transportation, cell proliferation, and signal transduction (4). Food and hard water are the main sources of body magnesium (5,6), which is vital for numerous physiological and pathological conditions. Magnesium deficiency can result from a number of diseases or the administration of certain medications, and can in turn predispose to many diseases, such as cardiovascular diseases, diabetes, and mental disorders (1).

The liver is one of the most vital organs, being involved in many aspects of metabolism, immune responses, and the synthesis of complex biomolecules. In addition, it regulates the transportation and distribution of many trace elements, including magnesium (3). The relationship between magnesium levels and liver disease is intriguing: in many liver diseases, patients are magnesium deficient, while insufficient magnesium levels in turn aggravate these diseases (3,7-9). In fact, every 100 mg increase in magnesium intake is associated with a 49% decrease in the risk of mortality due to all liver diseases (10).

Liver cirrhosis, alcoholic liver disease (ALD), liver cancer and viral hepatitis are common liver diseases. This review provides an overview of the differences in magnesium concentration associated with these diseases and whether such differences might affect disease processes.

Magnesium and liver cirrhosis

Cirrhosis is characterized by magnesium deficiency

Liver cirrhosis is the end stage of a variety of liver diseases, and is characterized by the disruption of liver structure, fibrosis, and the formation of regenerative nodules (11). Patients with liver cirrhosis usually have low body magnesium levels (12-14). Since our understanding of the mechanisms involved in magnesium homeostasis has improved, it has been shown that both serum and cellular magnesium levels are significantly lower in cirrhosis patients (3). Several mechanisms may account for this situation. Liver function is impaired in cirrhosis, and some patients develop portal hypertension, resulting in the development of gastroesophageal varices and intestinal edema. Magnesium supply may be poor because of malnutrition and lower absorption in the distal jejunum. In addition, the liver synthesizes albumin, which is an important transporter of magnesium in the circulation. Serum albumin decreases significantly in cirrhosis patients, such that magnesium transportation and balance may be disturbed. The inactivation of many hormones also takes place in the liver, and if this function is impaired, the resulting higher serum levels of aldosterone, growth hormone, and glucagon enhance the excretion of urinary magnesium. In addition, magnesiuric diuretics (such as furosemide) are often used in cirrhotic patients to alleviate ascites, but this also increases the excretion of magnesium into the urine (15). Finally, many cirrhosis patients have a long history of alcohol intake, and magnesium deficiency is universally recognized in chronic alcoholics (8). The mechanism of this association will be explored below.

Magnesium insufficiency aggravates cirrhosis

It was shown by Rayssiguier that hepatic magnesium loss is associated with greater collagen deposition in the liver (16). This observation might suggest that a decrease in hepatic magnesium content may lead to the aggravation of hepatic cirrhosis. Among patients with liver diseases, only 15–20% progress to cirrhosis (8). Thus, although investigations are lacking to date, there is a significant possibility that the patients that progress to cirrhosis may be those with particularly abnormal hepatocyte magnesium concentrations.

A number of studies have focused on exploring the reason why low magnesium levels result in the deterioration of liver cirrhosis.

As is widely known, magnesium is highly compartmentalized, being present in mitochondria in particular, where it is an important cofactor involved in metabolic function. In cirrhosis, a reduction in intracellular magnesium content has a negative impact on mitochondrial bioenergetics, which heavily depend on the appropriate intramitochondrial magnesium concentration (17,18). When mitochondrial function is impaired, oxidation in the hepatocyte is affected, which is associated with a 17% reduction in ATP production and hepatocyte damage. The subsequent liver repair process leads to additional fibrosis and worsens the cirrhosis.

Recent studies have found that (protein kinase Cε) PKCε can regulate fibrinogen deposition, and although these findings were made in cardiac tissue (19,20), this enzyme may also regulate fibrinogen deposition in the liver. The PKCs are a family of protein kinase enzymes that regulate the function of many cellular proteins. Activated PKC translocation induces the accumulation of magnesium within the cell, and PKCε displays the highest affinity for magnesium (21). An Mg^{2+} concentration of 1 mM is enough for PKCε activation and translocation, and is well within the normal concentration range of free cytoplasmic Mg^{2+} (22). Hence, it may be that lower magnesium concentrations in cirrhosis patients would lead to the defective translocation of PKCε to the cell membrane, which in turn would result in lower Mg^{2+} accumulation within the hepatocyte. This further reduction in cytoplasmic magnesium would exacerbate the reduction in PKCε activity, generating a positive feedback loop. This decrease in PKCε translocation and activity in liver cells increases fibrinogen and collagen deposition, which aggravates cirrhosis.

In the 1930s, clinical signs of inflammation were observed in magnesium-deficient rats (7), which displayed erythema, hyperemia, and splenomegaly (23). Thereafter, many investigators have recognized these pathologies in association with inflammation (24-27). In blood, the most prominent effect is leukocytosis, which may arise from cellular hyperplasia in the bone marrow and higher levels of substance P (28,29). In the liver, there is greater infiltration with leukocytes and macrophages, the activities of both of which are improved in magnesium-deficient animals (30), along with that of Kupffer cells. As a consequence, IL-6 concentration rises and stress-induced overproduction of TNF-α is apparent (31).

The underlying mechanisms of the inflammatory response in magnesium deficiency are not clear, but the following events may be involved (32-34). Firstly, the
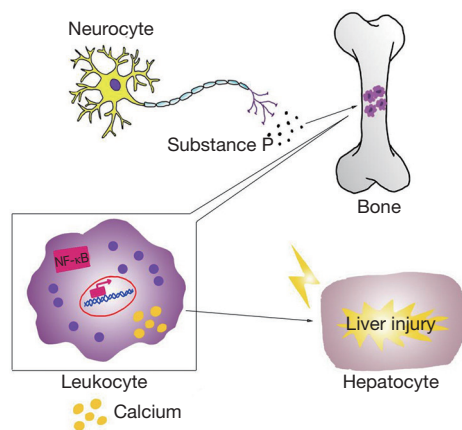
Figure 1 Mechanisms of the inflammatory response mediated liver injury in magnesium deficiency. Magnesium deficiency activates neuroendocrinological pathways and increases the production of neuromediators, such as substance P. Elevated substance P results in leukocytosis in the bone marrow. Decreased magnesium lead to further activation of these leukocytes through increased intracellular calcium and regulation of NF-κB, which then move to the liver and cause liver injury. NF-κB, nuclear factor-κB.

activation of inflammatory cells is involved in signal transduction, in which intracellular Ca^{2+} plays a vital role. We have observed that *in vitro* stimulation leads to a greater Ca^{2+} response (35). However, magnesium is a natural calcium antagonist (36); therefore, it is likely that a lower extracellular magnesium concentration would lead to an increase in intracellular calcium, triggering inflammation. Consequently, oral magnesium administration and higher intracellular magnesium concentrations may have beneficial anti-inflammatory effects (37,38). Secondly, the induction of inflammation by magnesium deficiency should be considered alongside the role of neuromediators, which are also important in inflammation. Mental stress alone can incite an inflammatory response (39), but in addition, the nervous and immune systems interact with one another. Magnesium deficiency initiates a systemic stress response by activating neuroendocrinological pathways, through greater production of neuromediators, such as substance P (33), which can cause an inflammatory response. Thirdly, the activation of nuclear factor-κB (NF-κB) may be one of the major mechanisms whereby an inflammatory response is initiated due to magnesium deficiency. The NF-κB family consists of a group of transcription factors that are crucial in the regulation of inflammatory responses, through

regulation of inflammatory gene expression, including that of numerous cytokines (40). Inappropriate regulation of NF-κB is involved in a wide range of inflammatory disorders. However, there is specific evidence for a role in the effects of magnesium deficiency, because Altura *et al.* (34) found that in cultured canine cerebral vascular smooth muscle cells, decreased extracellular magnesium concentrations induce lipid peroxidation and the activation of NF-κB.

When the magnesium content of liver cells is low, leukocytes and macrophages become very active locally, releasing many inflammatory cytokines and recruiting more inflammatory cells to the liver (30). This inflammatory response causes damage to liver cells and the repair process that follows involves fibrosis, which aggravates liver cirrhosis (*Figure 1*).

Previous studies have shown that reactive oxygen species (ROS) play a crucial role in hepatic fibrogenesis (3,7,8). Various liver injuries, caused for example by alcohol abuse, hepatitis B virus (HBV) infection, or chronic cholestasis, can increase hepatic ROS concentrations. ROS are directly fibrogenic, because they stimulate the proliferation and activation of hepatic stellate cells (HSCs). HSCs are the main cell type responsible for fibrosis in the liver. Quiescent HSCs are desmin-positive perisinusoidal cells, which are also responsible for the storage of vitamin A. Once stimulated, quiescent HSCs transform to activated myofibroblasts, becoming the main pro-fibrotic cell type and producing type I collagen, which is the key extracellular matrix component in the liver (11,41).

Activation of HSCs is the result of the presence of free radicals and lipid peroxidation products, which activate mitogen-activated protein kinase (MAPK) pathways, NF-κB signaling, and c-myb. Greater expression of fibrosis-related genes, including those encoding transforming growth factor-β1 (TGF-β1), α-smooth muscle actin (α-SMA), and type I collagen, are found in activated HSCs. TGF-β1 is one of the key pro-fibrotic cytokines that is mitogenic in HSCs (42,43). It also activates the Smad-signaling pathway and can cause hepatic fibrosis experimentally (44). The administration of antioxidants, such as α-tocopherol, can prevent such fibrosis.

Magnesium as an anti-cirrhotic therapy

Having established that magnesium deficiency can aggravate liver cirrhosis, it is of interest whether magnesium intake

could ameliorate this pathology. *In vivo* studies have shown that magnesium administration can alleviate cirrhosis, with both acetylcysteine magnesium and magnesium lithospermate B (MLB) having similar effects (44,45). After 8 weeks' treatment with acetylcysteine magnesium, TGF-β1, nitric oxide, total (tNOS) and inducible (iNOS) nitric oxide synthase levels were significantly lower in cirrhotic tissue, and hepatic lymphocyte infiltration and formation of pseudolobuli were alleviated (46). In a rat model of cirrhosis, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were significantly lower following oral MLB administration. This was because MLB strongly suppressed H_2O_2-induced ROS generation and inhibited NF-κB transcriptional activation in HSCs. In addition, it suppressed platelet-derived growth factor (PDGF)-induced HSC proliferation and expression of α-SMA, TGF-β, and type I collagen (46). These results suggest that magnesium might have potential as a novel therapy for liver cirrhosis.

Few studies have investigated the association between magnesium level and viral hepatitis. The only report we have identified showed that magnesium supplement can prevent HCV replication by binding to hepatitis C virus NS3 helicase (47).

Magnesium deficiency and ALD

Alcohol intake causes magnesium loss

Chronic alcohol abuse remains one of the most important causes of liver disease (48,49). ALD is one of a class of diseases caused by excessive alcohol intake, ranging from fatty liver to alcoholic hepatitis and alcoholic cirrhosis. Fatty liver (alcoholic steatosis) is the most common syndrome and the earliest type of ALD, and is characterized by the excessive accumulation of lipid inside hepatocytes. It is benign and reversible, seldom progressing to alcoholic hepatitis and cirrhosis. Alcoholic hepatitis (alcoholic steatohepatitis) is a more severe type of ALD, and is characterized by hepatocyte injury, accompanied by acute or chronic inflammation. About 40% of such patients will progress to alcoholic cirrhosis, a form of the liver cirrhosis mentioned above. In ALD, serum ALT, AST, and α-glutamyltransferase (GGT) concentrations are usually high, and the serum levels of these enzymes are often used as markers for the diagnosis of ALD.

Clinical magnesium deficiency is now recognized frequently among ALD patients, not only in the serum, but also intracellularly (8), with the degree of deficiency being directly proportional to the severity of the disease. Experimental research has shown that consumption of 6% ethanol in water for 3 weeks leads to a marked decrease in total tissue magnesium content in rats (50). Urinary magnesium excretion increases 2–3-fold upon alcohol consumption, and this occurs independently of glomerular filtration rate, renal plasma flow, or the administration of magnesium diuretics (3,51). The greater renal excretion of magnesium might be the result of greater lactate production and the accumulation of organic acids, which form complexes with magnesium and impair its reabsorption in the renal tubules (52). Another explanation is that alcohol or its intermediate metabolites might have a direct effect on magnesium transporters in the renal tubular membrane (3).

Recently, evidence has accumulated which indicates that two magnesium transporter systems exist in the plasma membrane of all eukaryotic cells: Na^+-dependent and Na^+-independent transporters (2,22). Eukaryotic cells tightly control magnesium transport across the plasma membrane through these two kinds of transporters, under a variety of physiological conditions. These transporters involve channels (TRPM6 and TRPM7), solute transport carriers (SLC41-A1 and A2), and other proteins (e.g., MagT1, MMgT1, MMgT2 and ACDP2) (53). The Na^+-dependent Mg^{2+} transporter is a Na^+/Mg^{2+} exchanger that is activated via a cAMP-dependent pathway (54-56), and can also operate in reverse mode (57).

Alcohol consumption is associated with a reduction in liver Mg^{2+} content (58). Acute alcohol administration affects the Na^+/Mg^{2+} exchanger as follows. It affects G protein signaling, leading to greater cAMP generation within hepatocytes, which activates the PKC pathway and disrupts PKCε translocation to the cell membrane (59-61), resulting in greater magnesium extrusion via the Na^+/Mg^{2+} exchanger. Biochemical analysis also indicates that Mg^{2+} loss by hepatocytes is the result of a decrease in cellular ATP concentrations (62,63), which is consistent with magnesium deficiency being characterized by markedly lower Mg^{2+} content in the mitochondria and cytoplasm, the two main cellular compartments containing both Mg^{2+} and ATP (64). Chronic alcohol administration results in an impairment of the function of both Na^+-dependent and Na^+-independent Mg^{2+} transporters (by ~75%) (50,65). The same defect in PKCε translocation is observed, and the magnesium deficiency is associated with a 17% decrease in cellular ATP concentration (50).
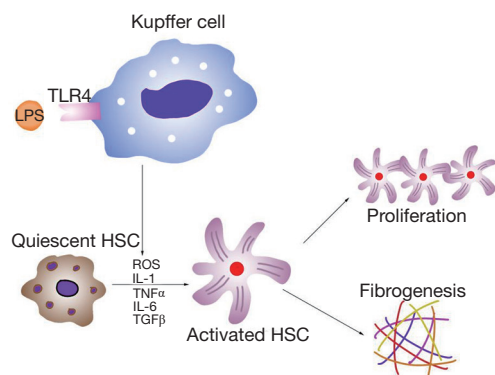
Figure 2 The role of Kupffer cells and HSCs in progression of ALD. In ALD patients, high levels of circulating LPS bind to TLR4 and activate Kupffer cells in liver. A large amount of ROS and pro-inflammatory cytokines (TNF-α, TGF-β, IL-1 and IL-6) are generated and released. When received oxidative and inflammatory stimulation, quiescent HSCs transform into activated HSCs, resulting in HSCs self-proliferation and fibrogenesis. HSC, hepatic stellate cell; ALD, alcoholic liver disease; LPS, lipopolysaccharide; TLR4, toll-like receptor type 4; ROS, reactive oxygen species; IL, interleukin.

Magnesium deficiency worsens ALD

ALD patients suffering magnesium deficiency have been shown in both *in vitro* and *in vivo* studies to be more sensitive to septic shock during endotoxin infection (31,35). After endotoxin stimulation, magnesium-deficient phagocytic cells demonstrate a stronger immune response, which is consistent with the higher death rate observed in magnesium-deficient rats (31).

Other studies have also found that ALD patients have high levels of circulating endotoxins (66). In magnesium deficient liver, endotoxin activates Kupffer cells through toll-like receptor type 4 (TLR4), and these cells play a key role in the inflammatory responses in the liver. In activated Kupffer cells, a large amount of ROS is generated by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which becomes the main source of ROS in the liver (67). Pro-inflammatory cytokines, such as TNF-α, TGF-β, interleukin (IL)-1 and IL-6, as well as the chemokine IL-8, are also released from activated Kupffer cells (68,69). Of these cytokines, TNF-α is the key mediator of ALD. ROS and cytokines activate HSCs and accelerate the progression of ALD to the cirrhotic stage (*Figure 2*). Magnesium administration before an endotoxin challenge can reduce the severity of the disease condition and improve

survival rate in rats (31). In addition, magnesium treatment decreases serum GGT and AST in alcoholic patients (70). Thus, we strongly recommend magnesium supplementation in ALD patients to prevent septic shock and slow disease progression.

Impairment in fatty acid and glucose metabolism is a key component of the pathogenesis of ALD, which initially manifests as alcoholic steatosis. Although it has been shown that alcohol can directly impair fatty acid oxidation and glucose metabolism, recent studies have also found that low magnesium content is another cause of the metabolic disorders present in ALD patients (71).

Fatty acid oxidation mainly takes place in mitochondria, and magnesium is an important cation for mitochondrial oxidative function. Low mitochondrial magnesium affects the nicotinamide adenine dinucleotide (NAD) H/NAD+ redox potential in liver, which in turn impairs fatty acid oxidation and tricarboxylic acid cycle activity (31,33). Indeed, in magnesium deficiency, obvious defects are the marked increase in triglyceride levels and the reduction in the concentration of serum high density lipoproteins (HDL) (71). An accumulation of triglyceride-rich lipoproteins (TGRLP), which is associated with a marked increase in plasma apo B concentration, is also observed (72). The reduction in HDL is accompanied by lower plasma levels of both apo E and apo A1. In addition, experiments have shown there are complex changes in the expression of genes involved in lipid metabolism in magnesium-deficient rats (72). The lipid metabolism disorder resulting from magnesium deficiency may also be related to the inflammatory response, because the same condition has been observed in rats with activated immune responses (73).

In terms of glucose metabolism, large epidemiologic studies have shown an association between lower serum magnesium and insulin resistance (74,75). Recent studies have also shown that magnesium deficiency aggravates insulin resistance, because of the associated inflammatory response and oxidative stress (76,77).

In summary, magnesium deficiency in ALD patients represents a significant additional factor that can further disrupt normal metabolism and cause greater lipid deposition, both in the liver and other tissues.

Magnesium and liver cancer

Magnesium is an enzyme cofactor involved in the DNA repair mechanisms which plays a major role maintain genomic stability and fidelity. It has critical roles in the

modulation of cell cycle progression, cell proliferation, differentiation, and apoptosis. Magnesium deficiency could therefore cause dysfunction of these systems, leading to DNA mutations, which may result in tumorigenesis (1,4).

The relationship between liver cancer and body magnesium content has not been fully established, so whether liver cancer leads to reductions in serum and tissue magnesium concentrations is still unknown. However, we have shown that magnesium supplementation can protect the liver and reduce the morbidity and mortality associated with liver cancer (78).

An *in vitro* study has shown that magnesium cantharidate has an inhibitory effect on human hepatoma SMMC-7721 cell proliferation by blocking the MAPK signaling pathway. Specifically, the phosphorylation levels of C-jun N-terminal kinase (JNK) and extracellular signal-related kinase (ERK) decrease significantly upon treatment (79).

Magnesium plays a vital role in inhibiting the progression of HBV infection to hepatocellular cancer (HCC). HBV infection remains one of the most frequent cause of HCC in the world (80,81). Once an infection is established, the viral regulatory protein hepatitis B virus X (HBx) amplifies the TGF-β signal, which works as a tumor promoter to induce epithelial-mesenchymal transition (EMT), enhancing cancer metastasis and invasion by HCC. However, magnesium administration can increase the expression of protein phosphatase magnesium dependent 1A (PPM1a), blocking TGF-β signaling by dephosphorylating of p-Smad2/3, and thus preventing the transcription of specific genes needed for HCC growth (9).

Finally, magnesium deficiency in cancer patients increases the risk of cancer metastasis to the liver (82).

Conclusions

Magnesium status is closely linked with liver function. Liver diseases have a significant effect on body magnesium content, and magnesium levels in turn influence these disease processes. In liver cirrhosis and ALD, patients show magnesium deficiency that results from low dietary uptake, greater urinary secretion, lower plasma albumin concentrations, and hormone inactivation. Conversely, magnesium deficiency aggravates cirrhosis and ALD, and can cause liver cancer progression, due to disrupted mitochondrial function, defective PKC translocation, inflammatory responses, oxidative stress, and metabolic disorders. Magnesium supplementation can not only preserve liver function, but also slow the progression

of liver disease, and reduce the mortality associated. Although these findings provide a foundation, there is still a great deal to investigate in this field. Few studies have investigated the relationship between magnesium and HCC or viral hepatitis. In addition, the reason why magnesium deficiency triggers an inflammatory response is still not fully understood, and no clinical studies have explored the therapeutic effects of magnesium in liver patients. In conclusion, this review demonstrates the importance of links between magnesium and liver function or disease, and implies that novel therapeutic approaches targeting magnesium may be used to improve liver function in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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