Exploring the Role of Magnesium Deficiency in Liver Cirrhosis: A Comprehensive Review

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Abstract

The in-depth analysis explores the link between low magnesium levels and liver cirrhosis, a chronic condition marked by the development of fibrous bands and nodular regeneration due to ongoing liver damage. It explains the vital role of magnesium, an essential ion within cells, in various biological processes crucial for maintaining liver function. Despite advancements in our understanding of cirrhosis, the causes and treatment of mineral metabolism issues remain unknown. The review emphasizes the crucial role of magnesium in maintaining liver function and its direct correlation with the progression of cirrhosis. Cirrhosis is exacerbated by magnesium deficiency, particularly in liver diseases linked to alcohol consumption. Research is looking into magnesium supplementation as a potential treatment. Preliminary results indicate benefits such as reducing oxidative stress, improving gut barrier function, and altering inflammatory pathways in cirrhosis. Further studies are needed to verify the effectiveness, appropriate dosage, and long-term impacts of magnesium supplementation in patients with cirrhosis. Correcting magnesium deficiency can improve treatment methods and patient outcomes in cirrhosis, ultimately benefiting liver health. This could lead to cirrhotic patients experiencing a better quality of life with fewer complications.

Keywords: Magnesium, Liver, Cirrhosis, Oxidative Stress, Mineral Metabolism

Abbreviations:

DNA Deoxyribonucleic acid
RNA Ribonucleic acid
mRNA Messenger Ribonucleic Acid
ATP Adenosine Triphosphate
ALD Alcoholic-related Liver Disorder
NAFLD Non-alcoholic fatty liver disease
NASH Non-alcoholic steatohepatitis

Introduction

A chronic liver injury's histological reaction, cirrhosis is described as the development of regenerating nodules encircled by fibrous bands. This condition causes portal hypertension and end-stage liver disease. Understanding the stages of liver cirrhosis is crucial for effective treatment. The two stages of liver cirrhosis are compensated and decompensated. [1]

In compensated liver cirrhosis, patients have a relatively favourable prognosis with a median survival time of around 12 years. However, if the disease progresses to a decompensated stage, the survival rate drops significantly to 2-4 years. Decompensation is associated with the onset of serious complications, such as ascites, hepatic encephalopathy, variceal bleeding, and hepatorenal syndrome, all of which can lead to a rapid deterioration of liver function and overall health. It is crucial to monitor the progression of liver cirrhosis carefully and manage any complications promptly to improve patient outcomes and prolong survival. This highlights the importance of early detection and management of compensated cirrhosis to prevent progression to decompensation. Regular monitoring and timely interventions can significantly impact patient outcomes and quality of life.[1]

For quite some time, mineral metabolism disorders have been linked to hepatic illnesses, but their root causes and possible complications are still shrouded in mystery. Certain components, besides acting as catalyst cofactors, have a crucial role in the operation of metalloproteins and metalloenzymes in the human body. These substances are primarily processed in the liver, which has made the study of minerals in liver problems a highly interesting subject in recent years. However, despite the attention that this field of research has received, the exact reasons behind mineral metabolism disorders and liver diseases remain elusive. One plausible factor to consider is that cirrhosis of the liver and other hepatic pathologies involve the purposeful degradation of liver tissue, which could impact the levels of crucial minerals in the body. This could have a significant effect on the pathological process of hepatic fibrosis. Further research is necessary to gain a better understanding of the intricate relationship between mineral metabolism and liver health[2].

Recent developments in the aetiology, natural history, and therapy of cirrhosis-related comorbidities have improved management, increased life expectancy, and enhanced quality of life for cirrhotic patients. To further enhance outcomes for individuals with this illness, cirrhosis is still a major source of morbidity and mortality worldwide.

One of the four inorganic ions found in the human body, magnesium is the most prevalent intracellular ion after potassium. In order for DNA, RNA, and mRNA to remain stable, it is essential for them to bind to ribosomes. The reactions in which ATP is involved, such as the production of nucleotides, the utilization of glucose, protein, and fat, as well as the metabolism of nucleic acids, require magnesium and ATP as the substrate. These two compounds are crucial in many biological processes and play a vital role in maintaining the stability and functionality of genetic material.

One such process is the membrane-associated ATP-dependent sodium and potassium pump system, which plays a vital role in maintaining the cell's homeostasis. This system works to pump sodium ions out of the cells while simultaneously pumping potassium ions into the cells. This process is essential in regulating the concentration of ions within the cell, which in turn helps to maintain its osmotic balance. Apart from this, magnesium is a crucial mineral

that plays a vital role in maintaining the proper functioning of the human body. The natural serum magnesium levels in a healthy individual range from 1.7 to 2.3 mg/dl. Research has shown that serum magnesium levels are linked to both acute and chronic liver diseases. However, the degree of cirrhosis did not prove to be a decisive factor in determining a clear correlation.

Magnesium metabolism abnormalities can arise from a variety of conditions. Elevated serum magnesium levels are linked to acute liver disorders; this increase is correlated with elevated serum bilirubin levels. As the acute process begins to heal, the levels progressively return to normal. Alcoholic liver disorders and liver cirrhosis are associated with low serum magnesium levels.[4]

The purpose of this research is to explore the link between serum magnesium levels and different causes of cirrhosis, as well as how serum magnesium levels relate to the severity and consequences of this condition. These findings will expand our understanding of the potential role of magnesium in the onset and advancement of cirrhosis. By analyzing these connections, medical professionals can gain a more comprehensive understanding of how magnesium levels may affect liver function and the overall well-being of patients. Additionally, this study has the potential to offer valuable insights for future investigations and treatment strategies for those affected by cirrhosis.

Lack of magnesium is a hallmark of cirrhosis.

The liver is an important organ responsible for many vital functions, including digestion, metabolism, and removal of toxins from the body. Cirrhosis impairs liver function, leading to a decrease in the production of essential proteins and enzymes, and in some cases, portal hypertension develops. This can cause increased pressure in the veins that carry blood from the intestines to the liver, leading to the development of intestinal edema and gastroesophageal varices.

Patients with cirrhosis may also experience low absorption of magnesium in the distal jejunum and malnutrition, which can contribute to insufficient magnesium supply in the body. Additionally, the liver plays a crucial role in producing albumin, a protein that acts as a magnesium transporter in the bloodstream. In patients with cirrhosis, the production of albumin is significantly reduced, which can disrupt the balance of magnesium transportation and lead to a decrease in serum magnesium levels.

Furthermore, the liver is responsible for inactivating numerous hormones in the body. If liver function is compromised, these hormones can accumulate in the bloodstream, leading to increased excretion of magnesium in the urine. For instance, elevated blood levels of growth hormone, glucagon, and aldosterone can stimulate the kidneys to excrete more magnesium, leading to magnesium deficiency in patients with cirrhosis[7].

It is a well-established fact that low levels of magnesium are prevalent among patients suffering from liver cirrhosis. This can lead to various symptoms such as muscle weakness and cramps. Moreover, patients with liver cirrhosis may be at risk of experiencing seizures or irregular heart rhythms due to low magnesium levels[5,6] .

Exacerbation of Cirrhosis

According to Rayssiguier's research, there appears to be a potential link between hepatic magnesium deficiency and an increase in collagen deposition within the liver. This finding highlights the importance of maintaining proper levels of magnesium to avoid any potential negative impacts on liver health[8]. In instances where the magnesium levels in liver cells are depleted, certain immune cells such as leukocytes and macrophages tend to become exceptionally active within the affected region. As a result of their hyperactivity, they start discharging a significant amount of inflammatory cytokines that subsequently attract more inflammatory cells to the liver. This situation can lead to an increase in inflammation within the affected area[9].

This inflammatory reaction damages the liver cells, and fibrosis is involved in the subsequent repair process, aggravating liver cirrhosis(fig.1).

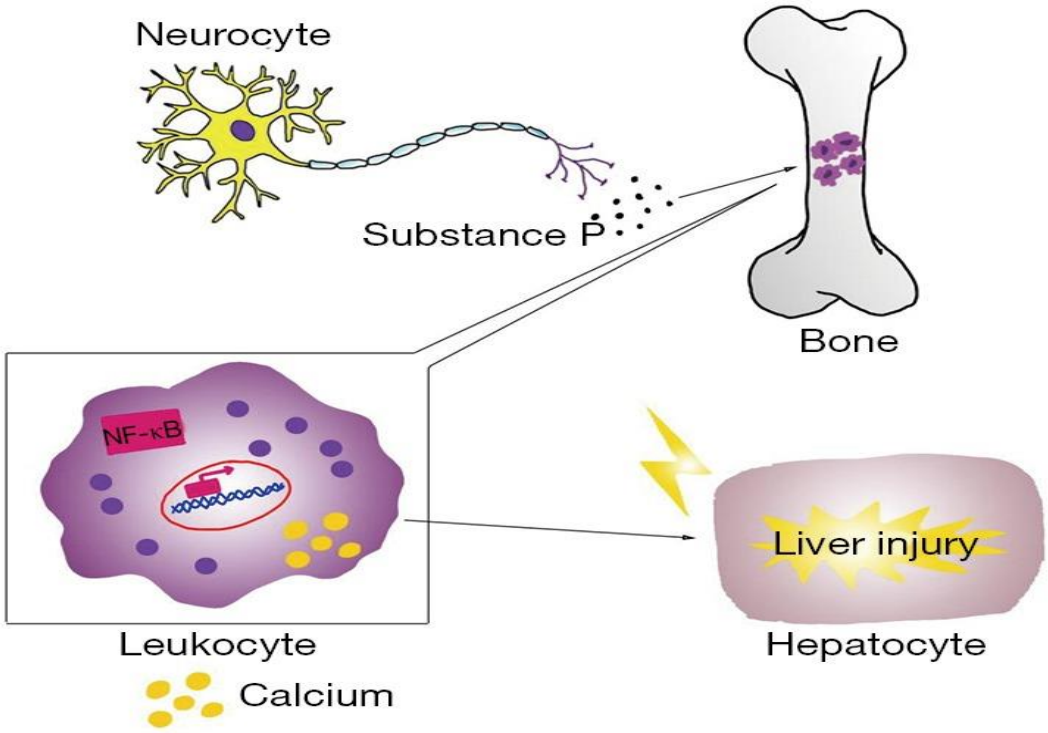

Fig.1 : Magnesium deficiency can cause liver damage through inflammation. It increases the production of neuromediators like substance P, which activates neuroendocrinological pathways and causes leukocytosis. Leukocytes become more activated due to increased intracellular calcium and NF-κB regulation resulting in liver damage[10].

While it is true that inflammation and fibrosis can contribute to liver cirrhosis, there are many other factors such as alcohol consumption, viral infections, and genetic predisposition that also play a significant role in the development of the disease.

It is noteworthy to mention that a deficiency of magnesium in one's diet has been associated with ALD. The correlation between the two is quite interesting and worth considering.Magnesium deficiency has been found to have a strong correlation with ALD.

Alcohol depletes magnesium.

Alcohol-related liver disorders (ALDs) include fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. These diseases are all brought on by excessive alcohol consumption. The most prevalent condition and the original form of ALD is fatty liver (alcoholic steatosis), which is defined by an abnormal buildup of lipid inside hepatocytes. It rarely develops into alcoholic hepatitis and cirrhosis and is benign and reversible. A more severe form of ALD known as "alcoholic hepatitis" (also known as "alcoholic steatohepatitis") is characterised by acute or chronic inflammation along with hepatocyte damage. Of these patients, about 40% will develop alcoholic cirrhosis, which is a variant of the liver cirrhosis previously described.

Nowadays, it is common knowledge that individuals with ALD have a clinical magnesium deficit, both intracellularly and in the serum , with the severity of the deficiency closely correlated with the severity of the disease. Rats' total tissue magnesium level significantly decreases after three weeks of consuming 6% ethanol in water, according to experimental research . Drinking alcohol causes a two- to three-fold increase in urinary magnesium excretion, which happens regardless of renal plasma flow, glomerular filtration rate, or the use of magnesium diuretics . Increased lactate production and the buildup of organic acids, which combine with magnesium to hinder its reabsorption in the renal tubules, may be the cause of the increased magnesium excretion in the kidneys .

Recent research has revealed that each eukaryotic cell's plasma membrane contains two distinct magnesium transporter systems.These transporter systems are known as Na+-dependent and Na+-independent transporters. Magnesium transport across the plasma membrane by these two types of transporters is strictly regulated by eukaryotic cells, depending on various physiological situations[11].

In addition to these transporters, there are several other proteins, channels, and solute transport carriers that are involved in the transport of magnesium across the plasma membrane. These include MagT1, MMgT1, MMgT2, and ACDP2 proteins, TRPM6 and TRPM7 channels, and SLC41-A1 and A2 solute transport carriers.

The transport of magnesium across the plasma membrane is a complex process that involves the activation of the Na+-dependent Mg2+ transporter through the cAMP-dependent route. This transporter acts as a Na+/Mg2+ exchanger and can also function in reverse mode. With the help of these transporters and other proteins, magnesium is transported in and out of eukaryotic cells, helping to regulate various physiological processes.

It has been observed that excessive alcohol consumption can lead to a decrease in the levels of magnesium in the liver. The acute administration of alcohol has been found to affect the Na+/Mg2+ exchanger, which plays a crucial role in maintaining magnesium levels in the body[12]. This results in the production of more cAMP by hepatocytes, which activates the PKC pathway and prevents PKCε from translocating to the cell membrane. As a result, magnesium extrusion through the Na+/Mg2+ exchanger is increased. Magnesium deficiency is associated with a marked reduction in Mg2+ content in both the mitochondria and cytoplasm, which are the two primary cellular compartments that contain both Mg2+ and ATP. The loss of Mg2+ by hepatocytes is caused by a decrease in cellular ATP

concentrations. Furthermore, long-term alcohol consumption has been found to reduce the activity of Mg2+ transporters that are both Na+-dependent and Na+-independent by approximately 75%[13].

Exploring the Potential of Magnesium Supplementation in the Management of Cirrhosis: A Promising Therapeutic Avenue

Studies have revealed that liver cirrhosis can be aggravated by a deficiency of magnesium. Therefore, it is worth exploring the possibility of using magnesium supplementation to ameliorate this condition. In vivo experiments have demonstrated that administering magnesium can alleviate cirrhosis. Magnesium lithospermate B (MLB) and acetylcysteine magnesium have shown similar benefits[14], while magnesium isoglycyrrhizate (MgIG) appears to hold potential as a therapy for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH)[15].

The use of acetylcysteine, magnesium, TGF-β1, nitric oxide, total (tNOS) and inducible (iNOS) nitric oxide synthase, has shown promising results in reducing cirrhotic tissue nitric oxide synthase levels, hepatic lymphocyte infiltration and pseudolobuli formation in an 8-week treatment course[16]. Additionally, an oral treatment with MLB was found to significantly reduce blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in a rat model of cirrhosis. This was achieved by MLB's potent suppression of H2O2-induced ROS production and inhibition of HSCs' NF-κB transcriptional activation. Moreover, MLB inhibited the proliferation of HSCs stimulated by platelet-derived growth factor (PDGF) and the production of type I collagen, TGF-β, and α-SMA. These results suggest that magnesium may be a promising treatment option for liver cirrhosis.

A structurally modified substance called magnesium isoglycyrrhizinate (MgIG) is made from Glycyrrhiza uralensis Fisch extract. This chemical has been the subject of numerous studies, which have demonstrated its effectiveness as a hepatoprotective agent. In fact, MgIG is known to have a good hepatoprotective effect, making it a promising treatment option. It can be administered via injection, and its potential benefits are certainly worth exploring.

As the NF-κB signalling pathway is known to be crucial in controlling the immune response to infection, previous research has shown that Magnesium Isoglycyrrhizinate (MgIG) has the ability to prevent hepatic inflammatory injury. As inflammatory mediators like cytokines and chemokines are known to cause and worsen liver inflammation, MgIG has been demonstrated to suppress their production.

Additionally, MgIG has been found to upregulate the expression of tight junction proteins, which are essential for maintaining the integrity of the intestinal barrier[16]. By doing so, it helps to decrease intestinal permeability, which is an important factor in the development of liver disease. Moreover, MgIG has been found to reduce the accumulation of lipids in the liver, which is a hallmark of non-alcoholic fatty liver disease (NAFLD). Studies have shown that oleic acid-induced cell death was also prevented by MgIG, indicating that it has a protective effect against liver injury caused by free fatty acids. Despite these promising findings, very few investigations have explored the possibility of MgIG protecting against NAFLD/NASH.

The NAFLD/NASH model was created by subjecting C57bl/6 mice to a high-fat diet (HFD) supplemented with 1% dextran sulphate sodium (DSS) for a period of 12 weeks. During the last seven weeks of this period, the mice were administered MgIG via alimentation. The effects of MgIG therapy on multiple parameters associated with NAFLD/NASH, such as inflammation, liver damage, hepatic steatosis and fibrosis, were evaluated. Hepatocyte apoptosis and hepatic oxidative damage were also monitored. Additionally, the impact of MgIG on intestinal permeability and the levels of short-chain fatty acids (SCFA) in the intestinal contents of the mice were investigated to assess its overall effectiveness[16].

When NAFLD/NASH mice were given MgIG, the effects of the HFD were mitigated, hepatic steatosis and fibrosis were induced less severely, serum biochemical levels were enhanced, hepatocyte apoptosis and oxidative stress in the liver were decreased, intestinal permeability was enhanced, and faecal SCFA levels were elevated.

Conclusion

In opinion, magnesium deficiency exacerbates liver cirrhosis, particularly in alcohol-related liver disorders. Studies suggest that magnesium supplementation, including compounds like magnesium lithospermate B and magnesium isoglycyrrhizinate, can mitigate cirrhosis-related complications by modulating inflammatory pathways, reducing oxidative stress, and improving intestinal barrier integrity. Magnesium supplementation shows promise in alleviating symptoms and attenuating liver damage in conditions like NAFLD and NASH.
However, further research is needed to validate its efficacy, dosage, and long-term effects in cirrhotic patients. Addressing magnesium deficiency could be integrated into comprehensive cirrhosis management strategies alongside lifestyle modifications and pharmacological therapies. Overall, exploring magnesium supplementation offers a potential therapeutic avenue to improve liver health and patient outcomes in cirrhosis.

References

1. Schulz, M. S., Angeli, P., & Trebicka, J. (2024). Acute and non-acute decompensation of liver cirrhosis (47/130). Liver International.
2. Elin, R. J. (1988). Magnesium metabolism in health and disease. Disease-a-month, 34(4), 166-218.
3. Henry JB., Clinical Diagnosis and Management, 17th ed., W.B. Saunder Co. Philadelphia,157 (1984)
4. Gowda, P. G. M., & Tembad, M. M. (2015). Study of serum magnesium in liver diseases. Journal of Evolution of Medical and Dental Sciences, 4(18), 3047-3057.
5. Kar K, Dasgupta A, Vijaya Bhaskar M, et al. Alteration of micronutrient status in compensated and decompensated liver cirrhosis. Indian J Clin Biochem 2014;29:232-7. 10.1007/s12291-013-0349-5
6. Zhao XY, Li J, Wang JH, et al. Vitamin D serum level is associated with child-pugh score and metabolic enzyme imbalances, but not viral load in chronic hepatitis B patients. Medicine (Baltimore) 2016.

7. Koivisto M, Valta P, Hockerstedt K, et al. Magnesium depletion in chronic terminal liver cirrhosis. Clin Transplant 2002;16:325-8.
8. Rayssiguier Y, Chevalier F, Bonnet M, et al. Influence of magnesium deficiency on liver collagen after carbon tetrachloride or ethanol administration to rats. J Nutr 1985;115:1656-62.
9. Malpuech-Brugère C, Nowacki W, Daveau M, et al. Inflammatory response following acute magnesium deficiency in the rat. Biochim Biophys Acta 2000;1501:91-8.
10. Liu, M., Yang, H., & Mao, Y. (2019). Magnesium and liver disease. Annals of translational medicine, 7(20), 578.
11. Wolf FI, Torsello A, Fasanella S, et al. Cell physiology of magnesium. Mol Aspects Med 2003;24:11-26
12. Romani A, Scarpa A. Hormonal control of Mg2+ transport in the heart. Nature 1990;346:841-4.
13. Cefaratti C, Young A, Romani A. Effect of ethanol administration on Mg2+ transport across liver plasma membrane. Alcohol 2005;36:5-18.
14. Zhuang RX, Wang FG, Zhou HP, et al. The protective effects of N-acetylcysteine magnesium against liver cirrhosis with portalhypertension in rat. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2012;26:366-9
15. Xueying Lai, Hong Zhou, Yu Wan, Jiesi Kuang, Yuhui Yang, Limei Mai, Yumei Chen, Bin Liu,Magnesium isoglycyrrhizinate attenuates nonalcoholic fatty liver disease by strengthening intestinal mucosal barrier,International Immunopharmacology,Volume 128,2024,111429,ISSN 1567-5769,https://doi.org/10.1016/j.intimp.2023.111429.
16. Paik YH, Yoon YJ, Lee HC, et al. Antifibrotic effects of magnesium lithospermate b on hepatic stellate cells and thioacetamide-induced cirrhotic rats. Exp Mol Med 2011;43:341-9.