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How Magnesium Can Protect You From Liver Damage

Analysis by Dr. Joseph Mercola | February 29, 2024

STORY AT-A-GLANCE

- Acetaminophen overdose is one of the leading causes of liver injury in the U.S. and some parts of Europe, but magnesium may offer some protection
- The enzyme cytochrome p450 2E1 (CYP2E1) is involved, as it breaks down acetaminophen into toxic byproducts that can harm the liver in high concentrations
- In a study on mice, oral magnesium stimulated metabolism of gut bacteria called Bifidobacterium, which increased indole-3-carboxylic acid (I3C) levels; I3C inactivates CYP2E1
- Every 100-milligram increase in magnesium intake is linked with a 49% decrease in mortality risk from liver disease
- N-acetylcysteine (NAC), a precursor for glutathione biosynthesis, also protects against liver damage in cases of acetaminophen overdose

Magnesium, an essential mineral involved in more than 300 metabolic reactions,[1] may also play an important role in liver health. Due to the way it interacts with your gut microbiome, magnesium may offer protection from liver damage caused by one of the most common liver toxins — acetaminophen, also known as Tylenol.[2]

Acetaminophen overdose is one of the leading causes of liver injury in the U.S. and some parts of Europe. In these areas, acetaminophen is responsible for more than 50% of acute liver failure cases.[3]

Treatment for acetaminophen-induced liver failure is limited, with liver transplant the only option in severe cases, making liver injury caused by acetaminophen an emerging "public health issue."[4] Magnesium, however, has the potential to help, according to research published in Cell Host & Microbe.

Magnesium Alleviates Acetaminophen-Induced Liver Failure

When excess amounts of acetaminophen are metabolized, it depletes glutathione and increases N-acetyl-p-benzoquinone imine (NAPQI) levels, causing oxidative stress, DNA damage and cell death in the liver.[5] The enzyme cytochrome p450 2E1 (CYP2E1) is also involved, as it breaks down acetaminophen into toxic byproducts that can harm the liver in high concentrations.[6] As explained by the Cell Host & Microbe team:[7]

> *"During ALF [acute liver failure], toxins are normally metabolized by phase I enzymes such as cytochrome p450 2E1 (CYP2E1) and transformed into reactive species, which cause cell oxidative damage and liver failure.*
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> *Specifically, APAP can be transformed into N-acetyl-p-benzoquinone imine (NAPQI), which further attacks functional proteins and finally causes cell death. Restricting the harmful effects of reactive species is recognized as the main effective approach to alleviating ALF."*

In a study on mice, oral magnesium stimulated metabolism of gut bacteria called Bifidobacterium, which increased indole-3-carboxylic acid (I3C) levels. I3C inactivates CYP2E1, in turn reducing the generation of harmful reactive intermediates and oxidative damage. The study highlights the importance of magnesium for gut and liver health and demonstrates its bodywide benefits:[8]

> *"Although the importance of Mg [magnesium] in host cells has been investigated in depth, far less attention has been given to the interaction between the commensal microbiota and Mg. Indeed, akin to host cells, commensal bacteria also need Mg to survive, since the modulation of many enzymes requires the presence of key mineral elements, including Mg.*

Mg deficiency or exposure possibly alters commensal microbial function and further influences host pathophysiology … our findings show that the beneficial effect observed with oral Mg administration can likely be attributed to the interaction between Mg and commensals."

Magnesium May Promote the Growth of Liver-Protective Gut Bacteria

Further, the findings suggest Bifidobacterium may be hepatoprotective probiotics. The study evaluated the impact of four main species of Bifidobacterium, and all of them were protective against acute liver failure. They were also enriched by magnesium exposure, which means the mineral could potentially promote their growth. According to the team:[9]

"We speculate that Mg may stimulate the metabolism of Bifidobacterium, and the enhanced metabolic rate may be associated with elevated proliferation — namely, many growth and metabolic modulation proteins in Bifidobacterium may respond to Mg stimulation, which activates downstream pathways to activate metabolism and facilitate the growth of the bacteria. However, the detailed mechanism requires further investigation."

Since Bifidobacterium increased I3C levels, which effectively inhibits CYP2E1, it's possible it could be useful not only for acetaminophen-induced acute liver failure but also other types of liver failure, including that caused by alcohol. "Collectively, our findings may extend to the whole spectrum of chemicals that induce ALF," the researchers explained, adding:[10]

"In conclusion, our work identified Bifidobacterium and its metabolite I3C as potential targets for Mg upon oral intake, and I3C could inhibit harmful reactive intermediate formation by directly binding to CYP2E1 after APAP treatment, ultimately dampening hepatocyte damage and protecting against ALF. We provide a valuable approach, oral Mg intake, as a potentially safe and effective strategy to prevent CYP2E1-mediated ALF."

Magnesium Is Linked to Many Liver Diseases

Your liver, in addition to playing a role in metabolism, immune function and the synthesis of biomolecules, regulates the transport and distribution of magnesium.[11] Studies have revealed that magnesium deficiency is common in many patients with liver diseases, while insufficient levels may make liver disease worse.

It's even been found that every 100-milligram increase in magnesium intake is linked with a 49% decrease in mortality risk from liver disease.[12] For instance, magnesium deficiency is common in liver cirrhosis and alcoholic liver disease. Low magnesium levels aggravate these conditions due to:[13]

- Disrupted mitochondrial function
- Defective protein kinase C (PKC) translocation
- Inflammatory responses
- Oxidative stress
- Metabolic disorder

"Magnesium supplementation can not only preserve liver function, but also slow the progression of liver disease, and reduce the mortality associated," researchers wrote in the Annals of Translational Medicine.[14] Nonalcoholic fatty liver disease, which is often driven by insulin resistance, may also benefit from magnesium. According to scientists with Amrita Institute of Medical Science & Research Center in India:[15]

> *"Mg2+ [magnesium] is involved in regulating the proper functioning of insulin by decreasing the tyrosine kinase activity, and its deficiency may cause insulin resistance. Mg2+ level is also altered in non-diabetic patients and in hepatic steatosis."*

Magnesium deficiency may also promote the progression of liver cancer.[16] The researchers continued:[17]

"Mg2+ plays an important role in enzyme reaction by mediating the stability of the genome, which is important in regulating cell proliferation, differentiation, and apoptosis. Thus Mg2+ deficiency may impair this mechanism, causes DNA mutation or initiation of the cancer process.

Liver cancer is reported to be associated with Mg2+ deficiency, and magnesium supplementation through drinking water is reported to have a beneficial effect in it."

Many People Are Deficient in Magnesium

As noted in review published in BMJ Open Heart, "Because of chronic diseases, medications, decreases in food crop magnesium contents, and the availability of refined and processed foods, the vast majority of people in modern societies are at risk for magnesium deficiency."[18]

According to this review, most fail to meet the recommended daily allowance (RDA) for magnesium; 48% of Americans do not get sufficient magnesium from their diet. Among postmenopausal women with osteoporosis, the rate of magnesium deficiency is 84%.[19]

Type 2 diabetics also tend to be more prone to magnesium deficiency, and magnesium depletion has been found in 75% of patients with poorly controlled Type 2 diabetes based on serum magnesium status.[20] Magnesium is necessary for the healthy functioning of most cells, especially your heart, kidneys and muscles. Low levels impede cellular metabolic function and deteriorate mitochondrial function.

Magnesium is also intricately involved in psychoneuroendocrine system activity and plays a role in biological pathways associated with the development of depression.[21] It's also required for the activation of vitamin D, and deficiency may hamper your ability to convert vitamin D from sun exposure and/or oral supplementation.

What's the Best Source of Magnesium?

Dark green leafy vegetables are a good source of magnesium, and juicing your greens is an excellent way to boost your intake, although supplementation is likely necessary for most people. Many factors, including alcohol consumption, prescription drugs such as statins, stress and heavy sweating,[22] can affect your magnesium absorption and excretion.

When it comes to oral supplementation, my personal preference is magnesium threonate, as it appears to be the most efficient at penetrating cell membranes, including your mitochondria and blood-brain barrier. Magnesium is also absorbed through your skin, so you can use a topical solution or take Epsom salt (magnesium sulfate) baths to increase your levels.

The RDA for magnesium is around 310 to 420 milligrams (mg) per day depending on your age and sex,[23] although some researchers believe we may need as much as 600 to 900 mg/day for optimal health. I believe many may benefit from amounts as high as 1 to 2 grams (1,000 to 2,000 mg) per day.

As a general rule, I recommend starting out with a dose of 200 mg of oral magnesium citrate per day, gradually increasing your dose until you develop slightly loose stools. To use this method, you need to use magnesium citrate, as it's known for having a laxative effect. Once you know your cutoff, you can switch to other forms if you like.

NAC Can Protect Against Acetaminophen Overdose

While the featured study raises intriguing points that magnesium may be useful for staving off liver damage due to acetaminophen, N-acetylcysteine (NAC), a precursor for glutathione biosynthesis, is also protective in such cases.

As mentioned, one way acetaminophen causes liver damage is by depleting glutathione. NAC helps increase glutathione, which is why anyone who overdoses on acetaminophen receives large doses of NAC in the emergency room. NAC also reduces acetaldehyde toxicity,[24] which causes many hangover symptoms. NAC may also be useful for chronic liver diseases. As noted in an article in the World Journal of Gastroenterology:[25]

> *"Consistently, we found that N-acetylcysteine (NAC) modulates the expression of iNOS [editor's note: iNOS is an inducible and calcium-dependent isoform of the enzyme nitric oxide synthase or NOS, which helps synthesize nitric oxide] in human hepatocytes stimulated by proinflammatory cytokines,"* the authors write.
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> *"The effect occurs by blocking the activation of the iNOS promoter, and is associated with modulation of NF-κB activity, a central transcription factor for induction of iNOS expression. The biological phenomenon might well be the basis of the therapeutic effects of NAC on chronic liver diseases different from those caused by acetaminophen intoxication."*

Like magnesium, research into NAC's role in overall health is ongoing. Both are inexpensive and, for now, widely available.

Sources and References

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