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Review Article

# Association of Dietary Magnesium Intake and Non-Alcoholic Fatty Liver Disease: A Narrative Review

**Mohammad Mirzaei[1], Elham Rahmanipour[2], Sara Saffar Soflaei[3,4], Leila Etemad[4,5], Sara Samadi[6], Gordon A. Ferns[7], Maryam Saberi-Karimian[3]*, Majid Ghayour-Mobarhan[3,4]**

1. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
4. International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran
5. Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
6. Depatment of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
7. Brighton and Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK

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**Corresponding author:*
Maryam Saberi-Karimian, PhD, Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
**Tel:** +98 513 8002288
**Email:** saberikm@mums.ac.ir; maryamsabery2012@gmail.com
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ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD), now known as metabolic dysfunction-associated steatotic liver disease (MASLD), is the most common chronic liver disorder globally. It is closely linked to obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. Dietary factors and micronutrient status may influence its development and progression. Magnesium (Mg), an essential mineral involved in glucose and lipid metabolism, has been suggested as a potential modulator of NAFLD, although the evidence remains inconclusive. This narrative review aimed to summarize experimental, observational, and interventional studies published since 2000 that have explored the relationship between Mg intake and NAFLD.

**Results:** Preclinical studies indicated that Mg deficiency contributes to mitochondrial dysfunction, oxidative stress, and hepatic lipid accumulation, while supplementation may reduce inflammation and fibrosis. Observational studies showed a negative association between Mg intake and NAFLD risk, although, findings vary among different populations. Randomized controlled trials were limited and demonstrated mixed results, with some revealing improvement in liver enzymes and lipid profile, while others illustrated no significant benefits.

**Conclusion:** While there is biological plausibility and initial data supporting a potential protective role of Mg in NAFLD, the current evidence did not establish a causal relationship. Larger, well-designed clinical trials are needed to determine whether Mg supplementation could be an effective preventive or therapeutic approach in NAFLD.

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## Introduction

Non-alcoholic fatty liver disease (NAFLD), now known as metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by the accumulation of fat in the liver exceeding 5% of its weight, without significant alcohol consumption or other underlying causes of steatosis (1-3). NAFLD encompasses a range of conditions, from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to advanced fibrosis, cirrhosis, and even liver cancer (4, 5). The global incidence and prevalence of NAFLD have increased significantly in the past decade, with an estimated 46.9 cases per 1000 person-years and a prevalence of 32.4% (6). The combined impact of NAFLD is substantial, with reports indicating a combined burden of approximately $103 billion in the US and around €35 billion in the UK, Germany, France, and Italy (7). Additionally, Iran has the highest reported prevalence of NAFLD in Asia, at approximately 40.8% (6).

The development of NAFLD is multifactorial, with insulin resistance regarded as a central pathogenic mechanism (8). Insulin resistance promotes increased lipolysis and free fatty acid influx into the liver, enhancing hepatic de novo lipogenesis while impairing β-oxidation (8). Other major contributors include obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, which together constitute the metabolic syndrome (9). Additional risk factors include dietary composition (high fructose and saturated fat intake), sedentary lifestyle, gut microbiota alterations, genetic predispositions (such as PNPLA3 and TM6SF2 variants), and environmental factors (10, 11). Drugs (e.g., corticosteroids, tamoxifen), toxins, and certain extrahepatic conditions (such as inflammatory bowel disease and cardiac failure) may also contribute to disease onset (12, 13).

While lifestyle modification, including dietary adjustments and physical activity, remains the cornerstone of management (14), research increasingly emphasizes the role of micronutrients in hepatic metabolism (15, 16). Magnesium (Mg), an essential cofactor over 300 enzymatic reactions, plays a crucial role in glucose homeostasis, lipid metabolism, oxidative stress regulation, and inflammatory pathways (17, 18). Low Mg level have been linled to insulin resistance, obesity, and cardiovascular diseases, all of which commonly coexist with NAFLD (19). Experimental studies suggested that Mg deficiency may contribute to hepatic fat accumulation and the progression toward steatohepatitis, by promoting mitochondrial dysfunction, oxidative stress, and inflammation (20).

It is important to note that while there is evidence supporting an association between Mg intake and NAFLD risk, a clear causal relationship has not yet been established. Some observational studies suggest that higher dietary Mg intake may have protective effects against liver steatosis (21, 22), while others did not confirm significant associations (23, 24). Interventional trials have provided mixed results. Therefore, while Mg may hold promise a dietary factor influencing NAFLD pathophysiology, further high-quality studies are needed before definitive conclusions can be made. This review aimed to summarize *in vitro*, *in vivo*, and human studies published since 2000 on the relationship between Mg intake and NAFLD, encompassing *in vitro*, *in vivo*, and human research. By highlighting both supportive findings and research gaps, this article seeks to provide a comprehensive overview of the current understanding of how Mg intake may impact NAFLD.

## Materials and Methods

In this narrative review, we searched PubMed, Scopus, and Web of Science for studies published between January 2000 and June 2023 using following keywords and MeSH terms of "non-alcoholic fatty liver disease," "NAFLD," "fatty liver," "NASH," "magnesium," "dietary magnesium," "micronutrients," and "supplementation." Eligible articles included (i) *in vitro* studies investigating mechanistic effects of Mg on hepatocyte lipid metabolism, oxidative stress, or inflammation. (ii) Animal studies assessing dietary Mg intake or supplementation in NAFLD models. (iii) Human studies including observational (cross-sectional, case-control, cohort) and interventional (randomized controlled trials, clinical trials) designs evaluating Mg intake, supplementation, or serum levels in relation to NAFLD outcomes. Reference lists of relevant publications and reviews were screened for additional studies. Only articles published in English were included. Data were extracted on study design, population, exposure/intervention, outcomes, and major findings.

### *Mechanistic Insights (In vitro/In vivo Studies)*

#### *In vitro Studies*

Regarding the effect of Mg on hepatic cell line, Mg was shown to reduce the intracellular lipid accumulation, increase microsomal triglyceride transfer and hepatic very-low-density lipoprotein (VLDL) secretion, as well as up-regulation of lipoprotein lipase (LPL). It also down-regulates Nuclear factor-κB (NF-κB), interleukin-6 (IL-6), transforming growth factor-β (TGF-β) and basic fibroblast growth

factor (bFGF) and reduces endoplasmic reticulum (ER) stress. *In vitro* studies were summarized in Table 1. Chen *et al.* used L02 cells treated with 1 mM free fatty acid (FFA) for 24 hours in order to simulate the NAFLD model and as a result, intracellular lipid accumulation occurred. Mg supplementation reduced the lipid accumulation by enhancing the adenosine monophosphate-activated protein kinase/mechanistic target of rapamycin (AMPK/mTOR) pathway and increasing autophagy in hepatocytes. Western blotting also showed that Mg could decrease lipid synthesis by downregulating fatty acid synthase (FASN) and sterol regulatory element-binding protein 1 (SREBP1) and increase lipid oxidation by increasing the expression of LPL (25).

In another study using HepaRG cells, Lu *et al.* utilized palmitic acid (PA) to induce lipotoxicity. When cells were treated simultaneously with 0.25 mM Mg isoglycyrrhizinate (MGIG), a Mg salt of glycyrrhizic acid, and 0.2 mM PA for 24 hours, their relative survival rate increased from 42% to 87% which was significantly higher than cells treated with PA-alone ($p$<000.1). Additionally, DNA synthesis showed a dramatic increase using the 5-ethynyl-2′-deoxyuridine (EdU) method after MGIG usage (26). Using ER-Tracker Red and tetramethylrhodamine methyl ester (TMRM) staining, ER and mitochondria damage appeared after PA administration, but MGIG intervention showed protective effects against these circumstances. Moreover, MGIG showed an inhibitory effect on triacylglycerol (TAG) biosynthesis by decreasing the expression of glycerol 3-phosphate acyltransferases (GPAT1/2/3/4) and diacylglycerol acyltransferase (DGAT1) genes and also preventing the uptake of saturated fatty acids (SFAs) by cells (27).

These results are consistent with a similar study by Xu *et al.* conducted on L02 cells with 2 mM oleic acid (OA) as a lipotoxicity inducer. Again, administration of 1 mg/ml MGIG resulted in reduction of intracellular lipid concentration. Hoechst 33258 staining demonstrated that MGIG significantly inhibited cell apoptosis by reversing pathologically increased expression of genes related to unfolded protein response (UPR), a well-known apoptosis pathway. Pro-inflammatory cytokines such as NF-κB, IL-6, TGF-β and bFGF were also downregulated after MGIG intervention (28).

Simon *et al.* examined the feasibility of silencing cyclin M4 (CNNM4), a gene that over-expresses in hepatic steatosis and exports intracellular Mg to out of the cell. They cultured mouse primary hepatocytes in a methionine and choline-deficient (MCD) medium to create non-alcoholic steatohepatitis (NASH). Immunohistochemical analysis revealed increased expression of CNNM4 in NASH cells. They then used DharmaFECT or jetPRIME® to transfect NASH cells with CNNM4 silencing siRNA. As a result, intracellular Mg concentration increased and in confirmation of previously mentioned studies, ER and mitochondrial damage was compensated due to reactive oxygen species (ROS) reduction. CNNM4 silencing also up-regulated the microsomal triglyceride transfer protein (MTP) that promoted liver VLDL secretion (20).

**Table 1:** Results of *in vitro* studies.

| Author and year | Cellular model | Lipotoxicity Inducer | Treatment | Therapeutic outcome |
|---|---|---|---|---|
| (25) | L02 human hepatic cell line | 1 mM FFA for 24h | Mg supplementation | ↓ expression of FASN and SREBP1.<br>↑ expression of LPL.<br>↑ AMPK/mTOR pathway activity and autophagy. |
| (20) | mouse primary hepatocytes | Methionine choline-deficient (MCD) medium | CNNM4 silencing siRNA by DharmaFECT or jetPRIME® | ↑ intracellular $Mg^{2+}$.<br>↓ ER stress.<br>↑ microsomal triglyceride transfer and hepatic VLDL secretion. |
| (27) | HepaRG cells | palmitic acid (PA) | magnesium isoglycyrrhizinate (MGIG) | ↑ hepatic cell proliferation and DNA synthesis.<br>↓ ER stress.<br>↓ intracellular lipid accumulation and TAG biosynthesis. |
| (28) | L02 human hepatic cell line | oleic acid (OA) | magnesium isoglycyrrhizinate (MGIG) | ↓ intracellular lipid accumulation.<br>↓ UPR activity and hepatic cell apoptosis.<br>↓ NF-κB, IL-6, TGF-β and bFGF expression. |

Abbreviations: FFA, Free Fatty Acids; FASN, Fatty Acid Synthase; SREBP 1, Sterol Regulatory Element-Binding Protein 1; LPL, Lipoprotein Lipase; AMPK/mTOR, Adenosine-Monophosphate Activated-Protein Kinase/Mammalian Target of Rapamycin; MCD, Methionine Choline-Deficient; CNNM4, Cyclin and CBS Domain Divalent Metal Cation Transport Mediator 4; siRNA, Small interfering RNA; THLE-2, Transformed Human Liver Epithelial-2; ER, Endoplasmic Reticulum; VLDL, Very Low-Density Lipoprotein; PA, Palmitic Acid; MGIG, Magnesium Isoglycyrrhizinate; TAG, Triacylglycerol; OA, Oleic Acid; UPR, Unfolded Protein Response; NF-κB, Nuclear factor-kappa beta.

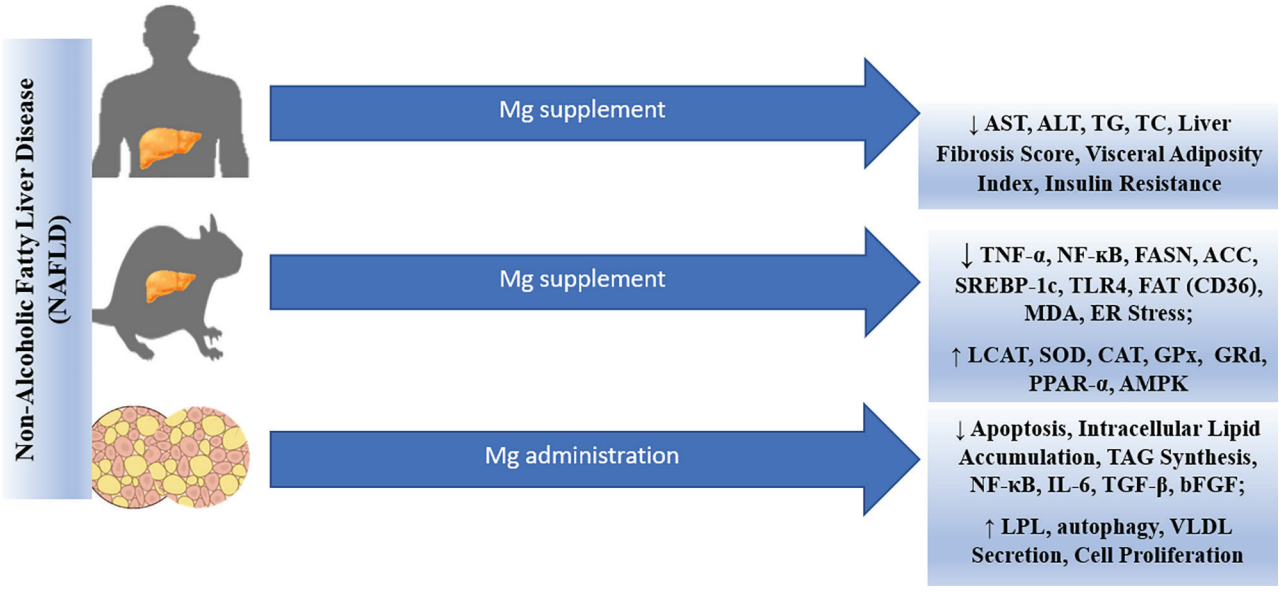


**Figure 1:** NAFLD and magnesium (Mg) administration.

*In vivo Studies (Animal Models)*

Table 2 shows the animal studies. The accumulation of lipid droplets is the precursor to NAFLD. Understanding the mechanisms behind the pathophysiology of NAFLD and the development of NASH has been made possible by comparing animal models of hepatic steatosis. In line with *in vitro* studies, Mg supplementation in animal models reduces inflammation, NFKB and ER stress as well as, glycemia, serum insulin and dyslipidemia (29). Nehmi *et al.* examined the effects of a unique oral supplement formulation that included prebiotics, yeast β-glucans, minerals, and silymarin (*Silybum marianum*) on lipid and glycemic metabolism, inflammatory markers, and liver mitochondrial proteins. Thirty-two male C57BL/6 mice were separated into the following groups after an acclimation period: a nonfat diet (NFD) vehicle, a nonfat diet supplemented, a high-fat diet (HFD) vehicle, and a high-fat diet supplemented. The vehicle and experimental formulations were administered orally by gavage once daily for 28 consecutive days during the last four weeks of the diet (25).

They then examined the expression of mitochondrial proteins, inflammation, and energy homeostasis in the mouse groups. According to this investigation, the new supplement enhanced positive systemic effects. The metabolic and inflammatory indices in the liver of the NFD-control and HFD-supplemented animals were decreased. After four weeks of supplementation, the benefits were reported to be most likely due to the modulation of the expression of essential proteins and pathways involved in cellular energy adenosine 5'-monophosphate (AMP)-activated protein kinase-1a (AMPK-1a), mitochondrial biogenesis [peroxisome proliferator-activated receptor alpha (PPAR-a), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), sirtuin 1 (SIRT1), and nuclear respiratory factor 1 (NRF-1)], inflammation [p38 mitogen-activated protein kinases (p38 MAPK), inhibitory-κB kinase-a (IKK-a), and nuclear factor-jB (NF-jB)], and oxidative stress [superoxide dismutase (SOD1), malondialdehyde (MDA), and carbonyl protein]. Furthermore, they discovered that the supplement's combined and synergistic effects altered the cortisol/C-reactive protein (CORT/CRP) ratio, which is relevant indicator for evaluating the underlying biological abnormalities associated with the HPA axis and immune system (30).

Mg deficiency is linked to various metabolic diseases, such as metabolic syndrome and T2DM, which are risk factors for NAFLD. Fengler *et al.* investigated how Mg restriction affects the onset of NAFLD. C57BL/6 mice were given a Mg-deficient diet, which caused Mg insufficiency. Assessments were made using metabolic, inflammatory, and liver function markers. Liver tissue was also histopathologically examined and compared with samples from mice fed a high-fat diet and control mice. Finally, hepatic IL-6, TNF, and monocyte chemoattractant protein-1 (MCP-1) quantified the hepatic inflammatory response. Compared to mice with a high-fat diet and control mice, animals with Mg restriction had at least two times lower serum Mg level. However, mice fed a high-fat diet had lower Mg level in their livers. No changes in metabolic indicators were seen in mice with Mg restriction, while animals fed a high-fat diet had higher cholesterol levels. The liver histology of the mice with Mg restriction also showed larger hepatocytes and inflammation.

**Table 2:** Findings of animal studies.

| Author and year | Animal model | Lipotoxicity inducer | Treatment (Supplement) | Therapeutic outcomes of Mg supplement |
|---|---|---|---|---|
| (30) | Male C57BL/6 mice at 9 weeks of age | A high-fat diet (HFD) containing 5.25 kcal/g composed of 30% saturated fat, mainly lard, 15.95% carbohydrate, and 20% protein for 14 weeks | zinc (Zn) 0.63%; selenium (Se) 0.003%; magnesium (Mg) 4.35%; FOS 49.69%; GOS 31.05% and 1.3/1.6-(**β**-glycosidic bonds) yeast **β**-glucans (S. cerevisiae) 11.18% (Yes Sinergy, Campinas, São Paulo, Brazil); and S. marianum extract 3.11% (Ningbo Vitax Biotech Co., China) for the last 4 weeks | ↓ glycemia, dyslipidemia, fat, and hepatic fibrosis levels.<br>↑ proliferator-activated receptor-α, AMP-activated protein kinase-1α, peroxisome proliferator activated receptor γ co-activator-1α, and mitochondrial transcription factor A expression levels.<br>↓ inhibitor of nuclear factor-k**β** kinase subunit α and p65 nuclear factor-k**β** expression, and oxidative markers.<br>Modulation of cortisol/ c-reactive protein ratio. |
| (31) | C57BL/6 mice at 10 weeks of age | The Mg-deficient-diet group (crude fat 4.2%, Mg < 0.02%) for 4 weeks, and High-fat-diet group (46.23% fat: 28.17% corn oil, 16.49% olive oil, 1.57% safflower oil, Mg 0.13%) for 7 weeks | | ↓ inflammation and enlarged hepatocytes in liver histology.<br>↓ hepatic TNFα levels |
| (32) | Male Sprague–Dawley rats | A high-fat diet (HFD) containing 16% protein, 39.4% fat, and 44.6% carbohydrate (high-fat 5S8X Rodent TestDiet, St. Louis, MO, USA) for 12 weeks | Magnesium Lithospermate B (MLB): 10 mg/kg/day OR Zinc Lithospermate B (ZLB): 1, 2.5, 5, and 10 mg/kg/day | ↓ Body weight gain, epididymal fat, liver weight, liver cholesterol, serum AST and ALT levels.<br>↓ serum insulin, FBS and HOMA-IR.<br>↓ expression of SREBP-1c and CD36.<br>↑ expression of IRS-1 and PI3-k p85α.<br>↓ TNF-α, leptin and malondialdehyde (MDA) levels. |
| (33) | Male Sprague Dawley rats | A high fat diet (HFD) made up of 63.6% standard diet, 20% sucrose, 15% lard, 1.2% cholesterol and 0.2% cholic acid sodium for 12 weeks | HF+LSe+LMg Group: low-dose sodium selenite (0.05 mg/kg·bw Se) and low-dose magnesium gluconate (5.83 mg/kg·bw Mg) for the last 8 weeks<br>HF+HSe+HMg Group: high-dose sodium selenite (0.10 mg/kg·bw Se) and high-dose magnesium gluconate (58.33 mg/kg·bw Mg) for the last 8 weeks | ↓ serum and liver Total Cholesterol and serum LDL-C, serum and liver TG, AST and ALT levels, TC/HDL-C and TG/HDL-C ratios.<br>↓ MDA levels, hepatic intracellular triacylglycerol accumulation, liver steatosis.<br>↓ expression of LXRα, SREBP-1c, FASN and HMGR.<br>↑ Se-dependent glutathione peroxidase (GSH-Px) and SOD levels.<br>↑ expression of CYP7A1 and LCAT |
| (34) | male KKAy mice at 7 weeks of age | A Methionine-choline-deficient diet (MCD); 4 mg/d for 4 weeks | A combination of BCCAs, microelements (5.07 mg Mg) and vitamins for 4 weeks | ↓ 8-OHdG immunolocalization in liver tissue.<br>↓ ER stress signaling pathway. |

Abbreviations: FOS, Fructo-oligosaccharides; GOS, Galacto-oligosaccharides; AMP, Adenosine Monophosphate; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; ACC, Acetyl-CoA Carboxylase; FAS, Fatty Acid Synthase; PPAR-α, Peroxisome Proliferator Activated Receptor-Alpha; TNF-α, Tumor Necrosis Factor-Alpha; MCD, Methionine Choline Deficient; SREBP-1, Sterol Regulatory Element-Binding Protein-1; SCD1, Stearoyl-CoA Desaturase1; FAT (CD36), Fatty Acid Translocase (Cluster of Differentiation 36); TLR4, Toll-Like Receptor 4; TCA Cycle, Tricarboxylic Acid Cycle; NAD, Nicotinamide Adenine Dinucleotide; NADH, Nicotinamide Adenine Dinucleotide (NAD)+Hydrogen (H); MLB, Magnesium Lithospermate B; ZLB, Zinc Lithospermate B; FBS, Fasting Blood Sugar; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IRS-1, Insulin Receptor Substrate-1; PI3-K, Phosphatidylinositol 3-Kinase; MDA, Malondialdehyde; HF, High Fat; LSe, Low-dose Se; LMg, Low-dose Mg; BW, Body Weight; LDL-C, Low-Density Lipoprotein-C; TG, Triglycerides; TC, Total Cholesterol; HDL-C, High-Density Lipoprotein-C; LXRα, Liver X Receptor Alpha; FASN, Fatty Acid Synthase; HMGR, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; GSH-Px, Plasma glutathione peroxidase; SOD, Superoxide Dismutase; CAT, Catalase; AMPK, AMP-activated protein kinase; CYPA1, Cholesterol 7 Alpha-Hydroxylase; LCAT, Lecithin–Cholesterol Acyltransferase; BCCAs, Branched-Chain Amino Acids; 8-OHdG, 8-Hydroxyguanosine; ER, Endoplasmic Reticulum.

In addition, hepatic TNF levels were higher in mice given a high-fat diet and on a Mg-restricted diet than in control animals. They demonstrated that Mg limitation caused an increased degree of hepatic inflammation and NAFLD-related liver damage in mice. Therefore, in mice and humans, Mg shortage may influence hepatic inflammatory processes and hepatocyte degradation, which may then play a role in the development and progression of NAFLD (31).

In a model of metabolic syndrome, rats fed a high-fat diet (16% protein, 39.4% fat, and 44.6% carbohydrate) and were shown an improved metabolic alteration when given Mg lithospermate B (MLB) derived from a traditional Chinese medicine named Danshen (*Salvia miltiorrhiza*). The zinc lithospermate B (ZLB) complex was successfully formed by substituting Zn2+ for Mg2+ in MLB. The therapeutic effects of MLB (10 mg/kg/day) and ZLB (1, 2.5, 5, and 10 mg/kg/day) on the metabolic syndrome resulted in a high-fat diet rat for investigation. Both MLB and ZLB demonstrated the the ability to reverse or reduce the pathological changes caused by a high-fat diet in rats. These changes included excessive weight gain, deposition of epididymal fat, hepatic steatosis, impaired lipid and glucose metabolism likely linked to insulin resistance, elevated leptin levels, proinflammatory cytokine activity, and oxidative stress. Overall, this study indicated that ZLB supplementation was more helpful than MLB supplementation in helping high-fat-fed rats recovered from metabolic syndrome. In this study, Zn2+ was used in place of Mg2+ to create the ZLB complex. In high-fat diet–induced metabolic syndrome, ZLB supplementation was shown to provide greater therapeutic efficacy compared to MLB supplementation. It appears that ZLB has the potential to be a beneficial supplement for individuals with metabolic syndrome (32).

Selenium (Se) supplementation has been reported to decrease circulating cholesterol level; while enhancing tissue concentrations of the antioxidant glutathione (GSH). However, the combined effects of selenium and Mg supplementation on hyperlipidemia induced by high-fat diet have not been previously investigated. Using a hyperlipidemic rat model, Zhang *et al.* demonstrated that oral co-supplementation with selenium and Mg has both antihyperlipidemic and hepatoprotective antioxidant effects, partially mediated through the modulation of gene expression. Four groups of forty male Sprague Dawley rats were used including the control group (CT) which received a control diet; a high-fat diet group (HF); low-dose selenium (0.05 mg/kg BW) and low-dose Mg (5.6 mg/kg BW) supplements; and high-dose selenium (0.10 mg/kg BW) and high-dose Mg (58.33 mg/kg BW) supplements (33).

The rats were fed a high-fat diet for the first four weeks of the experiment to induce hyperlipidemia, followed by an eight-week period of selenium and Mg co-supplementation. Lipid profile was assessed on days 0, 20, 40, and 60 of the intervention. Final blood and liver samples were taken after the 12-week trial to analyze the lipid profile and antioxidative indices, perform a pathological analysis and quantify the gene expression associated with the liver's lipid metabolism. Rats who were given a high-fat diet also saw significant antihyperlipidemic benefits from the combination of Se and Mg, with low dose co-supplementation of Se and Mg showing a tendency toward more pronounced hypocholesterolemic effects. The effectiveness of selenium and Mg co-supplementation in regulating dyslipidemia, alleviating hyperlipidemia, and improving hepatic steatosis suggested its potential as a nutraceutical intervention for managing hyperlipidemia, reducing cholesterol level, and enhancing antioxidant capacity. Se coupled with Mg could reduce endogenous cholesterol synthesis (HMGR), increase the transport of cholesterol into hepatocytes (CYP7A1), and increase cholesterol esterification to reduce serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and hepatic TC lecithin-cholesterol acyltransferase (LCAT). Se and Mg co-supplementation reduced HF-induced fatty liver and hyperlipidemia through modulating the liver X receptor/sterol regulatory element binding transcription factor-1c (LXR/SREBP-1c) pathway, which in turn-controlled hepatic genes involved in de novo fatty acid synthesis (33).

Tanaka *et al.* conducted a study to examine the effect of antioxidant-rich nutrients, such as branched-chain amino acids (BCAAs), trace elements, and vitamins, both individually and in combination, on liver function in a mouse model of NASH. Their research aimed to provide insights into the mechanisms underlying these effects. At seven weeks old, male Yellow Kuo Kondo (KKAy) mice were divided into seven groups and assigned specific diets for an extra four weeks including A (normal diet), B [methionine- and choline-deficient diet (MCD); control], C (MCD with rich microelements), D (MCD with rich BCAAs), E (MCD with rich microelements and BCAAs), and F (MCD with rich microelements, BCAAs, and vitamins). The liver samples from the mice in each group were then subjected to biochemical tests, histological examinations, immunohistochemistry for 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 4-hydroxy-2′-nominal (4-HNE), as well as Western blotting for insulin glucose signaling, lipid metabolism, and

endoplasmic reticulum (ER) stress-related signaling. The average level of 8-OHdG immunolocalization and the morphometric grades of all NASH-related observations in groups D through F were significantly lower than those in group B. The expression levels of phosphatidylinositol 3-kinase (PI3K85), p-AcelCoA, and PKR-like endoplasmic reticulum kinase (PERK) in group F were comparable to those seen in group A, as well as the insulin receptor subunit (IR) and phosphorylated-eukaryotic initiation factor (p-elF) in groups E and F. Trace elements, BCAAs, and vitamins function as antioxidant agents that may mitigate the progression of NASH by attenuating oxidative stress, particularly through modulation of the ER stress pathway. Accordingly, BCAAs, in conjunction with micronutrients, represente a promising antioxidant-based therapeutic approach for NASH (34).

### *Human Studies*

Table 3 has summarized the human studies. Regarding to the effect of dietary patterns rich in Mg and hepatic steatosis, most of studied including case-controls, cohorts and clinical trials revealed that Mg supplementation could be beneficial in both prevention and treatment of NAFLD.

**Table 3:** Review of human studies

| Author & Year | Country | Study Design | Patients' Demographics | NAFLD Diagnosis | Intervention | Outcomes | Conclusion & Recommendations |
|---|---|---|---|---|---|---|---|
| Salehi-Sahlabadi et al., 2022 (20) | Iran | case-control | 675 participants: 225 NAFLD cases, 450 controls | US scan | - | A nutrient pattern consisted of fructose, vitamin C, vitamin A, pyridoxine, and potassium was associated with low risk of NAFLD. A nutrient pattern including plant protein, zinc, copper, magnesium, manganese, chromium, and selenium was not linked to low risk of NAFLD. | Mg intake may not be beneficial for NAFLD treatment. |
| Lu et al., 2022 (18) | USA | cohort | 2685 participants: 629 NAFLD cases, 2056 controls | Non-contrast CT scan | - | NAFLD Odds was 55% lower in highest quintile of Mg intake compared to lowest quintile. Whole-grain consumption had inverse association with NAFLD. | Higher intake of Mg in adulthood may guarantee lower risk of NAFLD in middle age. |
| Hazzan et al., 2022 (42) | Israel | RCT | 22 NAFLD participants: 11 cases, 11 controls | Liver biopsy or share wave elastography | CIRRHOS: 2 gr L-carnitine, 150 mg magnesium-hydroxide and 10 mg vitamin C for 16 weeks | Serum levels of AST and ALT in treatment group decreased progressively, unlike controls, but this did not reach statistical significance. | L-carnitine and Mg supplementation may not be beneficial in NAFLD treatment. |

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|---|---|---|---|---|---|---|---|
| Gravina et al., 2022 (39) | Italy | prospective longitudinal interventional study | 66 participants: 55 hepatic steatosis cases, 11 controls | US scan | Fonte Essenziale® water: bicarbonate–sulfate–calcium–magnesium and low sodium, 400 ml every morning for 6 months | ↑ serum levels of GLP-1 and PYY (insulin resistance inhibitors). ↓ SeP and aHSGF (insulin resistance inducers). | Mg-containing Fonte Essenziale® mineral water may have anti-NAFLD effects. |
| Crommen et al., 2022 (38) | Germany | RCT | 48 participants: 25 NAFLD cases, 23 controls | FLI > 60 | Three capsules containing 56 mg Mg, daily for 12 weeks | ↓ Serum AST, NAFLD fibrosis score, serum triglycerides and visceral adiposity index. | Supplementation with a micro-nutrient rich probiotic containing various vitamins and minerals, specially Mg, may improve NAFLD-related markers in obese patients after MGB surgery. |
| Emamat et al., 2021 (35) | Iran | Case-control | 999 participants: 196 NAFLD cases, 803 controls | US scan | - | The third (Q3) and fourth (Q4) quartile of Ca/Mg intake ratio was associated with higher risk of NAFLD. After adjusting energy, Ca/Mg intake ratio showed a positive correlation to serum ALT level. | Higher Ca/Mg intake ratio may be a predisposing factor of developing NAFLD. |
| Tao et al, 2021 (36) | USA | Case-control | 4166 participants: 628 liver fibrosis cases, 3538 cases | FibroScan | - | Total Mg intake was nearly associated with lower odds of liver fibrosis. Ca intake had no association with liver fibrosis. Ca/Mg intake ratio was not associated with liver fibrosis. | High amounts of Mg intake may reduce the risk of liver fibrosis in NAFLD. |
| Haiyan et al., 2021 (40) | China | RCT | 60 NAFLD patients: 30 observation cases, 30 controls | ? | Magnesium Isoglycyrrhizinate (MGIG) | TC, TG, AST and ALT levels were significantly lower in cases compared to controls. | MGIG may be effective in improving lipid profile and liver enzymes in NAFLD patients. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Aktary et al., 2020 (30) | Canada | Descriptive cross-sectional | 42 NAFLD patients | FibroScan and ALT level > 1.5 ULN | - | Mg intake in NAFLD patients was below the recommended dose. Mg intake was negatively correlated with liver fat. | Consumption of recommended amount of Mg may prevent or regress NAFLD. |
| Mazidi et al., 2020 (32) | USA | Analytic cross-sectional | 20643 participants: 9433 NAFLD cases, 11030 controls | FLI ≥ 30 | - | Individuals in top quarter of dietary pattern mostly containing minerals such as Mg, vitamins and fiber experienced a 34% lower fatty liver odds. | A Dietary pattern rich in minerals such as Mg may reduce the risk of NAFLD. |
| Tayyem et al., 2019 (34) | Jordan | Case-control | 120 participants: 60 NAFLD cases, 60 controls | US scan | - | Mg intake along with iron, phosphorus, potassium, selenium, sodium and zinc showed negative correlation with NAFLD. | More Mg intake is a preventive factor against NAFLD. |
| Vahid et al., 2019 (37) | Iran | Case-control | 999 participants: 295 NAFLD cases, 704 controls | FibroScan | - | A negative association between NAFLD risk and intake of Mg, Zn, riboflavin, biotin and pantothenic acid was showed. The INQ of Mg, Zn, and vitamins B1, B2, B3, pantothenic acid, biotin and B12 was higher in controls. | Higher amounts of Mg intake is a protector against NAFLD. |
| Li et al., 2018 (33) | USA | Analytic cross sectional | 13489 participants: 2423 fatty liver disease cases, 5818 prediabetic cases, 1511 fatty liver and prediabetic cases, 6399 controls | US scan | - | An association was seen between Mg intake and 30% reduction in odds of fatty liver disease and prediabetes. | High Mg intake may result in lower risk of fatty liver disease and prediabetes. |

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| Wu et al., 2017 (17) | USA | Cohort | 13504 participants: 3081 patients with hepatic steatosis, 10423 controls | US scan | - | There was a 49% decline in mortality risk of liver disease for every 100 mg increase in daily Mg intake. | Higher amounts of Mg consumption is associated with lower liver-disease mortality risk in hepatic steatosis. |
| Bender et al., 2017 (31) | Croatia | Descriptive Cross-sectional | 30 NAFLD patients | US scan | - | Patients consumed high amounts of SFA and insufficient amounts of Mg, Ca, Zn, Fe and vitamins. | Mg intake is below the recommended amounts in NAFLD patients. |
| Zolfaghari et al., 2016 (19) | Iran | Case-control | 317 participants: 159 NAFLD cases, 158 controls | US scan | - | NAFLD patients had more SFA and sugar intake, but less fiber, folic acid, Vitamin D, zinc, and potassium. | The amount of Mg intake may not be associated with NAFLD risk. |
| Tian et al., 2014 (41) | China | RCT | 42 NASH cases: 21 observation cases, 21 controls | ? | Simvastatin + Magnesium Isoglycyrrhizinate (MGIG) for 6 weeks | MGIG group had significantly lower AST and ALT levels after treatment. Levels of liver fibrosis markers PC III, HA, C-IV decreased in MGIG group, while no change occurred in control group. | MGIG can improve liver function tests and lower the liver fibrosis stage. |
| Karandish et al., 2013 (43) | Iran | RCT | 68 participants: 34 NAFLD cases, 34 controls | US scan | 350 mg elemental Mg, daily for 90 days | There were significant decreases of AST, ALT, fasting serum insulin and body weight within both case and control groups, but there was no significant difference between two groups. | Mg supplementation is not beneficial in lowering liver enzymes in NAFLD patients with normal serum Mg levels. |

Abbreviations: AST, Aspartate transaminase; ALT, Alanine transaminase; aHSGF, human glycoprotein Fetuin-A; C IV, collagen IV; FLI, fatty liver index; GLP-1, Glucagon-like peptide-1; HA, hyaluronic acid; INQ, Index of nutritional quality; MGB, mini gastric bypass; PYY, Peptide YY; PC-III, procollagen type 3; SFA, saturated fatty acids; SeP, selenoprotein P; TC, total cholesterol, TG, Triglycerides, ULN, Upper limit normal

*Observational Studies*

In a descriptive cross-sectional study in Canada by Aktary *et al*., they asked 42 NAFLD patients to record their 3-day weighed food intake. Liver fat content and stiffness were evaluated by magnetic resonance imaging (MRI) and transient elastography (FibroScan), respectively and serum biomarkers and anthropometric indicators were also measured. Compared to the adequate recommended amounts, NAFLD patients consumed lower fiber, Mg, calcium and vitamins D and E and had higher intake of energy, cholesterol, saturated fat, fructose, iron, sodium, phosphorus, selenium and vitamin B12. Liver fat had a negative correlation with Mg and phosphorus intake, while with a positive correlation with percent added sugar, serum TG and trunk fat. Linear regression revealed Mg intake as a negative predictor of liver steatosis. There was a positive correlation between liver stiffness and systolic blood pressure, serum α-2 macroglobulin and percent carbohydrate intake (35). Consistent with these results, the data from a study on 30 Croatian NAFLD patients by Bender *et al.* illustrated that in these patients, daily Mg intake was only 58.27% of recommended amounts, and women's intake was less than men (36).

Mazidi *et al.* carried out a cross-sectional study on 20643 participants (9433 NAFLD cases and 11030 healthy controls) in the USA. Ultrasonography and fatty liver index (FLI) ≥ 30 was used for the diagnosis of NAFLD, and a 24-hour diet record was obtained from patients. Based on patients' answers, three dietary patterns were represented that explained 50.8% of variance in nutrients intake. The first one mostly contained saturated and mono-unsaturated fatty acids (MUFA), total fat and carbohydrates; the second dietary pattern comprised of vitamins, minerals such as magnesium and dietary fiber; and the third one was rich in poly-unsaturated fatty acids (PUFAs). The findings showed that being in the top quarter of the second dietary pattern is associated with 34% lower odds of fatty liver, while top quarter of the first dietary pattern resulted in 86% higher odds of fatty liver (37). Similar to these findings, a previous study on 13489 participants with NAFLD and prediabetes in the USA by Li *et al.* revealed when the highest and lowest quartile of magnesium intake were compared, 30% reduction in NAFLD odds was associated with higher intake of magnesium (38).

Tayyem *et al.* used a case-control study design of 120 Jordanian participants (60 NAFLD cases and 60 healthy controls). NAFLD was diagnosed by ultrasonography and patients' nutrient consumption and physical activity were gathered by validated questionnaires. Blood samples were also obtained for biochemical analysis. They found that magnesium intake along with some other minerals and vitamins were negatively correlated with NAFLD, but daily calorie intake, protein, carbohydrate, MUFA, PUFA, saturated fat and cholesterol had positive correlations with NAFLD. They also discovered that the calcium consumption was considerably greater in patients with NAFLD compared to those in the control group (39). This result was also confirmed by Emamat *et al.* as a case-control study on 999 Iranian participants (196 NAFLD cases and 803 healthy controls). The findings revealed that Ca/Mg intake ratio was inversely associated with NAFLD risk, but positively correlated with ALT levels (40). In this regard, Tao *et al.* showed that total intake of Mg had a marginal association with lower odds of liver fibrosis ($p$=0.14), and this association was stronger when total daily calcium intake was below 1200 mg, but no significant association was found between Ca/Mg intake ratio and odds of liver fibrosis (41).

Vahid *et al.* conducted a case-control study on 295 NAFLD patients and 704 healthy controls in central Iran. They used a validated food frequency questionnaire (FFQ) for recording nutritional status of the participants and calculated the Index of Nutritional Quality (INQ), a tool for qualitative and quantitative assessment of diets. Comparing two groups, they found that NAFLD patients had lower INQ numbers for Mg, zinc and vitamins D, E, B1, B2, B3, pantothenic acid and biotin. Also, there was a negative correlation between the risk of NAFLD and INQ number of Mg, zinc and vitamins B2, pantothenic acid and biotin (42).

Despite a prominent number of studies that have depicted the beneficial effects of Mg intake on NAFLD, the protective and positive effects of this element was not proven in some studies. Two Iranian case-control studies by Salehi-sahlabadi *et al.* (on 225 NAFLD cases and 450 healthy controls) and Zolfaghari *et al.* (159 NAFLD cases and 158 healthy controls) did not discover any significant difference in Mg consumption between NAFLD patients and healthy controls; instead, they mentioned the importance of consuming other micro-nutrients such as potassium and zinc (23, 24).

In a cohort study by Wu *et al.* based on the Third National Health and Nutrition Examination Study (NHANES III), 13504 American participants were included and based on hepatic steatosis severity in ultrasonography, were divided into moderate/severe hepatic steatosis (3081 individuals) and normal/mild hepatic steatosis (10423 individuals). The median follow-up period was 14.6 years and participants' demographic, nutritional and mortality status data was recorded. They found that for every

100 mg increase in Mg consumption, the risk of mortality from liver disease decreased by 49% and this relationship was particularly significant among individuals with fatty liver disease or those who consume alcohol (21). In another American cohort of 2685 participants by Lu *et al.* from the Coronary Artery Risk Development in Young Adult (CARDIA) study with a 25-year follow-up, NAFLD was identified by non-contrast CT scan at exam year 25. A total of 629 participants were diagnosed with NAFLD. They showed that individuals in the highest quintile of total Mg intake had a 55% reduced likelihood of developing NAFLD compared to those in the lowest quintile. Moreover, consumption of Mg-rich whole grain was announced to be negatively associated with NAFLD odds (22).

### *Interventional Studies*

A group of interventional studies tried to examine the feasibility of various Mg-containing compounds as supplements for NAFLD patients, which some of them showed reliable results.

Crommen *et al.* conducted a double-blind randomized controlled trial on 48 German, obese patients with NAFLD after mini gastric bypass surgery to compare the therapeutic effects of a supplement of multi-strain probiotic and micro-nutrient mixture containing 56 mg Mg and some other minerals, vitamins and phytochemicals with a basic compound containing lower doses of micro-nutrients based on recommendations of American Society for Metabolic and Bariatric Surgery. Twenty-five patients were given the probiotic and high-dose micro-nutrients for 12 weeks after discharge, while 23 patients received the basic low-dose supplement. In both groups, capsules containing micro-nutrient mixture were taken 3 times a day with principal meals, and probiotic or placebo powders (2 g per serving) were mixed with yogurt or water and ingested two times a day. Results clarified that the mixture of a selected multi-strain probiotic and high dose micronutrients significantly lowered serum levels of aspartate aminotransferase (AST) and triglyceride (TG), while also enhancing the liver fibrosis score and visceral adiposity index when compared to the control group; however, there was no notable difference in serum levels of alanine aminotransferase (ALT) between the two groups. (43).

In a prospective longitudinal interventional study by Gravina *et al.* in Italy, they evaluated the possible positive effect of a mineral water containing bicarbonate, sulfate, calcium, Mg and low amounts of sodium, known as Fonte Essenziale®, on hematologic and metabolic parameters as well as gut microbiota in patients with hepatic steatosis. They recruited 55 ultrasound-validated hepatic steatosis patients and 11 hepatic steatosis-free individuals. Participants drank 400 mL of Fonte Essenziale® every day before breakfast for 6 months, and then had a 6 month of withdrawal. The analysis of obtained data showed significant increases in serum levels of glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY) (insulin resistance inhibitors) and significant increases in selenoprotein P (SeP) and human glycoprotein Fetuin-A (aHSGF) (as insulin resistance inducers) (44).

Consistent with some of previously mentioned cellular and animal studies, the effects of Mg isoglycyrrhizinate (MGIG) in NAFLD and NASH was tested in two Chinese RCTs by Haiyan *et al.* (60 NAFLD patients) and Tian *et al.* (42 NASH patients). Haiyan *et al.* found that the treatment group's levels of AST, ALT, total cholesterol, and TG were considerably lower than those of the control group. In Tian *et al.*'s study, AST and ALT levels, as well as the indicators of liver fibrosis type III pre-collagen (PC III), hyaluronic acid (HA), and collagen IV (C-IV), were considerably lower in the treatment group (45, 46).

On the other hand, a few studies were not able to find significant beneficial effects of Mg intake in NAFLD patients. This may be due to their small number of participants or short follow-up. Hazzan *et al.* conducted a double-blinded randomized controlled trial (RCT) on 22 NAFLD patients in Israel. They introduced a combination of 2 g of L-carnitine, 150 mg Mg hydroxide and 10 mg vitamin C as "CIRRHOS" for intervention. Treatment group (11 patients) received 15 mL/day CIRRHOS for 16 weeks and control group (11 patients) received placebo (mineral water) for 8 weeks and then 15 mL/day CIRRHOS for the next 8 weeks. During the study, they monitored patients weekly by calling them and they had monthly check-up in which they collected anthropometric data and blood samples of patients for biochemical analysis. To evaluate the effects of CIRRHOS on NAFLD, they measured lipid profile by blood sampling and liver fibrosis by shear wave elastography at baseline and at the study end. Results revealed that Mg-containing compound "CIRRHOS" made AST and ALT levels in treatment group decrease by 25% ($p$=0.08) and 20% ($p$=0.1), respectively; although these findings did not reach the statistical significance and final AST and ALT levels did not significantly differ between the treatment and control groups. Additionally, there was no discernible difference between the treatment and control groups in terms of liver fibrosis score in elastography, C-reactive protein (CRP), cholesterol, TG, LDL-C, and HDL-C levels (47).

In an Iranian double-blind randomized controlled

trial by Karandish *et al*., they tried to investigate how weight loss and Mg supplementation affected NAFLD. Sixty-eight NAFLD patients were identified by ultrasonography and randomly divided into treatment and control groups (34 patients in each group). Treatment group received 350 mg elemental Mg for 90 days, while control group received placebo. The serum levels of AST, ALT, TG, cholesterol, LDL-C, HDL-C, fasting blood sugar, insulin and Mg were recorded at baseline and upon completion of the study. Weight, fasting insulin serum level, AST, and ALT levels significantly decreased in each group, but there was no significant difference between the two groups (48).

### *Conflicting Evidence and Research Gaps*

Despite several studies suggesting a beneficial association between Mg intake and reduced risk of NAFLD, the overall evidence remains inconsistent. Some case-control and cohort studies demonstrated inverse correlations between Mg consumption and hepatic steatosis, while others fail to detect significant associations. It seems role of diet is of crucial importance. Especially the impact at cellular level (49-52).

These discrepancies may reflect heterogeneity in study design, populations, diagnostic methods [e.g., ultrasound, fibroscan, computed tomography (CT), or biopsy], and dietary assessment techniques (food frequency questionnaires vs. 24-hour recalls). Interventional studies are limited in number and often involve small sample sizes, short follow-up periods, or combined supplementation regimens, making it difficult to isolate the independent effects of Mg. Additionally, variations in Mg formulation, dose, and baseline nutritional status can complicate interpretation. Importantly, the majority of accessible data are observational, making it impossible to draw conclusions on causality.

Key research gaps included (i) Lack of longitudinal investigations on the connection between Mg intake and NAFLD incidence or development. (ii) Limited RCTs lack power to identify significant changes in fibrosis or long-term outcomes. (iii) Diagnostic techniques vary among research, limiting comparability. (iv) Biological mechanisms in humans remain unclear, despite plausible pathways from experimental models (e.g., impacts on insulin resistance, oxidative stress, and lipid metabolism). (v) Little research exists on potential interactions with other nutrients, such as the calcium-to-magnesium ratio, which could impact disease risk. Future research should prioritize large-scale, well-controlled clinical trials with standardized NAFLD diagnostic criteria, dose-response evaluations of Mg supplementation, and mechanistic studies integrating metabolic and genomic approaches.

## Conclusion

Magnesium plays a critical role in metabolic homeostasis and has been implicated in pathways relevant to NAFLD pathogenesis, including insulin sensitivity, lipid metabolism, oxidative stress, and inflammation. Its possible protective role is substantially supported by evidence from animal and *in vitro* investigations. Higher Mg consumption may be linked to a lower incidence of NAFLD, according to observational human research; however, the results are mixed and subject to methodological limitations. The lack of clinical trials and their inconsistent results make it difficult to establish causality. Overall, Mg is a promising yet unproven component in the management and prevention of NAFLD. While additional well-designed RCTs are required to ascertain whether magnesium supplementation has a therapeutic effect on NAFLD, clinicians may advise adequate dietary Mg consumption as part of a balanced diet until more conclusive evidence is available.

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## Authors' Contribution

MM and MSK: Conceptualization and supervision. MM, ER, SSS, LE and MSK: Writing, review and editing. MM, ER, SSS, LE, SS and MSK: Literature search. GAF, MGM and SS: Review and editing. All authors reviewed the manuscript.

## Conflict of Interest

None to declare.

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