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Micronutrients in the Supportive Management of Metabolic Dysfunction–Associated Steatotic Liver Disease and Dyslipidemia: Current Evidence, Mechanisms, and Future Prospects

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ABSTRACT: Metabolic dysfunction–associated steatotic liver disease (MASLD) and dyslipidemia are interconnected metabolic conditions associated with insulin resistance, adipose tissue dysfunction, oxidative stress, and chronic low-grade inflammation. Micronutrients have attracted attention because of their physiological roles in antioxidant defenses, one-carbon metabolism, mitochondrial function, and immune regulation. This narrative review examines the mechanistic rationale and clinical evidence for vitamin E, vitamin D, vitamins B6/B9/B12, zinc, selenium, and the related nutrients choline and omega-3 fatty acids. The PIVENS trial identified histological benefits of vitamin E in selected adults with non-diabetic steatohepatitis, whereas evidence for routine supplementation with other micronutrients remains insufficient. Omega-3 fatty acids can lower triglycerides but should not be regarded as proven antifibrotic therapy. Major challenges include heterogeneous trial populations, surrogate endpoints, baseline nutritional status, dose-related toxicity, and limited long-term outcome data. Future studies should integrate nutritional phenotyping, validated liver outcomes, and randomized trials to establish whether targeted correction of deficiency improves clinical outcomes beyond established lifestyle and cardiometabolic interventions.

KEYWORDS: micronutrients; MASLD; MASH; dyslipidemia; vitamin E; vitamin D; oxidative stress; personalized nutrition.

1. INTRODUCTION

MASLD is a major manifestation of systemic metabolic dysfunction and frequently coexists with obesity, type 2 diabetes, hypertension, and atherogenic dyslipidemia. The 2023 multisociety nomenclature emphasizes metabolic risk rather than defining disease solely by the absence of alcohol consumption (Rinella et al., 2023). Its spectrum extends from isolated steatosis to metabolic dysfunction–associated steatohepatitis (MASH), advanced fibrosis, and cirrhosis. The liver coordinates lipid uptake, synthesis, oxidation, and export; disturbances in these pathways interact with inflammation and insulin resistance (Tilg & Moschen, 2010). Nutritional interventions are important, but a nutrient's essential biochemical role is not equivalent to proof that high-dose supplementation treats MASH. This review distinguishes mechanistic plausibility, observational associations, randomized evidence, and established clinical recommendations (EASL et al., 2024).

2. PATHOPHYSIOLOGICAL BASIS OF MASLD AND DYSLIPIDEMIA

Hepatic steatosis reflects the combined effects of excess substrate delivery, altered lipogenesis, inadequate lipid disposal, and metabolic stress. Several interacting insults, rather than a single sequential pathway, contribute to disease progression (Tilg & Moschen, 2010).

2.1. Hepatic Lipid Accumulation

Under normal conditions, hepatic lipid homeostasis balances circulating fatty-acid uptake, de novo lipogenesis, mitochondrial beta-oxidation, and triglyceride export through very-low-density lipoproteins (VLDL). Insulin resistance increases adipose lipolysis and fatty-acid flux to the liver; compensatory hyperinsulinemia and hyperglycemia can activate SREBP-1c and ChREBP, enhancing

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expression of lipogenic enzymes. When delivery and synthesis exceed oxidation and export, intracellular triglycerides accumulate. The contribution of each pathway varies with genetics, adiposity, diet, and metabolic status (Begriche et al., 2013; Rinella et al., 2023; Friedman et al., 2018; Rinella et al., 2023)

2.2. Oxidative Stress and Hepatocellular Injury

Reactive oxygen species arise from mitochondrial electron transport, lipid oxidation, and other enzymatic sources. Excessive oxidative stress can promote lipid peroxidation, reactive aldehyde formation, protein damage, inflammatory signaling, and stellate-cell activation. Nevertheless, reactive oxygen species also have physiological signaling roles; indiscriminate antioxidant supplementation cannot be assumed to reverse injury. The multiple-parallel-hits framework links oxidative stress to immune, adipose, and gut-derived signals (Tilg & Moschen, 2010; Pacana & Sanyal, 2012; Day & James, 1998; Tilg & Moschen, 2010)

2.3. Mitochondrial Dysfunction and Energy Metabolism

Mitochondria support ATP generation and fatty-acid oxidation. Early increases in oxidative flux may be adaptive, but sustained substrate overload can disrupt respiratory efficiency, redox balance, and mitochondrial quality control. Micronutrients act as enzyme cofactors or support redox defenses, providing biological hypotheses for intervention; restoration of mitochondrial function or reversal of fibrosis by supplementation remains a separate clinical question (Begriche et al., 2013; Friedman et al., 2018; Tilg & Moschen, 2010)

2.4. Association Between MASLD and Dyslipidemia

Insulin resistance and increased hepatic triglyceride production favor VLDL secretion and a lipid profile often characterized by elevated triglycerides, remnant lipoproteins, small dense LDL particles, and reduced HDL cholesterol. Because cardiovascular disease contributes substantially to the burden of MASLD, assessment must include blood pressure, glucose, lipid fractions, adiposity, and other cardiometabolic risk factors. Liver-directed nutritional strategies must complement—not displace—evidence-based cardiovascular risk reduction (EASL et al., 2024; Rinella et al., 2023; Targher et al., 2010; EASL et al., 2024)

3. MICRONUTRIENTS AND RELATED NUTRIENTS IN SUPPORTIVE MANAGEMENT

The following sections evaluate biochemical functions alongside human outcome evidence. Choline and omega-3 fatty acids are included as related nutrients, although they are not classified as vitamins or trace minerals.

3.1. Vitamin E: Antioxidant Activity and Hepatocyte Protection

Vitamin E encompasses fat-soluble tocopherols and tocotrienols; alpha-tocopherol is an important membrane antioxidant. By limiting lipid peroxidation, vitamin E may mitigate some oxidative injury pathways relevant to steatohepatitis (Pacana & Sanyal, 2012). In the PIVENS randomized trial involving adults with NASH without diabetes, histological improvement occurred in 43% of participants receiving vitamin E versus 19% receiving placebo (Sanyal et al., 2010). This finding does not establish benefit for every patient with MASLD, advanced fibrosis, or cirrhosis. Long-term safety, optimal selection, and fibrosis outcomes remain uncertain. European guidance does not recommend routine vitamin E as a specific MASH-targeted therapy, emphasizing the need for individualized specialist decisions (EASL et al., 2024; Sanyal et al., 2010; Chalasani et al., 2018)

3.2. Vitamin D: Immunomodulation and Metabolic Regulation

Vitamin D supports calcium–phosphate homeostasis and acts through the vitamin D receptor in several tissues, including immune cells. Observational associations between low circulating 25-hydroxyvitamin D and obesity, diabetes, or steatosis may reflect confounding and reverse causality rather than a direct therapeutic target. The systematic review cited in the source manuscript reported improvements in some liver enzymes but inconsistent effects across biomarkers (Vajdi et al., 2026). Enzyme changes do not establish histological improvement, antifibrotic efficacy, or reduced cardiovascular events. Deficiency should be assessed and corrected when clinically indicated; routine high-dose vitamin D for MASLD itself is not supported by current guidelines (EASL et al., 2024; Manco et al., 2010; EASL et al., 2024)

3.3. Vitamins B6, B9, and B12: One-Carbon Metabolism

Vitamin B6, particularly pyridoxal phosphate, participates in amino-acid metabolism, whereas folate and vitamin B12 support remethylation of homocysteine to methionine. These pathways influence S-adenosylmethionine availability, methylation reactions, and phospholipid metabolism. A disturbed one-carbon cycle could therefore affect hepatic lipid handling, although mechanistic plausibility does not demonstrate clinical efficacy. There is insufficient evidence that supplementation in people without deficiency reverses steatosis or fibrosis. Identification and correction of deficiency remain appropriate within general nutritional care (Corbin & Zeisel, 2012; EASL et al., 2024; Dongiovanni et al., 2018; Friedman et al., 2018)

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3.4. Zinc: Enzyme Function and Antioxidant Defense

Zinc contributes to numerous enzymes and transcriptional proteins, immune function, and cellular redox homeostasis. It is a structural component of Cu/Zn-superoxide dismutase and is linked to metallothionein-mediated cellular protection. Observational relationships between zinc status and fibrosis should not be interpreted as evidence that zinc supplementation prevents fibrosis (Abdallah et al., 2026). High-dose chronic intake can impair copper absorption. Targeted deficiency correction is more defensible than routine supraphysiological supplementation (EASL et al., 2024; Dongiovanni et al., 2018; EASL et al., 2024)

3.5. Selenium: Selenoproteins and Redox Regulation

Selenium is incorporated into selenoproteins, including glutathione peroxidases and thioredoxin reductases, which regulate peroxide metabolism and redox signaling. The association between lower serum selenium and hepatic fibrosis reported in an observational cohort remains hypothesis-generating and susceptible to confounding (Abdallah et al., 2026). Both insufficient and excessive selenium exposure can be harmful, and its therapeutic window is relatively narrow. Current evidence does not justify routine selenium treatment for MASLD in the absence of an established deficiency or other clinical indication (EASL et al., 2024). (Dongiovanni et al., 2018; EASL et al., 2024)

3.6. Choline: Phospholipid Synthesis and Triglyceride Export

Choline is an essential nutrient used in phosphatidylcholine biosynthesis, cell membrane maintenance, VLDL assembly, and methyl-group metabolism through betaine. Human choline deprivation can cause hepatic fat accumulation and liver injury, supporting the importance of adequate intake (Corbin & Zeisel, 2012). However, prevention of deficiency must be distinguished from treating established MASLD with pharmacological choline doses. There is no guideline-supported recommendation for routine high-dose choline to reverse fibrosis (EASL et al., 2024; Dongiovanni et al., 2018; Friedman et al., 2018)

3.7. Omega-3 Fatty Acids: Triglyceride Regulation

The long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid can modify hepatic triglyceride synthesis and lipoprotein metabolism. A meta-analysis of randomized trials reported improvements in some hepatic fat and biochemical measures, with substantial heterogeneity across interventions and outcomes (Yan et al., 2018). Their triglyceride-lowering effect is clinically relevant in appropriate patients, but cannot be equated with proven resolution of MASH or reversal of fibrosis. Prescription formulations, dosing, and indications should not be conflated with heterogeneous over-the-counter fish-oil supplements (EASL et al., 2024; Yan et al., 2018; Kim et al., 2025)

4. CHALLENGES IN MICRONUTRIENT APPLICATION

Clinical translation requires demonstrating a favorable benefit–risk balance beyond correction of recognized deficiencies.

4.1. Insufficient Long-Term Evidence

Many supplementation studies are short and rely on transaminases or imaging rather than progression to cirrhosis, cardiovascular events, or mortality. Given the chronic course of MASLD, durable benefit and safety require adequately powered long-term studies (EASL et al., 2024; Rinella et al., 2023; Angulo et al., 2015; EASL et al., 2024)

4.2. Risks of Excess Supplementation

High-dose vitamin E raises safety considerations; excessive vitamin D may cause hypercalcemia; prolonged excessive zinc intake can induce copper deficiency; and selenium excess may produce toxicity. The nutritional necessity of these substances should not be mistaken for unlimited safety at pharmacological doses. Supplement use should account for comorbidities and professional guidance (EASL et al., 2024; Pacana & Sanyal, 2012; Chalasani et al., 2018; EASL et al., 2024)

4.3. Challenges in Determining Optimal Dosage

Requirements differ by age, diet, absorption, baseline nutrient status, organ function, and concurrent illness. Obesity and metabolic dysfunction can also alter circulating nutrient concentrations. Future dose-finding studies should stratify baseline deficiency, evaluate bioavailability, and distinguish correction of inadequate intake from supra-nutritional treatment (EASL et al., 2024; Dongiovanni et al., 2018; EASL et al., 2024)

5. FUTURE PROSPECTS AND RESEARCH DIRECTIONS

Promising work should integrate molecular insights with rigorous outcome-oriented clinical designs.

5.1. Personalized Nutritional Strategies

A targeted approach would evaluate nutritional status, metabolic risk, comorbidities, and likely response before supplementation. For example, vitamin D deficiency warrants assessment on its own merits, whereas marked hypertriglyceridemia requires evidence-

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based lipid management. Personalized interventions should be tested prospectively rather than assumed beneficial from biomarker associations (Cheng et al., 2012; EASL et al., 2024; Romeo et al., 2008; Rinella et al., 2023)

5.2. Metabolomics, Lipidomics, and Proteomics

Metabolomics quantifies small-molecule patterns, lipidomics characterizes lipid species, and proteomics examines protein abundance and function. Integrating these platforms could reveal metabolic subtypes, candidate markers of nutrient responsiveness, and mechanisms of hepatic injury. Preliminary vitamin E response profiling illustrates this research direction; omics-guided micronutrient prescription is not yet established clinical practice (Cheng et al., 2012; Friedman et al., 2018; Rinella et al., 2023)

5.3. Integration of Basic and Clinical Research

Preclinical models can test whether nutrient interventions alter lipid storage, oxidative stress, mitochondrial function, or inflammatory pathways. Promising findings should progress to randomized controlled studies with reproducible exposure assessment, validated endpoints, sufficiently long follow-up, and transparent adverse-event reporting. Mechanistic endpoints alone cannot substitute for patient-important outcomes (Begriche et al., 2013; Rinella et al., 2023; Kleiner et al., 2005; Cusi et al., 2016)

5.4. Combining Nutrition with Modern Therapies

Management should concurrently address hepatic disease, obesity, diabetes, dyslipidemia, and cardiovascular risk. Disease-specific MASH pharmacotherapy should follow the relevant jurisdiction's approvals and patient selection criteria. The appropriate potential role of micronutrients is complementary nutritional optimization rather than replacement of established lifestyle or pharmacological interventions (EASL et al., 2024; Armstrong et al., 2016; Harrison et al., 2024)

6. CONCLUSIONS

Micronutrients are essential for cellular metabolism, antioxidant defenses, and physiological liver function, but their biochemical importance does not itself establish efficacy as MASLD treatments. Vitamin E has demonstrated histological benefit in a selected trial population; routine therapeutic supplementation with vitamin D, B vitamins, zinc, or selenium lacks sufficient evidence. Adequate choline supports hepatic lipid export, while omega-3 fatty acids can improve triglycerides without proven antifibrotic efficacy. Future research should combine deficiency assessment, personalized phenotyping, rigorous randomized trials, clinically meaningful endpoints, and long-term safety surveillance (EASL et al., 2024; Sanyal et al., 2010).

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