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Advances in Metabolic Liver Diseases and Nutritional Management of Liver Disease

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Abstract: ***Metabolic liver diseases (MLD) are a group of hepatic disorders directly or indirectly caused by metabolic dysregulation, with a global prevalence of 32. 6% as of 2024. The core pathophysiological features include energy imbalance, insulin resistance, and chronic inflammation, which together drive progression to fibrosis and hepatocellular carcinoma. With the rising global burden of obesity, diabetes, and metabolic syndrome, MLD have become the leading cause of chronic liver disease worldwide. Nutritional intervention, as the cornerstone of MLD management, offers unique therapeutic potential by targeting metabolic derangements. This review systematically summarizes the pathological mechanisms of MLD subtypes—including metabolic dysfunction-associated fatty liver disease (MAFLD), alcoholic liver disease (ALD), and hereditary disorders such as Wilson's disease—and evaluates evidence-based nutritional strategies, including Mediterranean diet, ketogenic diet, high-protein intake, and antioxidant supplementation, to provide a practical reference for clinical practice.***

Keywords: Metabolic liver diseases, Nutritional intervention, Metabolic dysregulation, Insulin resistance, Gut-liver axis**.**

1. Introduction

Metabolic liver diseases (MLD) encompass a spectrum of hepatic conditions arising from inherited or acquired metabolic disturbances [1]. The global prevalence of MLD has reached 32. 6%, according to The Lancet 2024 report, and continues to rise in parallel with the pandemic of obesity, type 2 diabetes, and metabolic syndrome. Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most recent nomenclature, intended to unify diagnostic criteria and better capture the metabolic basis of the disease. The core pathological triad — energy dysmetabolism, insulin resistance, and inflammation — establishes a vicious cycle culminating in liver fibrosis and hepatocellular carcinoma [2]. Conventional pharmacotherapies have limited efficacy, whereas nutritional management, by directly modulating metabolic pathways, has emerged as a promising and accessible strategy. This review aims to dissect the pathogenic mechanisms of major MLD subtypes and to summarize current evidence-based nutritional interventions.

2. Classification and Epidemiology of MLD

Non-alcoholic fatty liver disease (NAFLD): Defined by hepatic steatosis in the absence of significant alcohol intake, closely associated with obesity and insulin resistance. Metabolic dysfunction-associated fatty liver disease (MAFLD): A newer nomenclature (2020) that emphasizes the direct link between metabolic abnormalities and liver injury, covering a broader patient population. Alcoholic liver disease (ALD): Liver damage resulting from chronic excessive alcohol consumption, progressing from steatosis to hepatitis, fibrosis, and cirrhosis. Hereditary metabolic liver diseases: Wilson's disease (copper accumulation) and hemochromatosis (iron overload), caused by specific gene defects. Epidemiologically, MAFLD has surpassed viral hepatitis as the most common chronic liver disease globally, with a prevalence of 6%–27% among Chinese adults and a worrying trend toward younger age in Asia [3]. ALD remains the leading cause of cirrhosis in Western countries; the proportion of drinkers in China increased from 0. 21% in the 1980s to 26. 98% in the early 2000s [4].

3. Pathophysiological Mechanisms

MLD pathophysiology involves multi-organ crosstalk, with shared pathways and subtype-specific drivers.

3.1 Insulin Resistance and Lipid Dysmetabolism

Insulin resistance is the initiating event. Reduced hepatic insulin sensitivity accelerates peripheral lipolysis, increasing free fatty acid (FFA) flux to the liver. Inadequate mitochondrial β-oxidation and enhanced triglyceride synthesis, coupled with reduced VLDL secretion, lead to fat accumulation. Insulin resistance also upregulates sterol regulatory element-binding protein 1c (SREBP-1c), promoting de novo lipogenesis (DNL) and exacerbating steatosis [5].

Recent studies have identified TRIM32 as an E3 ubiquitin ligase that targets the insulin receptor for ubiquitin-mediated degradation, thereby contributing to high-fat diet-induced hepatic insulin resistance. In the setting of increased lipid exposure, hepatic insulin resistance is associated with elevated diacylglycerol (DAG) levels and activation of protein kinase C ε (PKCε). Moreover, excessive hepatic glucose and fructose metabolism further drives insulin resistance through pathways linked to glycolytic overload [6].

3.2 Oxidative Stress and Inflammatory Cascade

Excess lipids impair mitochondrial function, generating excessive reactive oxygen species (ROS). ROS oxidize membrane lipids and activate NF-κB and JNK pathways, inducing pro-inflammatory cytokines such as TNF-α and IL-6. These mediators not only damage hepatocytes but also activate hepatic stellate cells (HSCs), driving fibrogenesis [7]. Hepatic lipid accumulation generally triggers lipotoxicity by mediating endoplasmic reticulum stress, oxidative stress,

organelle dysfunction, and ferroptosis, and induces metabolic dysfunction-associated steatotic liver disease (MASLD) or progresses to metabolic dysfunction-associated steatohepatitis (MASH). The progression from simple steatosis to MASH is characterized by hepatic inflammation, hepatocyte ballooning degeneration, activation of hepatic stellate cells, and fibrogenesis, and may further advance to hepatocellular carcinoma [8].

3.3 Gut Microbiota Dysbiosis and the Gut-liver Axis

Intestinal barrier dysfunction allows lipopolysaccharide (LPS) from Gram-negative bacteria to enter the portal circulation, activating Toll-like receptor 4 (TLR4) on Kupffer cells and promoting inflammatory responses [9]. Probiotic supplementation has emerged as a novel therapeutic approach for treating metabolic-related diseases via the gut-liver axis. Clostridium butyricum has been shown to alleviate liver damage and hepatitis through the gut-liver axis, representing a potential nutritional intervention strategy. Additionally, 2′-fucosyllactose (2′-FL) has been found to ameliorate nonalcoholic steatohepatitis by remodeling the gut microbiota, specifically by increasing Bacteroidota and decreasing Firmicutes at the phylum level. Effective MASLD management should address both nutritional deficiencies and microbial imbalances, with interventions such as prebiotic and probiotic supplementation helping to restore microbial equilibrium [10].

3.4 Alcohol-specific Mechanisms

In ALD, ethanol metabolite acetaldehyde causes injury via: (1) formation of acetaldehyde-protein adducts that trigger immune-mediated hepatocyte necrosis; (2) depletion of NAD^+, impairing the TCA cycle and stimulating fatty acid synthesis; and (3) increasing intestinal permeability, exacerbating endotoxemia in a “gut-liver-gut” loop [11].

3.5 Genetic and Epigenetic Factors

Polymorphisms in PNPLA3 and TM6SF2 affect lipid metabolism and increase MAFLD susceptibility. Epigenetic modifications (DNA methylation, histone acetylation) regulate fibrotic genes such as PPARγ and TGF-β, facilitating HSC activation and fibrosis progression [12].

4. Nutritional Intervention Strategies for Different MLD Subtypes

Personalized nutrition based on subtype-specific metabolic disturbances is essential.

4.1 MAFLD Core Abnormalities: Multi-organ Metabolic Imbalance, Visceral Adiposity, Insulin Resistance, and Gut Dysbiosis.

Recommended: Mediterranean diet (low fat, low carbohydrate, rich in polyunsaturated fatty acids and polyphenols), ketogenic diet, and high-protein intake with modified amino acid profiles [13].

The Mediterranean diet has been extensively studied and demonstrated to improve outcomes in patients with metabolic syndrome. Meta-analyses have shown that, compared with control diets, the Mediterranean diet significantly reduces body weight (weighted mean difference: −2. 38 kg) and improves hepatic health in patients with MASLD/MASH. The Mediterranean diet is characterized by low fat, low carbohydrate content, and richness in polyunsaturated fatty acids and polyphenols. A calorie-restricted Mediterranean diet combined with structured exercise has been proven to significantly improve clinical and biochemical markers in patients with MASH. The very low-calorie ketogenic diet (VLCKD) has also shown promise. An 8-week VLCKD intervention demonstrated that higher baseline steatosis levels were associated with greater reductions in MASLD. Sex differences were observed in the response to VLCKD, with distinct patterns of improvement in hepatic steatosis and fibrosis between overweight and obese male and female patients. Intact ketogenesis was associated with a reduced risk of moderate-to-severe MAFLD. Intermittent fasting (IF) represents an emerging dietary strategy. Studies indicate that intermittent calorie restriction (ICR) and continuous calorie restriction (CCR) have similar effects on reducing liver fat content, suggesting that the ICR 5:2 diet can be an effective alternative for treating MASLD with good adherence. Time-restricted eating is also being investigated as a potential intervention for improving hepatic steatosis and cardiometabolic health [14].

Supplementation with natural antioxidants (polyphenols: resveratrol, quercetin, coumestrol, anthocyanins, epigallocatechin gallate, curcumin; carotenoids: lycopene, astaxanthin, fucoxanthin) helps reduce oxidative stress, inflammation, and fibrosis [15].

4.2 ALD Core Abnormalities: NAD^+ Depletion Due to Ethanol Metabolism, Inhibited Protein Synthesis, and Thiamine Deficiency.

Since ethanol and its metabolites can exacerbate liver damage, complete alcohol abstinence is therefore mandatory.

Diet: high-quality protein, vitamins, trace elements, and high-calorie low-fat meals; recommend 4–6 small meals daily with a nighttime snack (≈200 kcal) given 30–60 min before bedtime. In mild hepatic encephalopathy, protein should be introduced gradually and adjusted according to tolerance [16]. For patients with cirrhosis, daily protein requirements generally range from 1. 2 to 1. 5 g/kg body weight. It is recommended to consume both animal and plant proteins, with a general distribution of 50% from vegetable sources and 50% from animal sources (of which 25% from dairy products and 25% from white meat). For patients with decompensated cirrhosis and severe malnutrition, protein intake may be increased to the upper limit of 1. 5 g/kg/day [17].

4.3 Wilson’s Disease Core Abnormality: Defective ATP7B Protein Leading to Copper Accumulation and Oxidative Damage.

Pharmacological chelation (e. g., penicillamine) combined with nutritional therapy: high protein (2–3 g/kg/day) to promote ceruloplasmin binding; dietary copper restricted to 1–1. 2 mg/day; and supplementation with vitamin B6 and zinc to alleviate symptoms [18].

5. Conclusion

MLD are driven by insulin resistance, oxidative stress, and gut-liver axis dysregulation, affecting nearly one-third of the global population. Nutritional interventions—through precise modulation of glucose-lipid metabolism, mitochondrial repair, and targeted micronutrient restriction—represent a cornerstone of disease management. Future challenges include improving patient adherence, personalizing microbiome-based strategies, and translating novel technologies into practice. Embracing the concept of "food as medicine" will be key to building a precision management framework that reprograms metabolic health and provides sustainable solutions for liver disease prevention and treatment.

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