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HEPATIK STEATOZUN MOLEKÜLER MEKANİZMALARI VE KARBONHİDRAT İLE LİPİD METABOLİZMASIYLA İLİŞKİSİ

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Öz

Metabolik disfonksiyonla ilişkili steatotik karaciğer hastalığı (MASLD), dünya genelinde en yaygın karaciğer hastalığı biçimidir ve hepatik yağ birikimi ile artmış morbidite ve mortaliteyle ilişkilidir. Bu derleme, MASLD'de hepatik steatozun moleküler mekanizmalarını; özellikle lipid ve karbonhidrat metabolizmasındaki bozulmaları değerlendirmeyi amaçlamaktadır. Güncel literatür, yağ asidi alımı, de novo lipogenez, yağ asidi oksidasyonu, lipid dışa aktarımı ve oksidatif stresin etkileşimi açısından anlatısal olarak gözden geçirildi. MASLD'de artmış yağ asidi alımı ve de novo lipogenez, karaciğerin yağ asidi oksidasyonu ve lipid dışa aktarım kapasitesini aşar. Başlangıçta oksidasyonu ve dışa aktarımı artıran telafi mekanizmaları, hastalık ilerledikçe yetersiz kalır. Bu dengesizlik; mitokondriyal işlev bozukluğu ile peroksizomal ve sitokrom P450 aracılı oksidasyonun artmasına bağlı oksidatif stresi artırır. Sonuçta gelişen lipid birikimi ve lipoapoptoz, hepatik hasarı, inflamasyonu ve fibrogenezi destekler. Bu mekanizmaların anlaşılması, hedefe yönelik tedavilerin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Hepatik steatoz, Lipid metabolizması, Metabolik disfonksiyonla ilişkili steatotik karaciğer hastalığı, Oksidatif stres.

THE MOLECULAR MECHANISMS OF HEPATIC STEATOSIS AND ITS RELATIONSHIP WITH CARBOHYDRATE AND LIPID METABOLISM

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent form of liver disease worldwide, affecting approximately one-quarter of the global population. It is characterized by hepatic fat accumulation (steatosis) and is linked to increased morbidity, comorbidities, and mortality. Objectives: This review aims to explore the molecular mechanisms underlying hepatic steatosis in MASLD, with a particular focus on the metabolic pathways involved in lipid and carbohydrate dysregulation. Methods: A narrative review of current literature was conducted to examine the interplay between lipid influx, fatty acid oxidation, lipid export, and oxidative stress in the pathogenesis of MASLD. Special emphasis was placed on the compensatory and maladaptive responses of the liver's metabolic pathways. Results: In MASLD, increased fatty acid uptake and de novo lipogenesis exceed the liver's capacity for fatty acid oxidation and lipid export. While compensatory mechanisms initially upregulate lipid oxidation and export, these become insufficient as disease progresses. This imbalance contributes to oxidative stress through impaired mitochondrial function, as well as enhanced peroxisomal and cytochrome P450-mediated oxidation. The resulting lipid accumulation triggers lipoapoptosis, driving both hepatic injury and systemic metabolic dysfunction. Conclusions: Dysregulated hepatic lipid metabolism in MASLD fosters oxidative stress and cellular injury, thereby promoting disease progression and contributing to associated comorbidities such as cardiovascular disease, diabetes, and obesity. Understanding these mechanisms may inform the development of targeted therapeutic strategies.

Keywords: Hepatic steatosis, Lipid metabolism, Metabolic dysfunction-associated steatotic liver disease (MASLD), Oxidative stress.

1. INTRODUCTION

The global surge in obesity has precipitated a concomitant increase in related metabolic disorders, including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular complications. While simple hepatic steatosis is often deemed metabolically inert, it may evolve into a more progressive phenotype metabolic dysfunction associated steatotic liver disease (MASLD). MASLD has now emerged as a principal contributor to chronic liver pathology, with a worldwide prevalence nearing 25% (1-3). This pattern is prevalent across both industrialized and emerging nations. In the United States alone, MASLD affects nearly one-quarter of the population (4-5). The condition is intricately linked to a constellation of metabolic disturbances such as obesity, T2DM, hyperlipidemia, and systemic hypertension. Individuals afflicted with MASLD frequently present with cardiovascular comorbidities, including atherosclerosis, renal dysfunction, and hypertensive vascular disease (6-7). Epidemiological studies report that approximately 80–90% of obese individuals and 70–80% of those with T2DM exhibit MASLD features (7-8). Nonetheless, heterogeneity in cardiovascular risk among MASLD patients may be influenced by extrinsic modifiers like socioeconomic parameters (9). One prevailing hypothesis suggests that MASLD and T2DM arise from hepatic insulin resistance, which progressively transitions into systemic insulin dysfunction. Disruptions in lipid homeostasis are thought to impair insulin receptor signaling, thereby attenuating insulin secretion and exacerbating resistance (10). Alternatively, compromised insulin secretion and peripheral resistance may heighten hepatic steatosis through enhanced adipose tissue lipolysis. Elevated insulin concentrations in MASLD further promote hepatic de novo lipogenesis. Moreover, impaired insulin action in adipocytes facilitates unregulated lipolysis, increasing the influx of free fatty acids to the liver (11). Brown and Goldstein's concept of "selective and complete insulin resistance" also termed the "pathological paradox" underscores the complexity of these intertwined metabolic derangements (12). Further elucidation is needed regarding how these mechanisms operate in the later stages of hepatic disease, where steatotic content may paradoxically diminish. The liver orchestrates fatty acid dynamics via coordinated processes involving uptake, secretion, biosynthesis, and mitochondrial β-oxidation (2,13). This article delves into the molecular underpinnings of steatosis development in MASLD and its interplay with lipid and glucose metabolism.

1.1. Classification of Liver Diseases

MASLD is initiated by the intracellular accumulation of triglycerides within hepatocytes, accounting for at least 5% of liver mass (4). Steatosis is histologically graded based on the proportion of fat-laden hepatocytes: grade 0 (<5%), grade 1 (5–33%), grade 2 (34–66%), and grade 3 (>66%) (4-5). In the context of obesity, caloric excess overwhelms adipose tissue capacity, resulting in ectopic lipid deposition in visceral organs such as the liver, myocardium, and kidneys (2-3). Central adiposity is particularly deleterious, promoting a chronic pro-inflammatory milieu through the secretion of cytokines and activation of transcriptional networks (2,7). Over time, simple steatosis may transition into non-alcoholic steatohepatitis (NASH), a fibrogenic and inflammatory phenotype of MASLD (6). NASH significantly heightens the risk of adverse outcomes including cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC) (4,7).

1.2. Biomarkers for Liver Dysfunction

Traditional biochemical markers used to assess hepatic integrity include plasma concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin (4). AST and ALT elevations typically reflect hepatocellular injury, although bilirubin levels can be influenced by extraneous variables such as alcohol intake or caloric overload (4). Consequently, research is increasingly focused on discovering more specific and sensitive indicators for MASLD detection and staging. Novel biomarkers under investigation include fragmented cytokeratin-18 (fCK18), β-trophin, and adipokines such as adiponectin and visfatin, which may better reflect disease progression and inflammatory status (2,7).

1.3. Mechanistic Insights into MASLD-to-NASH Transition

Multiple pathophysiological pathways have been posited to account for the escalation from MASLD to NASH (2,10). Both intrinsic cellular disturbances and systemic metabolic insults contribute to this evolution. A pivotal element is adipose-derived inflammation, which aggravates insulin resistance and amplifies free fatty acid flux to the liver via unchecked lipolysis (11). Concurrently, dysbiosis in the gut microbiota may compromise intestinal barrier function, permitting translocation of microbial products such as lipopolysaccharides into the portal circulation. These microbial components stimulate hepatic Kupffer cells, initiating inflammatory cascades and activating hepatic stellate cells (HSCs) (2,14). Lipid overload within hepatocytes triggers endoplasmic reticulum (ER) stress and reactive oxygen species (ROS) generation, both of which are intensified by hypercaloric diets enriched in fat and fructose. The resultant oxidative stress and cytokine milieu including TGF-β, IL-1β, and various chemokines fuel HSC activation and extracellular matrix deposition (2,10). Key fibrogenic mediators include α-smooth muscle actin (α-SMA) and S100A6, which drive cytoskeletal remodeling and fibrosis propagation. Recent studies have further highlighted the contribution of inflammatory cytokines and immune-mediated signaling pathways to the progression of insulin resistance and hepatic inflammation in MASLD (2,3,10). Although MASLD is predominantly defined by hepatic insulin resistance, some data indicate a paradoxical restoration of insulin sensitivity in certain tissues during advanced disease states like cirrhosis. For example, insulin-treated T2DM patients with cirrhosis may experience higher mortality and metabolic complications than non-insulin users (11). Furthermore, insulin responsiveness may differ across tissue types erythrocytes may exhibit heightened insulin binding, whereas adipocytes and immune cells often show diminished receptor activity (10,12). These alterations likely result from progressive hepatocellular loss and fibrotic architectural changes, underscoring the importance of stage specific therapeutic approaches.

1.4. Molecular Mechanisms of Lipid Accumulation in MASLD

The core molecular mechanisms underlying hepatic steatosis are summarized in Table 1. This table highlights critical regulators of lipogenesis, lipid uptake, β-oxidation defects, and insulin signaling dysregulation

Table 1. The Fundamental Molecular Mechanisms of Hepatic Steatosis

Mechanism	Key Molecules/Pathways	Role in Hepatic Steatosis
Lipogenesis	SREBP-1c, ChREBP, ACC, FASN	Promotes fatty acid synthesis via carbohydrate-derived acetyl-CoA; overactivation causes lipid accumulation.
Lipid Uptake	CD36, FATP	Increased expression enhances fatty acid uptake, contributing to lipid overload.
Lipid Oxidation	PPARα, CPT1, AMPK	Impaired oxidation reduces lipid breakdown, worsening steatosis.
VLDL Secretion	MTTP, ApoB100	Dysregulation reduces hepatic lipid export, increasing TG retention.
Insulin Resistance	IRS-1/2, PI3K/AKT, mTORC1	Disrupted insulin signaling increases lipogenesis and hyperglycemia.
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Excessive Lipid Uptake

Fatty acid-binding protein 1 (FABP1), a cytosolic transporter predominantly expressed in hepatic tissue, facilitates the intracellular trafficking of long-chain fatty acids and mitigates lipotoxicity by directing lipids toward oxidation or esterification (10,15). Experimental ablation of FABP1 markedly reduces hepatic triglyceride accrual under fasting conditions. Mice deficient in FABP1 demonstrate resistance to diet-induced hepatic steatosis, although global knockout models may obscure hepatic-specific effects due to systemic metabolic alterations (15). Hepatocyte-targeted FABP1 knockdown via adenoviral short hairpin RNA attenuates steatosis and inflammatory responses (10). Clinically, elevated plasma FABP1 levels correlate with histologic steatosis severity in MASLD patients, though confounding expression in renal tissue may limit its diagnostic utility (2,10). Currently, no pharmacologic agents specifically targeting FABP1 are approved, though it remains an intriguing candidate for therapeutic intervention.

Hepatic lipid equilibrium is modulated by coordinated pathways involving uptake, de novo synthesis, oxidative catabolism, and lipid export. Fatty acid transport proteins (FATPs), particularly FATP2 and FATP5, along with the scavenger receptor CD36, govern hepatic lipid influx. Genetic ablation of FATP5 in murine models reduces hepatic lipid burden under standard dietary conditions (16). FATP5 silencing via adenoviral vectors improves insulin sensitivity in MASLD models, though these effects may partially reflect concurrent weight loss and reduced caloric intake (2,16). A promoter polymorphism enhancing FATP5 transcription is associated with increased hepatic steatosis in male MASLD patients (10). CD36 expression is likewise upregulated in response to high-fat diets and correlates with hepatic fat accumulation in MASLD patients (17). In murine studies, CD36 overexpression alone can induce steatosis, even in the absence of dietary lipid overload (2,17). While the causal link between lipotoxicity and FATP5/CD36 overexpression is well-established, additional investigations are necessary to delineate their precise roles in the transition from simple steatosis to fibrotic NASH.

De Novo Lipogenesis

Hepatic de novo lipogenesis (DNL) is orchestrated by a core set of lipogenic enzymes namely, acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoyl-CoA desaturase-1 (SCD1). ACC catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, a critical substrate for FAS-driven palmitate synthesis. SCD1 facilitates the desaturation of saturated fatty acyl-CoAs such as stearoyl-CoA and palmitoyl-CoA, yielding monounsaturated fatty acids like oleate and palmitoleate. These newly synthesized fatty acids undergo further modifications elongation, desaturation, and esterification prior to storage in the form of triglycerides or incorporation into very-low-density lipoprotein (VLDL) particles for systemic export. Hyperactivation of these enzymes is strongly implicated in hepatic steatosis and elevated plasma triglyceride levels. Notably, excessive palmitate accumulation has been linked to hepatocellular injury and inflammation, hallmarks of steatohepatitis (2,18). The transcriptional regulation of DNL is predominantly mediated by sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate-responsive element-binding protein (ChREBP). SREBP1c overexpression in hepatocytes significantly amplifies the transcription of lipogenic genes, exacerbating lipid deposition in the liver (2,10). ChREBP is indispensable for the physiological lipogenic response to dietary carbohydrates, particularly fructose and sucrose. Murine models lacking ChREBP demonstrate attenuated expression of key lipogenic genes, including ACC and FAS, under high-carbohydrate feeding, highlighting its critical role in carbohydrate-induced lipogenesis (19). Notably, RNA interference targeting ChREBP expression ameliorates hepatic lipid burden, diminishes plasma triglyceride levels, and reduces circulating unesterified fatty acids (10,19). Dysregulated DNL contributes not only to lipid overaccumulation in MASLD but also to the formation of lipotoxic intermediates such as ceramides, which have been implicated in the transition to non-alcoholic steatohepatitis (NASH) (2,11). Nonetheless, therapeutic inhibition of lipogenic enzymes must be approached judiciously, as such interventions risk perturbing essential lipid

homeostasis or fostering compensatory lipotoxic pathways. Table 2 illustrates how excessive carbohydrate intake drives hepatic lipid deposition.

Fatty Acid β-Oxidation

Mitochondrial β-oxidation is the principal catabolic pathway for fatty acid degradation, though very-long-chain fatty acids initially undergo partial oxidation within peroxisomes before entering mitochondrial pathways. Under conditions of lipid overload, such as in obesity, ω-oxidation mediated by cytochrome P450 enzymes emerges as an auxiliary route, albeit one that generates reactive oxygen species (ROS) and may potentiate oxidative stress, inflammation, and progression to NASH (2,10). Carnitine palmitoyltransferase 1 (CPT1), localized on the outer mitochondrial membrane, is pivotal for the translocation of long-chain fatty acids into the mitochondrial matrix. Peroxisome proliferator-activated receptor alpha (PPARα) acts as a master regulator of fatty acid oxidation, modulating the transcription of genes involved in mitochondrial (e.g., CPT1), peroxisomal (e.g., acyl-CoA oxidase, ACOX), and microsomal (e.g., cytochrome P450 4A) pathways (10,20). Hepatocyte-specific PPARα knockout mice subjected to high-fat feeding exhibit severe hepatic steatosis, heightened inflammatory infiltration, and significantly reduced CPT1 expression (2,21). Moreover, PPARα activity is modulated post-translationally by glycogen synthase kinase 3β (GSK3β), which phosphorylates PPARα at serine 73, thereby promoting its ubiquitination and subsequent proteasomal degradation (21). In clinical settings, PPARα expression inversely correlates with MASLD severity and fibrosis stage, underscoring its functional relevance in human disease (20). Pharmacological activation of PPARα alone or in conjunction with PPARγ isoforms represents a promising therapeutic paradigm for mitigating hepatic lipid accumulation and inflammation in MASLD (2,10).

Hepatic Lipid Export

Efficient export of triglycerides via VLDL particles is integral to maintaining hepatic lipid equilibrium. This process requires coordinated activity of apolipoprotein B100 (apoB100) and microsomal triglyceride transfer protein (MTTP). Within the endoplasmic reticulum, MTTP facilitates the lipidation of nascent apoB100, enabling VLDL assembly. Following maturation in the Golgi apparatus, VLDL particles are secreted into the circulation. While moderate lipid influx enhances VLDL secretion, excessive lipid exposure induces ER stress and impairs apoB100 synthesis, promoting intracellular triglyceride retention and hepatic steatosis (22). Genetic variations in MTTP have been linked to altered susceptibility to MASLD, as evidenced in population studies among Han Chinese cohorts (23). MTTP overexpression in murine MASLD models has been shown to rescue impaired VLDL secretion and attenuate hepatic triglyceride accumulation (2). Similarly, reduced apoB100 expression, commonly observed in NASH patients, likely contributes to insufficient lipid export and the development of advanced steatosis (2,22). Perturbations in MTTP or apoB100 function thus play a pivotal role in the pathogenesis of MASLD, particularly under conditions of sustained lipid overload. The dysregulated lipid metabolism pathways contributing to hepatic steatosis are detailed in Table 3.

Insulin Resistance

Insulin resistance (IR) critically amplifies hepatic lipid deposition through multiple mechanisms:

- Enhanced lipolysis in adipose tissue, elevating circulating free fatty acids (FFAs) (10-11).
- Augmented hepatic de novo lipogenesis, driven by hyperinsulinemia and increased substrate availability (2,11).
- Attenuated peripheral glucose uptake, particularly in skeletal muscle, promoting carbohydrate flux toward hepatic lipogenesis (24).

While triglycerides are relatively inert, lipotoxic species such as diacylglycerols, ceramides, and unesterified cholesterol are implicated in hepatocellular injury and fibrogenesis (2,11). Concomitantly, adipose tissue dysfunction leads to diminished adiponectin secretion-a key adipokine that exerts insulin sensitizing, anti-inflammatory, and anti-fibrotic effects on the liver (24).

Dysbiosis

Alterations in the gut microbiome (dysbiosis) are increasingly recognized as contributors to MASLD pathophysiology via:

- Increased intestinal permeability, facilitating translocation of endotoxins to the portal circulation (2,14). • Perturbation of choline metabolism, impacting hepatic lipid export (14). • Enhanced caloric extraction, promoting positive energy balance (2,14).

Notably, butyrate-producing taxa may exert hepatoprotective effects (14). The metabolic benefits observed post-bariatric surgery may, in part, derive from favorable shifts in gut microbial composition (2).

Table 4 summarizes the integrated crosstalk between carbohydrate and lipid metabolism.

Table 2. Interaction with Carbohydrate Metabolism

Metabolic Pathway	Key Regulators	Impact on Steatosis
Glycolysis	PFK-1, PKLR	Excess glucose increases acetyl-CoA, driving lipogenesis.
Gluconeogenesis	PEPCK, G6Pase, FOXO1	Insulin resistance increases gluconeogenesis and lipid synthesis.
Hexosamine Pathway	GFAT, O-GlcNAc	Enhances lipid synthesis via post-translational modification.
Fructose Metabolism	KHK, uric acid	Fructose metabolism increases lipogenesis and oxidative stress.

Table 3. Lipid Metabolism Pathways

Pathway	Key Components	Dysregulation Effects
De Novo Lipogenesis	ACC, FASN, SCD1	Upregulated synthesis leads to excess triglyceride production.
Fatty Acid Oxidation	PPARα, CPT1, ACOX1	Suppression reduces lipid breakdown and increases hepatic fat.
Lipid Droplet Formation	PLIN2, PNPLA3	Promotes fat storage and inhibits lipolysis.
Lipolysis (Adipose)	HSL, ATGL, FABP4	Releases FFAs that overload hepatic β-oxidation.

Table 4. The Interaction Between Carbohydrate and Lipid Metabolism

Interaction	Mechanism	Outcome
ChREBP Activation	Glucose activates ChREBP → lipogenic genes	Links high carbohydrate intake to lipid synthesis.
Insulin-SREBP-1c Axis	Insulin activates SREBP-1c → lipogenesis	Hyperinsulinemia drives lipid accumulation.
AMPK Suppression	High glucose/insulin inhibits AMPK	Reduces FA oxidation and promotes lipogenesis.

Management

Lifestyle Intervention

Sustained weight loss of 5–10% is associated with histological improvement, while reductions exceeding 10% can induce resolution of NASH in non-cirrhotic individuals (4,25). Structured, multidisciplinary weight reduction programs significantly outperform non-specific lifestyle advice (26). The integration of diet and physical activity yields superior outcomes (26), though behavioral inertia necessitates motivational strategies such as cognitive behavioral therapy (8,26).

Dietary Modification

Mediterranean and carbohydrate-restricted diets demonstrate efficacy in reducing hepatic steatosis (9,26). Fructose restriction and alcohol abstinence are advisable. Coffee consumption appears inversely associated with fibrosis progression (9,26). Adjunctive use of nutraceuticals (e.g., silymarin, curcumin, green tea catechins) and probiotics may favorably modulate liver biomarkers (2,9). Vitamin E supplementation has shown histological benefit in select MASLD populations (4).

Physical Activity

Aerobic exercise (150–200 minutes/week) confers greater benefit than resistance training (9,26). High-intensity interval training may exert additive effects in mitigating NASH and fibrosis progression (2,26).

Pharmacologic Therapies

- GLP-1 receptor agonists (e.g., liraglutide) ameliorate steatosis, lobular inflammation, and fibrosis (27-28).
- Tirzepatide, a dual GLP-1/GIP receptor agonist, exhibits promising efficacy in resolving MASH (28).
- SGLT2 inhibitors may surpass GLP-1 analogs in certain clinical endpoints (27).
- Statins are essential for mitigating cardiovascular risk (4,9).
- Resmetirom, a selective thyroid hormone receptor-β agonist, received FDA approval in 2024 for NASH treatment (11).

Current and emerging therapies targeting molecular pathways in hepatic steatosis are outlined in Table 5.

Table 5. Therapeutic Goals for Steatosis

Target	Agents/Approaches	Mechanism
ACC Inhibitors	ND-630, PF-05221304	Inhibit DNL by blocking ACC.
PPARα Agonists	Fenofibrate, pemafibrate	Enhance FA oxidation and VLDL export.
FGF21 Analogs	Pegbelfermin, efruxifermin	Improve insulin sensitivity & reduce lipogenesis.
SCD1 Inhibitors	Aramchol, MK-8245	Reduce TG synthesis via SCD1 inhibition.
GLP-1 R Agonists	Semaglutide, liraglutide	Reduce hepatic fat via weight loss & insulin sensitivity.

Bariatric Surgery

Metabolic surgery leads to resolution or substantial regression of NASH in obese patients without advanced fibrosis (29). Preoperative administration of very-low-calorie diets significantly reduces hepatic volume (6). According to APWG criteria, surgery is indicated in individuals with BMI >32.5 (Asians) or >35 (Caucasians) (6).

Screening and Surveillance

Cardiovascular risk stratification is imperative, given the preponderance of CVD-related mortality (9). Cirrhotic NASH patients necessitate HCC and variceal screening (4), whereas non-cirrhotic cases do not routinely warrant surveillance (8).

Liver Transplantation

MASLD currently ranks as the second-leading indication for liver transplantation in Western countries (6). Comprehensive pre-transplant cardiovascular evaluation is required due to elevated cardiac and renal morbidity. Long-term post-transplant outcomes parallel other etiologies, albeit with increased incidence of cardiovascular and renal complications (6,9).

Prognosis

Fibrosis progression in MASLD is highly variable, averaging one stage every seven years (7,30). NASH substantially elevates risks of cirrhosis, HCC, liver-specific mortality, and overall mortality (25.5 vs. 11.7 deaths per 1000 person-years) (27). Approximately 11% of NASH patients develop cirrhosis over 15 years compared to <1% with MASLD (31). Longitudinal data estimate cirrhosis development in 2–3% of MASLD and 15–20% of NASH patients over 10–20 years (7,30). Obesity independently predicts adverse hepatic and cardiovascular outcomes and contributes to hypertension, diabetes, and accelerated atherosclerosis in patients with MASLD (32-33). In Asia-Pacific regions, approximately 25% of MASLD cases evolve into NASH within three years; however, advanced fibrosis occurs in only ~3.7% (5). Presence of advanced fibrosis correlates with a decreased 10-year survival (~81.5%) (5). MASLD portends increased risks of renal impairment, arrhythmias, myocardial infarction, and cerebrovascular events (2,34). Cardiovascular disease constitutes the predominant cause of mortality, although MASLD also elevates risks of cirrhosis and HCC (7,27,35). Between 2002 and 2012, NASH-related HCC incidence quadrupled in the U.S., surpassing traditional etiologies (2,7). MASLD is now the third-leading cause of HCC, which may develop independently of cirrhosis, with approximately 50% of MASLD-associated HCC cases lacking histological cirrhosis (6-7). Though often considered a hepatic manifestation of metabolic syndrome, MASLD may also

exacerbate systemic metabolic dysfunction through reciprocal feedback (2,33). Importantly, fibrosis stage remains the most robust prognostic determinant for liver-related and all-cause mortality (6-7).

CONCLUSION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a predominant driver of chronic liver pathology and a growing global health concern. Despite its escalating prevalence, therapeutic options remain limited, with lifestyle modification representing the cornerstone of current management. This underscores the pressing need to elucidate the molecular underpinnings of hepatic steatosis and fibrogenesis to enable rational drug design and biomarker development. Therapeutic repurposing of agents originally developed for type 2 diabetes mellitus, obesity, and dyslipidemia such as GLP-1 receptor agonists, SGLT2 inhibitors, and selective thyroid hormone receptor modulators holds substantial promise (11,28). Moreover, integrated approaches targeting insulin resistance, adipose liver crosstalk, gut liver axis, and inflammatory signaling may offer synergistic benefits (2,11). Advancing our mechanistic understanding of lipid handling, mitochondrial dysfunction, immune-metabolic signaling, and fibrogenic activation in MASLD will be pivotal in guiding therapeutic innovation (10). As the disease burden intensifies, an urgent, multidisciplinary effort is required to translate emerging pathophysiologic insights into effective clinical interventions capable of altering the natural history of MASLD.

Abbreviations

ACC, acetyl-CoA carboxylase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; apoB100, apolipoprotein B100; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CCL3, C-C motif chemokine ligand 3; CCL5, C-C motif chemokine ligand 5; CCR1, C-C chemokine receptor type 1; CCR5, C-C chemokine receptor type 5; CD36, cluster of differentiation 36; ChREBP, carbohydrate-responsive element-binding protein; CPT1, carnitine palmitoyltransferase 1; DGAT2, diacylglycerol O-acyltransferase 2; DPP-4, dipeptidyl peptidase-4; ER, endoplasmic reticulum; FABP1, fatty acid-binding protein 1; FAS, fatty acid synthase; FATP, fatty acid transport proteins; fCK18, caspase-generated fragmented cytokeratin 18; FDA, Food and Drug Administration; FGF, fibroblast growth factor; GGT, γ-glutamyl transferase; GLP-1, glucagon-like peptide-1; GSK3β, glycogen synthase kinase 3β; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; HTN, hypertension; IL-1β, interleukin 1β; IR, insulin resistance; MASLD, Metabolic dysfunction-associated steatotic liver disease; MCP1, monocyte chemoattractant protein-1; mTOR, mammalian target of rapamycin; MTTP, microsomal triglyceride transfer protein; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family pyrin domain containing 3; PDE4, phosphodiesterase-4; PEMT, phosphatidylethanolamine N-methyltransferase; PPAR, peroxisome proliferator-activated receptor; RCTs, randomized controlled trials; SCD1, stearoyl-CoA desaturase-1; SGLT2, sodium-glucose cotransporter-2; shRNA, short hairpin RNA; SIRT1, Sirtuin 1; SREBP1c, sterol regulatory element-binding protein 1c; TGFβ, transforming growth factor-β; THR-β, thyroid hormone receptor-β; T2DM, Type 2 diabetes mellitus; VLDL, very-low-density lipoprotein.

ARAŞTIRMA VE ETİK BEYANI

Araştırma ve Yayın Etiği Beyanı	Bu çalışma araştırma ve yayın etiği ilkelerine uygun olarak hazırlanmıştır. Çalışmanın tüm sorumluluğu yazara aittir.
Bilgilendirme	Bu çalışma anlatısal derleme niteliğindedir.
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