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Review

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Metabolic Dysfunction–Associated Steatotic Liver Disease Complicated by Diabetes: Pathophysiology and Emerging Therapies

Hisanori Goto[1,2,*], Toshinari Takamura[1]

Departments of [1]Endocrinology and Metabolism, [2]Biochemistry and Molecular Vascular Biology, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a liver manifestation of diabetes that is often associated with obesity and insulin resistance, with hyperglycemia worsening its progression. Recent studies have shown a bidirectional relationship between MASLD and diabetes: MASLD contributes to insulin resistance, and hyperglycemia accelerates the progression of MASLD to metabolic dysfunction-associated steatohepatitis (MASH). Hepatokines upregulated by overnutrition and hyperglycemia are implicated in the link between liver steatosis and insulin resistance in skeletal muscle, highlighting inter-organ crosstalk in the progression of both MASLD and diabetes. In individuals with diabetes, hyperglycemia and free fatty acid influx promote *de novo* lipogenesis and enhance lipid oxidation and oxidative phosphorylation in the liver, potentially leading to increased oxidative stress, inflammation, and fibrosis. Transcriptome analyses of human MASH and diabetic MASH model animals have revealed liver endothelial cell damage in diabetic conditions. Most drugs proven effective for MASH in randomized controlled trials are antidiabetic agents. Recently, pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, and dual agonists of glucose-dependent insulinotropic polypeptide and GLP-1 have been recommended as preferred options for glycemic control in MASH patients with type 2 diabetes mellitus. Meanwhile, the efficacy of sodium-glucose cotransporter 2 inhibitors for MASH has also been reported, primarily in East Asia. Given the diversity in MASLD/MASH pathology among populations, ranging from lean to obese individuals with and without diabetes, population-specific approaches might help elucidate the pathogenesis of MASLD/MASH and develop treatment strategies.

Key words: Diabetes complications, Diabetes mellitus, Glucagon-like peptide-1 receptor agonists, Non-alcoholic fatty liver disease, Sodium-glucose transporter 2 inhibitors

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*Corresponding author
Hisanori Goto

https://orcid.org/0009-0008-4723-6156

Department of Endocrinology and Metabolism, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8640, Japan
Tel: +81-76-265-2711
Fax: +81-76-234-4214
E-mail: pitanori19890838@gmail.com

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) arises in the context of obesity and insulin resistance, with hyperglycemia serving as an exacerbating factor. Consequently, MASLD is regarded as a hepatic manifestation of type 2 diabetes mellitus (T2DM). This review discusses the bidirectional relationship between MASLD and T2DM, as identified through clinical and epidemiological studies. Additionally, we explore the inter-organ interactions and mechanisms underlying that relationship. Furthermore, we highlight the possibility that MASLD, along with its more severe form—metabolic dysfunction-associated steatohepatitis (MASH)—are complications of diabetes, focusing on insights gained from analyses of MASLD/MASH livers, predominantly from East Asian populations. Finally, we discuss therapeutic strategies informed by molecular pathophysiology.

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THE BIDIRECTIONAL RELATIONSHIP BETWEEN MASLD AND T2DM

Epidemiological studies suggest that MASLD might play a direct role in the pathogenesis of T2DM. A meta-analysis of observational studies revealed that individuals with MASLD have a 2.19-fold higher risk of developing T2DM over approximately 5 years than those without MASLD.[1] Furthermore, Mendelian randomization studies have shown that risk alleles of well-known MASLD susceptibility genes, such as patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*), are associated with an increased risk of developing T2DM.[2] Improvements in hepatic fat accumulation have been reported to lower the risk of developing T2DM.[3] Cohort studies involving MASLD patients have shown that higher histological fibrosis and steatosis scores are linked to an increased risk of developing T2DM.[4] In other words, a greater severity of MASLD corresponds to a greater impairment in glucose tolerance.

Animal studies using hyperinsulinemic-euglycemic clamps and stable isotope-labeled glucose have investigated the relationship between organ-specific insulin resistance and fat accumulation in the liver, skeletal muscle, and adipose tissue to shed light on the mechanisms through which MASLD contributes to abnormalities in glucose metabolism.[5] Hepatic fat accumulation is associated with insulin resistance in skeletal muscle and markers of basal hepatic glucose production (hepatic glucose production × fasting blood insulin) but not with hepatic insulin sensitivity (hepatic glucose production suppression rate). The link between hepatic fat and skeletal muscle insulin resistance will be discussed in the next section. Here, we focus on how hepatic fat enhances hepatic glucose production. Hepatic fat accumulation might increase basal glucose production through a mechanism independent of insulin action. Several mechanisms have been proposed to explain this phenomenon. Research has shown that, in the context of obesity, proteasome dysfunction in the liver inhibits the degradation of forkhead box O1 (FoxO1), facilitating its nuclear translocation and subsequent promotion of excessive gluconeogenesis.[6] Furthermore, obesity-associated insulin resistance in adipose tissue promotes increased lipolysis, elevating the supply of free fatty acids (FFAs) to the liver and contributing to the development of liver steatosis. This influx of FFAs also serves as an energy source via β-oxidation and activates gluconeogenesis by increasing acetyl-coenzyme A levels, which allosterically stimulate pyruvate carboxylase (PC).[7] Hepatic anaplerosis, driven by mitochondrial PC to replenish tricarboxylic acid (TCA) cycle intermediates, works in concert with cataplerotic efflux to support gluconeogenesis through phosphoenolpyruvate carboxykinase. Indeed, it has been reported that individuals with high intrahepatic triglyceride (IHTG) levels exhibit a 50% increase in anaplerotic flux and a 30% increase in gluconeogenesis, compared with those with low IHTG levels.[8]

The next question is, how does diabetes affect the onset and progression of MASLD? A prospective epidemiological study that analyzed a large electronic health record database reported that the presence of diabetes approximately doubled the risk of developing MASLD, even at the same body mass index (BMI).[9] Additionally, longitudinal liver biopsy studies have demonstrated that hyperglycemia not only exacerbates hepatic fat accumulation but also promotes liver fibrosis, the most critical prognostic factor for MASH.[10,11] In a multivariate analysis using a generalized linear mixed model to investigate factors associated with liver fibrosis progression in serial liver biopsies, glycosylated hemoglobin (HbA1c) levels correlated positively with fibrosis progression.[10] Diabetes thus contributes to both the onset and progression of MASLD.

Mechanistically, in the diabetic state, hyperglycemia and hyperinsulinemia activate carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element binding protein 1c (SREBP1c), respectively, thereby promoting *de novo* lipogenesis in the liver.[12] Additionally, insulin resistance in adipose tissue increases lipolysis, resulting in an excess supply of fatty acids to the liver, which further promotes hepatic fat accumulation.[13,14] These excess fatty acids are also oxidized in the liver, producing reactive oxygen species (ROS) in mitochondria[15] and peroxisomes.[16] These ROS induce the production of inflammatory cytokines and cause hepatocyte injury, leading to chronic inflammation and fibrosis progression.[17] On the other hand, studies using simple hepatic steatosis models induced by high-fat diets have shown no involvement of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase (NOX), an enzyme that generates ROS independently of mitochondria and peroxisomes, in ROS production.[18] However, elevated NOX4 expression has been observed in human MASH, and the

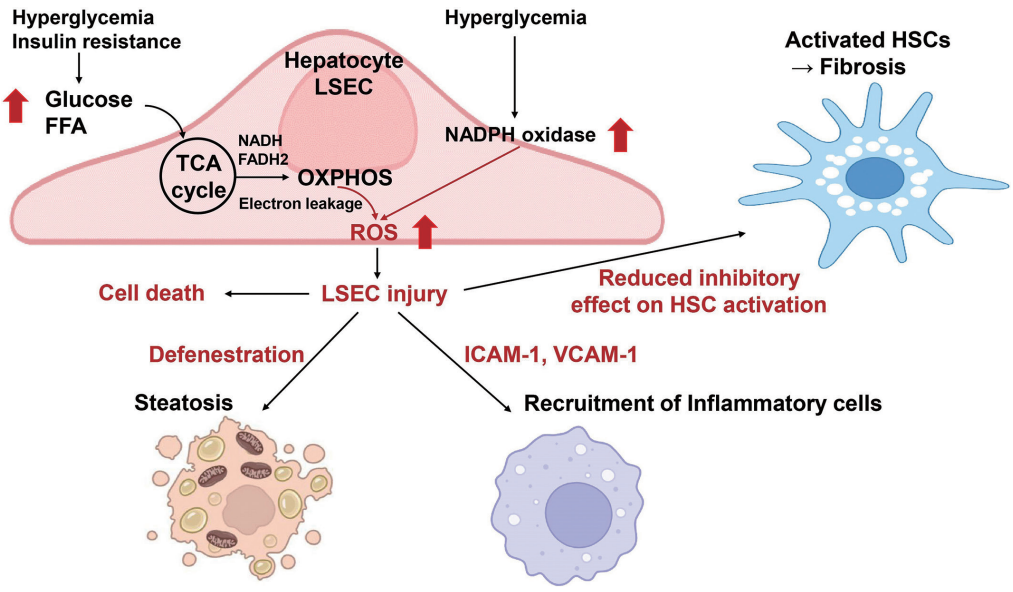


Figure 1. Molecular pathways by which hyperglycemia exacerbates hepatic injury. In type 2 diabetes mellitus, insulin resistance in adipose tissue promotes lipolysis, increasing the influx of free fatty acids (FFAs) into the liver. These excess FFAs contribute to hepatic steatosis and undergo oxidation, leading to the production of reactive oxygen species (ROS). Concurrently, hyperglycemia accelerates the tricarboxylic acid (TCA) cycle, increasing the generation of reducing equivalents, and upregulates the expression of oxidative phosphorylation (OXPHOS)-related genes. This overloads the electron transport chain, resulting in electron leakage and enhanced ROS production. Additionally, hyperglycemia can activate nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, further elevating hepatic ROS levels. Collectively, these mechanisms exacerbate oxidative stress and drive the progression of liver injury in type 2 diabetes mellitus. Importantly, this oxidative stress is not confined to hepatocytes but also affects liver sinusoidal endothelial cells (LSECs). Under physiological conditions, LSECs regulate liver-resident macrophages and hepatic stellate cells (HSCs), exerting anti-inflammatory and antifibrotic effects. However, LSEC injury caused by hyperglycemia can lead to both increased expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) and diminished inhibitory regulation of HSC activation, thereby promoting inflammation and fibrosis. Moreover, capillarization of damaged LSECs might further contribute to the progression of hepatic steatosis. Diabetes-induced endothelial cell damage might play a central role in the development and progression of metabolic dysfunction-associated steatohepatitis. NADH, nicotinamide-adenine dinucleotide; FADH2, flavin adenine dinucleotide.

inhibition of NOX4 expression has been shown to ameliorate fibrosis in dietary MASH models in mice.[19] Hyperglycemia has been reported to induce NOX4 expression in the kidney, myocardium, vascular endothelium, and Schwann cells, contributing to the progression of diabetic vascular complications.[20] Similarly, NOX4 might play a role in exacerbating MASH pathology in the liver in hyperglycemic conditions. Additionally, hyperglycemia has been shown to upregulate the expression of genes involved in oxidative phosphorylation (OXPHOS) in the livers of individuals with T2DM independently of obesity.[21] This upregulation appears to function as a compensatory mechanism to manage the increased glucose substrate supply, which accelerates the TCA cycle and elevates the production of reducing equivalents, such as nicotinamide-adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2). The resulting surplus of reducing equivalents imposes an excessive load on the electron transport chain, particularly at complexes I and III, where electron leakage is most likely to occur.[22] This electron backlog promotes ROS production as these electrons prematurely react with oxygen, generating superoxide and other ROS (Fig. 1). Consequently, hyperglycemia-driven upregulation of OXPHOS can inadvertently enhance ROS overproduction, disrupting the mitochondrial redox balance and contributing to oxidative stress. This oxidative burden likely exacerbates liver damage and accelerates the progression of diabetic liver pathology, leading to fibrosis, in T2DM. Notably, a longitudinal study of the liver transcriptome in patients with MASH complicated by diabetes observed increased expression of genes associated with hypoxia and oxidative stress responses in the liver when HbA1c levels progressively increased over time.[10]

Furthermore, even in persons with T2DM without MASH, profibrotic factors such as the transforming growth factor (TGF) superfamily and platelet-derived growth factor (PDGF)/vascular en-

Table 1. Gene set enrichment analysis of cell type–specific gene sets in MASH livers with type 2 diabetes mellitus

	Gene set	LS permutation *P*	Up or down
Trajectory analysis of fibrosis in MASH livers [10]			
MASH group with fibrosis progression	Zone 3 hepatocytes	< 0.00001	Down
	Zone 1 hepatocytes	< 0.00001	Down
	Hepatic stellate cells	0.00144	Up
	NK cells	0.0042	Down
	Noninflammatory macrophages	0.0043	Down
	Central LSECs	0.0049	Down
Comparisons before and after drug administration in randomized controlled trials [72]			
SGLT2 inhibitor treatment group	γδ T cells	< 0.00001	Down
	Zone 3 hepatocytes	< 0.00001	Up
	Zone 2 hepatocytes	< 0.00001	Up
	Inflammatory macrophages	< 0.00001	Down
	Hepatic stellate cells	< 0.00001	Down
	Plasma cells	0.00011	Down
	Central LSECs	0.00053	Up

This table was adapted and modified from Sako et al. [10], with permission from John Wiley and Sons and Takeshita et al. [72], with permission from John Wiley and Sons. Cell type–specific gene sets in the human liver were derived from MacParland et al. [24]. A gene set enrichment analysis revealed that gene groups showing changes before and after the progression of liver fibrosis over time and those showing changes before and after the administration of SGLT2 inhibitors were enriched in gene sets characteristic of specific liver-resident cell populations.
MASH, metabolic dysfunction-associated steatohepatitis; LS, least square; NK, natural killer; LSEC, liver sinusoidal endothelial cell; SGLT2, sodium-glucose cotransporter 2.

dothelial growth factor (VEGF), which activate hepatic stellate cells (HSCs), have been observed to be upregulated.[23] These findings suggest that diabetic livers might be predisposed to fibrosis.

In a longitudinal liver biopsy study that reported a positive correlation between HbA1c levels and liver fibrosis in persons with T2DM, longitudinal changes in the liver transcriptome were analyzed alongside clinical information.[10] An RNA-seq analysis of liver samples revealed that genes characteristic of HSCs were upregulated in patients with progressive fibrosis (Table 1). In contrast, in patients whose glucose control improved over time, the expression of HSC-related genes was downregulated. The critical role of glycemic control in preventing liver fibrosis is thus also supported by changes in gene signatures.

In addition, fibrosis progression in human diabetic MASH livers was associated with the coordinated downregulation of genes specific to liver sinusoidal endothelial cells (LSECs) in the pericentral region of the liver (zone 3) (Table 1).[10,24] To further elucidate the effect of diabetes on MASH pathology, we established a diabetic MASH model in which diabetes was induced by streptozotocin in MASH mice treated with carbon tetrachloride and a high-fat diet. The effect of diabetes on each liver-resident cell population was then examined using single-cell transcriptome analyses.[25] A single-cell RNA-seq analysis focusing on non-parenchymal cells of the liver revealed a significant decrease in the proportion of LSECs and an increase in the proportion of bone marrow-derived inflammatory macrophages in diabetic steatohepatitis, compared with nondiabetic steatohepatitis. A pathway analysis of gene expression in LSECs showed upregulation of genes associated with apoptosis and leukocyte migration.[25] LSECs are specialized vascular endothelial cells that lack a basement membrane and possess numerous fenestrae, enabling efficient exchange of substances. In their steady state, LSECs regulate the activation of Kupffer cells, the liver-resident macrophages, as well as HSCs, and exert anti-inflammatory[26] and antifibrotic effects[27] mediated by nitric oxide derived from endothelial nitric oxide synthase. In the pathogenesis of MASLD/MASH, capillarization—characterized by basement membrane formation and the loss of fenestrae in LSECs—occurs at a relatively early stage. In plasmalemma vesicle associated protein (*Plvap*)-deficient mice, in which the loss of fenestrae in LSECs is induced, a pronounced hepatic steatosis phenotype has been observed.[28] It is hypothesized that the capillarization of LSECs impairs material exchange, reducing the lipid supply to hepatocytes and thereby accelerating *de novo*

lipogenesis and exacerbating hepatic steatosis. As MASLD progresses, LSECs express adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which act as key initiators of inflammatory cell recruitment and activation.[29] When LSEC injury occurs, its inhibitory effect on HSC activation is diminished, leading to the progression of hepatic fibrosis (Fig. 1).[30,31] This LSEC injury phenotype appears to be a common feature across various animal models of MASH. In our diabetic MASH model, insulinopenic diabetes further exacerbated LSEC injury, compared with the nondiabetic MASH model.[25] These findings collectively suggest that diabetes-induced endothelial cell injury might play a central role in the pathogenesis of liver steatosis, inflammation, and fibrosis, as well as in other vascular complications of diabetes.

Furthermore, a study involving serial liver biopsies from persons with T2DM demonstrated that insulin therapy was an independent factor in reducing fibrosis in patients with MASH and T2DM.[11] Recently, in a MASH model with insulin-deficient diabetes (stelic animal model [STAM] mice), insulin therapy ameliorated hepatic steatosis, fibrosis, and hepatocarcinogenesis.[32] Notably, the hepatoprotective effect of insulin was abolished in mice with intestine-specific insulin receptor deficiency, suggesting that insulin action in the intestine, mediated through alterations in the gut microbiota, contributes to liver disease pathology.[32] In addition, in poorly controlled diabetes, the signaling of the growth hormone/insulin-like growth factor (IGF-1) axis is diminished.[33,34] In patients with growth hormone deficiency, the risk of MASH progression is elevated, and growth hormone supplementation has been shown to improve liver pathology in MASH.[35] In the general population, adults with higher serum IGF-1 levels have a lower risk of MASLD.[36] Among adults with MASLD, those with higher degrees of liver inflammation and fibrosis exhibit lower serum IGF-1 levels.[37] The potential role of IGF-1 signaling in anti-inflammatory and antifibrotic processes is supported by its effects on macrophages[38] and HSCs,[39] both of which directly contribute to liver inflammation and fibrosis. Studies of adipose macrophage phenotypes in obese myeloid type 1 IGF receptor (IGF-1R) knockout mice have demonstrated a reduction in transcripts associated with anti-inflammatory M2-like macrophage activation.[38] Additionally, IGF-1 has been shown to induce senescence in HSCs, inactivate them, and suppress fibrosis in a p53-dependent manner.[39] These findings regarding the association of IGF-1 with MASLD/MASH pathology suggest that IGF-1 signaling, similar to insulin signaling and also diminished in the diabetic state, might contribute to the onset and progression of MASLD/MASH.

In East Asian patients with MASLD complicated by T2DM, hyperglycemia, as mentioned earlier, is a key aggravating factor for inflammation and fibrosis, with insulin therapy potentially offering protective effects against liver fibrosis progression. In contrast, in Western countries, obesity and insulin resistance have been identified as the primary exacerbating factors in MASLD, and the influence of hyperglycemia is considered relatively minor, with no evidence supporting a protective effect of insulin therapy. In Western-type MASLD, the stronger impact of obesity and insulin resistance on worsening hepatic steatosis might overshadow the contribution of hyperglycemia and insulinopenic diabetes to MASLD progression. Furthermore, it is well established that East Asians have lower insulin secretory capacity than Western populations.[40,41] Differences in insulin secretory capacity might contribute to racial variations in the hepatoprotective effects of insulin therapy. Just as the pathophysiology of T2DM varies between East Asians and Western populations, the hepatic manifestations of MASLD/MASH associated with T2DM might also differ by ethnicity.

Thus, epidemiological and clinical studies have established a bidirectional causal relationship between MASLD/MASH and diabetes, and basic research using human and mouse models has elucidated its molecular mechanisms.

ORGAN CROSSTALK IN MASLD/MASH PATHOPHYSIOLOGY

As mentioned in the previous section, hepatic fat accumulation correlates negatively with insulin sensitivity in skeletal muscle. Although the causal relationship has not been fully elucidated in clinical studies, it is possible that hepatokines secreted by the liver, acting on skeletal muscle, contribute to the mechanism by which hepatic steatosis reduces insulin sensitivity in skeletal muscle. One such hepatokine is leukocyte cell-derived chemotaxin 2 (LECT2), whose serum levels correlate positively with BMI, waist circumference, and liver fat accumulation and whose expression is suppressed

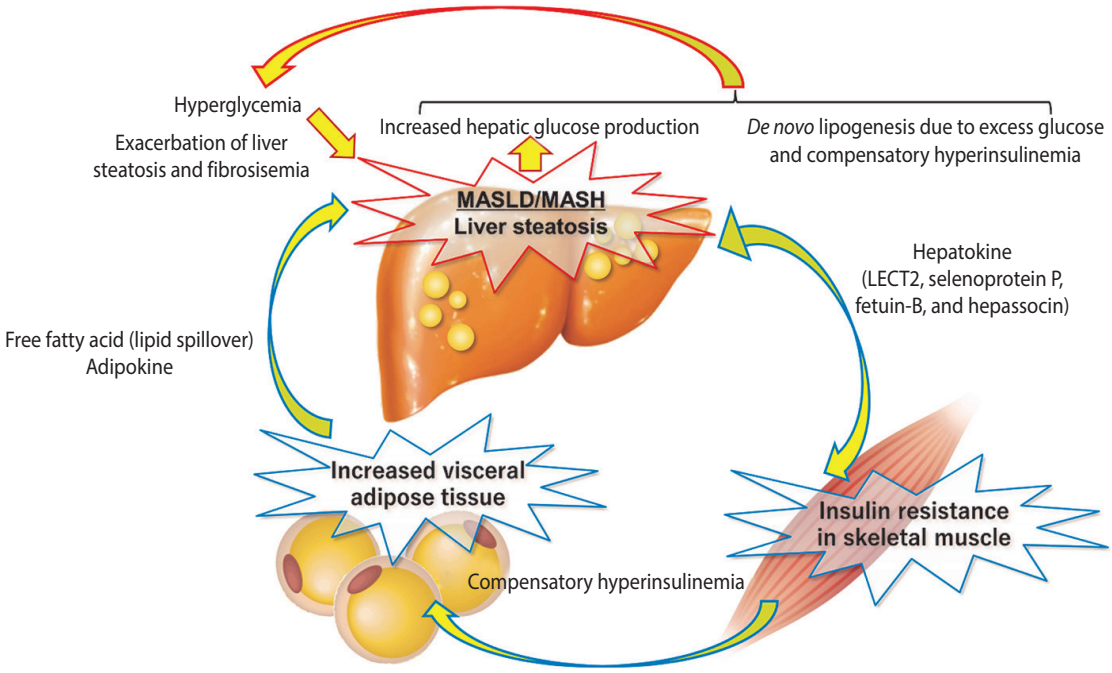


Figure 2. The bidirectional relationship between metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) and diabetes. The interplay between MASLD/MASH and the pathology of type 2 diabetes mellitus is bidirectional. In steatotic livers, hepatokines such as leukocyte cell-derived chemotaxin 2 (LECT2), selenoprotein P, fetuin-A, fetuin-B, and hepassocin are upregulated, contributing to insulin resistance in skeletal muscle. Skeletal muscle functions as a nutrient sink, preventing excess nutrient substrates from reaching the liver and adipose tissue. However, in the presence of skeletal muscle insulin resistance, excess glucose is directed to the liver, where it can drive *de novo* lipogenesis and increase the metabolic load on the liver. Moreover, hyperglycemia can aggravate hepatic steatosis and fibrosis, forming a vicious cycle between MASLD/MASH and diabetic pathology. Additionally, insulin resistance in adipose tissue further exacerbates hepatic steatosis by promoting lipid spillover of fatty acids.

by adenosine monophosphate (AMP) kinase activation. In response to overnutrition, LECT2 levels rise, inducing insulin resistance in skeletal muscle through the phosphorylation of the c-Jun N-terminal kinase.[42] This effect supports a causal relationship whereby hepatic fat accumulation promotes insulin resistance in skeletal muscle.

Another hepatokine that acts on skeletal muscle is selenoprotein P (SeP), which is suppressed by insulin but upregulated by high glucose and FFAs, contributing to insulin resistance in both the liver and skeletal muscle.[43] SeP also inactivates AMP-activated protein kinase in skeletal muscle by scavenging ROS generated during exercise, thereby hindering the development of aerobic capacity.[44] Fetuin-A is another hepatokine that is upregulated by FFAs and glucose and induces insulin resistance in both the liver and skeletal muscle by inhibiting the activity of the insulin receptor tyrosine kinase in these organs.[45] In complex with FFAs, fetuin-A activates toll-like receptor 4, inducing inflammatory signaling and insulin resistance in adipocytes and macrophages.[46] Other hepatokines linking hepatic fat accumulation to insulin resistance in skeletal muscle include fetuin-B and hepassocin, which are upregulated in the presence of hepatic fat accumulation and induce insulin resistance in both the liver and skeletal muscle.[47,48] Organ crosstalk between the liver and skeletal muscle, mediated by overnutrition-induced hepatokines, likely contributes to worsening glucose tolerance in MASLD patients (Fig. 2).

On the other hand, Mendelian randomization analyses have shown that not all cases of steatotic liver increase the risk of T2DM. Certain alleles that promote hepatic fat accumulation, such as those of glycerol-3-phosphate acyltransferase, mitochondrial (*GPAM*) and chromosome 2 open reading frame 16 (*C2orf16*), have been reported to reduce the risk of T2DM, suggesting the existence of metabolically healthy liver steatosis.[49] The term 'metabolically healthy liver steatosis,' in this context, describes a state in which liver steatosis is present but not accompanied by increased insulin resistance or worsening impaired glucose tolerance. In contrast, it has been

proposed that populations with increased hepatic insulin resistance and metabolically unhealthy steatotic liver-associated insulin resistance might be identified by analyzing the expression levels of hepatokines, such as fetuin-A.[45] These populations form a cluster distinct from those with visceral obesity-associated insulin resistance based on their higher hepatokine and lower adipokine profiles. They exhibit a similar degree of hepatic steatosis but greater hepatic insulin resistance, compared with those with visceral obesity. Considering this context, the relationships among liver steatosis, insulin resistance, and glucose intolerance could be explored in greater detail by integrating genetic backgrounds and hepatokine profiles.

Regarding the causal relationship between skeletal muscle insulin resistance and hepatic steatosis, it is worth exploring the hypothesis that skeletal muscle insulin resistance precedes and contributes to hepatic fat accumulation (Fig. 2). Skeletal muscle insulin resistance has been identified as the earliest detectable phenotype in individuals with a genetic predisposition to T2DM.[50,51] Moreover, observational studies have shown that glycogen synthesis in skeletal muscle is reduced in elderly individuals, compared with younger ones, whereas hepatic *de novo* lipogenesis is enhanced. This shift suggests that skeletal muscle insulin resistance redirects postprandial carbohydrate storage from muscle glycogen to hepatic *de novo* lipogenesis.[52] A recent randomized controlled trial (RCT) revealed that a 10-month energy restriction and exercise intervention significantly improved skeletal muscle insulin sensitivity in the intervention group, with this improvement strongly correlated with the NAFLD activity score (NAS) reduction, a metric for assessing MASH resolution.[53] Additionally, mice with skeletal muscle-specific insulin receptor knockout exhibit compensatory hyperinsulinemia and increased adipose tissue mass.[54] An observational study in humans has shown that insulin resistance in skeletal muscle is associated with increased adipose tissue mass and fat accumulation in the liver.[5]

These findings suggest that skeletal muscle acts as an energy sink, preventing excess nutrient substrates from reaching the liver and thereby reducing its metabolic load. In insulin-resistant skeletal muscle, unabsorbed glucose is redirected to the liver and adipose tissue, where it serves as a substrate for *de novo* lipogenesis. This process, combined with compensatory hyperinsulinemia, could promote hepatic fat accumulation. Additionally, the overspill of FFAs from increased adipose tissue can further exacerbate hepatic steatosis (Fig. 2).[13,14]

To establish a causal relationship between skeletal muscle insulin resistance and hepatic fat accumulation, further studies using skeletal muscle-specific genetically modified animal models, as well as intervention studies aimed at improving MASLD without altering skeletal muscle insulin resistance, are needed.

Regarding liver fibrosis, cross-sectional observational studies in humans have revealed that a decline in skeletal muscle quality—characterized by an increase in non-contractile tissue mass, including intramuscular fat—is significantly associated with worsening liver fibrosis indicators.[55] However, the causal relationship between liver fibrosis and skeletal muscle pathology remains unclear, and longitudinal studies are needed to establish causality.

THERAPEUTIC STRATEGIES BASED ON THE PATHOPHYSIOLOGY OF MASLD/MASH

RCTs have demonstrated that certain diabetes medications improve the histological features of MASLD/MASH, highlighting their secondary effects on liver pathology (Table 2). Among the thiazolidinediones, which act as peroxisome proliferator-activated receptor γ (PPARγ) agonists, pioglitazone has shown efficacy in improving MASLD/MASH in several randomized trials.[56,57] Those studies reported significant improvements in steatosis, inflammation, and ballooning degeneration, compared with placebo. Of note, one RCT demonstrated that pioglitazone produced a statistically significant improvement in liver fibrosis, the most important prognostic factor in MASLD/MASH,[58] compared with placebo.[57] Thiazolidinediones, as PPARγ ligands, are postulated to ameliorate MASLD/MASH by enhancing insulin sensitivity, inhibiting adipose tissue lipolysis, reducing the influx of FFAs into the liver, and mitigating hepatic lipid uptake and lipogenesis.[59,60] PPARγ activation promotes the differentiation of monocytes into anti-inflammatory M2 macrophages and exerts an anti-inflammatory effect by reducing inflammatory cytokines such as tumor necrosis factor-α and monocyte chemoattractant protein-1 (MCP-1) , which are essential in MASH pathogenesis.[61] Thiazolidinediones also inhibit the mitochondrial pyruvate carrier (MPC),[62] and preclinical studies have demonstrated that MPC inhibitors lacking PPARγ-activating properties reduce liver fibrosis by limiting HSC activation.[63]

Table 2. Randomized controlled trials in humans assessing the effects of antihyperglycemic therapies on liver histology

Author (year)	F1/F2/F3/F4 (%)	Drug/Dose (mg/day)	Duration (wk)	Number	Baseline HbA1c (%)	Improvement of fibrosis stage (%)	Improvement of fibrosis stage no worsening of MASH (%)	Improvement of histological stage		
								Steatosis (%)	Ballooning (%)	Inflammation (%)
Belfort et al. (2006)[56]	45/19/19/0	Placebo	24	21	6.2 ± 1.1	33	NA	38	24	29
		Pioglitazone 45	24	26	6.2 ± 1.5	46	NA	65	54	65
Cusi et al. (2016)[57]	NA	Placebo	72	51	6.3 ± 1.0	25	NA	26	24	22
		Pioglitazone 45	72	50	6.4 ± 1.0	39	NA	71	51	49
Armstrong et al. (2016)[64]	27/16/42/13	Placebo	48	20	5.9 ± 0.7	14	NA	45	32	55
		Liraglutide 1.8	48	23	6.0 ± 0.9	26	NA	83	61	48
Newsome et al. (2021)[65]	0/23/49/0	Placebo	72	58	7.3 ± 1.2	34	33	26	39	26
		Semaglutide 0.1	72	57	7.4 ± 1.3	53	49	53	53	41
		Semaglutide 0.2	72	59	7.2 ± 1.0	36	32	60	71	47
		Semaglutide 0.4	72	56	7.2 ± 1.2	46	43	63	74	38
Takeshita et al. (2022)[73]	45/28/13/3	Tofogliflozin 20	48	20	7.9 (7.4–8.4)	60	NA	65	55	50
		Glimepiride 0.5–6.0	48	20	8.2 (7.3–9.2)	35	NA	30	25	15
Loomba et al. (2024)[66]	0/43/57/0	Placebo	52	47	6.8 ± 1.2	NA	30	32	54	36
		Tirzepatide 5	52	47	6.6 ± 1.3	NA	55	62	77	61
		Tirzepatide 10	52	48	6.4 ± 1.1	NA	51	73	79	62
		Tirzepatide 15	52	48	6.4 ± 0.9	NA	51	75	82	62
Sanyal et al. (2024)[67]	24/41/35/0	Placebo	48	66	7.1 ± 0.9	26	22	NA	NA	NA
		Survodutide 2.4	48	56	6.8 ± 1.0	50	50	NA	NA	NA
		Survodutide 4.8	48	53	7.0 ± 1.1	45	45	NA	NA	NA
		Survodutide 6.0	48	44	6.8 ± 1.0	52	50	NA	NA	NA

Values are presented as mean ± standard deviation or median (interquartile range).
HbA1c, glycosylated hemoglobin; MASH, metabolic dysfunction-associated steatohepatitis; NA, not available.

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and semaglutide, reduced weight and achieved MASH resolution—defined as the absence of steatotic liver disease or simple steatosis without steatohepatitis or worsening fibrosis—in double-blind randomized trials.[64,65] Two recent reports have demonstrated the effectiveness of agonists targeting multiple receptors, including the GLP-1 receptor (GLP-1R). These include tirzepatide,[66] a dual agonist of the GLP-1R and glucose-dependent insulinotropic polypeptide (GIP) receptor, and survodutide,[67] a dual agonist of the GLP-1R and glucagon receptor. Both showed significantly higher rates of MASH resolution without worsening fibrosis than placebo.[66,67] The direct effects of GLP-1 receptor agonists (GLP-1RA) on MASH pathology, independent of their effects on body weight, insulin resistance, and glycemic control, remain a topic of active investigation.[68,69] Given that GLP-1Rs are not expressed in the human liver,[70] the effects of GLP-1R agonists on MASH are likely indirect, mediated through reductions in caloric intake, body weight, and insulin resistance, which collectively decrease hepatic lipid accumulation and inflammation. Notably, GLP-1R agonists reduce macrophage infiltration in adipose tissue.[69] Further investigation is needed to determine whether GLP-1R agonists exert weight loss-independent effects, including potential actions mediated by GLP-1R expression in non-parenchymal liver cells such as immune cells.

In light of this recent evidence, the 'Standards of Care in Diabetes 2025' have been updated to recommend pioglitazone, a GLP-1RA, or a dual GIP and GLP-1RA as preferred options for glycemic control in adults with T2DM and biopsy-confirmed MASH or those at high risk for liver fibrosis, due to their potential beneficial effects on MASH.[71]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently gained recognition for benefits beyond their glucose-lowering effects by demonstrating efficacy in reducing the risk of heart failure and chronic kidney disease.[72] With respect to liver pathology, an RCT in Japan compared the effect of tofogliflozin, an SGLT2 inhibitor, with that of sulfonylureas in patients with MASLD and T2DM (mean HbA1c, 8.1%). The RCT did not detect a statistically significant difference in liver fibrosis improvement between the tofogliflozin and glimepiride groups, partly due to the limited number of subjects and the use of an active comparator. However, it is noteworthy that in the tofogliflozin group, steatosis, ballooning, inflammation, and fibrosis scores all showed significant improvement from baseline, whereas, in the glimepiride group, only the ballooning score demonstrated significant improvement.[73] Moreover, as shown in Table 2, the tofogliflozin group demonstrated a high rate of improvement in the fibrosis stage, even compared with RCTs that examined the effects of other hypoglycemic drugs on liver fibrosis (Table 2). These results suggest that SGLT2 inhibitors might be effective in treating MASH. It should also be noted that the baseline HbA1c values in the RCT comparing SGLT2 inhibitors and sulfonylureas were relatively high. That RCT identified baseline HbA1c as a predictor of liver fibrosis improvement,[11] underscoring the importance of considering baseline glycemic control when evaluating evidence of liver fibrosis outcomes. Real-world data from Korea comparing the risk of liver-related events among various oral hypoglycemic agents showed that only SGLT2 inhibitors were significantly associated with a lower incidence of liver-related events, compared with sulfonylureas; thiazolidinediones and dipeptidyl peptidase-4 inhibitors were not.[74] This observation likely reflects the beneficial effects of SGLT2 inhibitors on liver fibrosis, a key factor contributing to liver-related events. However, most evidence for the hepatoprotective effects of SGLT2 inhibitors has been generated in Asian populations.[75] The 2025 'Standards of Care in Diabetes' from the American Diabetes Association do not currently recommend the preferential use of SGLT2 inhibitors for MASLD/MASH in persons with diabetes.[71] Additional studies are required to validate the hepatoprotective effects of SGLT2 inhibitors in Western populations and to determine whether those effects differ across racial groups.

An RNA-seq analysis of liver samples collected before and after intervention revealed that SGLT2 inhibitors significantly altered the expression of genes associated with zone 2 and zone 3 hepatocytes, as well as LSECs in the pericentral region, which are specifically affected in diabetes-complicated MASH (Table 1).[73] Mechanistically, SGLT2 inhibitors are reported to suppress hepatic lipid synthesis, enhance the β-oxidation of fatty acids, and reduce inflammation in white adipose tissue.[76] In line with those findings, a transcriptome analysis of human MASH livers before and after SGLT2 inhibitor treatment revealed a coordinated downregulation of genes associated with inflammation, apoptosis, and fibrosis, along with decreased expression of genes related to gamma delta T cells,

inflammatory macrophages, HSCs, and plasma cells (Table 1).[73] Although inflammatory macrophages and HSCs are well-established central players in MASH pathophysiology, emerging evidence suggests a potential role for plasma cells[77] and γδ T cells[78] in MASH, pointing to novel therapeutic targets for SGLT2 inhibitors. In a mouse MASH model, SGLT2 inhibitors reduced the accumulation of autoaggressive CD8+ T cells and decreased granzyme B levels.[79] Mechanistically, SGLT2 inhibitors suppress IRF4-dependent granzyme B production by enhancing ketogenesis in T cells. Further investigation is needed to determine whether SGLT2 inhibitors influence these immune cell fractions in human MASH and whether those effects improve clinical endpoints.

The thyroid hormone receptor beta-selective agonist resmetirom is also worth mentioning. In a phase 3 RCT, resmetirom demonstrated significant improvements in MASH resolution without worsening fibrosis and fibrosis improvement by at least one stage without worsening the nonalcoholic fatty liver disease activity score. Based on those results, it became the first U.S. Food and Drug Administration-approved treatment for MASH in 2024. Approximately 67% of the patients in that study had diabetes, suggesting that resmetirom is likely to be effective for MASH complicated by diabetes.[80]

Additionally, genome-wide association studies have identified several susceptibility genes for MASLD/MASH, providing new insights into disease pathophysiology and potential therapeutic strategies. The *PNPLA3* gene on chromosome 22, with the rs738409 variant encoding I148M and the rs6006460 variant encoding S453I, has been identified as a major risk allele for MASLD.[81] *PNPLA3* encodes a protein known as 'adiponutrin,' which is involved in triglyceride hydrolysis and retinol metabolism in HSCs.[82] The I148M variant of *PNPLA3* is associated with hepatic steatosis and fibrosis, independent of obesity and dyslipidemia.[83,84] Studies conducted in Japan have also strongly associated the I148M variant of *PNPLA3* with advanced MASH, classified as Matteoni type 4, and a common MASH risk factor across populations.[85] Single-nucleotide polymorphism allele frequency data from the 1000 Genomes Project[86] show that East Asians have a higher prevalence of *PNPLA3* risk alleles than Western populations, which might explain the higher prevalence of non-obese MASLD in Asia.[87] Currently, efforts are underway to develop nucleic acid–based therapies, such as antisense oligonucleotides, to inhibit the expression of the mutant *PNPLA3* gene in individuals carrying the risk allele.[88,89] This approach could represent a personalized treatment strategy for MASH based on genetic polymorphisms. Additionally, drugs targeting disease mechanisms supported by strong genetic evidence in humans are known to have a higher likelihood of success during development.[90,91] Future therapies are therefore expected to focus on candidate molecules identified through genetic association studies.

CONCLUSION

This review summarizes the pathophysiology of MASLD/MASH complicated by T2DM, focusing on the bidirectional association between them. Human and animal studies using MASH models have suggested that the pathology of diabetic MASH might be a diabetic vascular complication. This review also highlights that MASLD/MASH can present with different pathological conditions depending on the population. Therefore, population-specific approaches might be beneficial for elucidating its pathogenesis and developing treatment strategies.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: HG and TT; acquisition of data: HG; analysis and interpretation of data: HG; drafting of the manuscript: HG; critical revision of the manuscript: TT; statistical analysis: HG; obtained funding: HG; administrative, technical, or material support: TT; and study supervision: TT.

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