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Review Article

Metabolic Dysfunction–associated Steatotic Liver Disease and Circadian Rhythm: Current Understanding and Implications for Future Therapeutic Interventions

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Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD), defined by the American Association for the Study of Liver Diseases as hepatic steatosis with at least one cardiometabolic risk factor, affects approximately 30–40% of adults worldwide. This condition may progress to fibrosis, cirrhosis, and hepatocellular carcinoma. The rising prevalence, alongside obesity and type 2 diabetes, underscores the need for early risk stratification and integrated therapeutic strategies. Circadian homeostasis, orchestrated by the suprachiasmatic nucleus and core clock gene feedback loops, synchronizes hepatic metabolic pathways with environmental light–dark cycles. The objective of this review is to evaluate the role of circadian disruption and metabolic dysfunction in the development of hepatic steatosis, as well as to assess current and potential treatment modalities for both disorders. Circadian disruption through shift work, artificial light at night, sleep restriction, and chrono-nutritional misalignment destabilizes hepatic clocks, promoting insulin resistance, dyslipidemia, inflammation, and steatosis. Experimental models demonstrate that clock gene dysfunction alone can induce steatohepatitis, while progressive MASLD further impairs central circadian regulation, establishing a self-reinforcing chrono-metabolic cycle. Pharmacologic therapies, including glucagon-like peptide-1 receptor agonists and thyroid hormone receptor-β agonists, improve histologic endpoints and fibrosis regression, although heterogeneity among clinical trials precludes direct comparison. Recent evidence characterizing MASLD as a predominantly nocturnal metabolic disorder further highlights persistent nighttime insulin dysregulation despite weight loss, emphasizing the potential role of circadian-targeted interventions such as melatonin. In conclusion, the peripheral circadian clock is intricately linked with MASLD pathogenesis, and metabolic dysfunction, in turn, disrupts circadian pathways. Several pharmacologic therapies offer potential for the treatment of MASLD and circadian dysfunction.

Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a chronic condition characterized by fat accumulation in the liver, which can progress to a spectrum of liver inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma, with metabolic dysfunction playing a central role in its pathogenesis.[1,2] MASLD is the most recent nomenclature used for what was previously referred to as nonalcoholic fatty liver disease and metabolic dysfunction–associated fatty liver disease.[1,2] A more advanced form of this disease is termed metabolic dysfunction–associated steatohepatitis (MASH), previously known as nonalcoholic steatohepatitis (NASH).[1,2] MASLD affects approximately 30–40% of the adult population globally, making it the most prevalent chronic liver condition worldwide.[3,4] MASLD is much more common in specific patient demographics, with 60–70% of individuals with type 2 diabetes mellitus (T2DM) and 70–80% of individuals with obesity.[1] Accordingly, the MASLD disease burden continues to increase with the growing prevalence of T2DM and obesity.[4,5] The American Association for the Study of Liver Diseases defines MA-

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SLD as hepatic steatosis with one or more of five cardiometabolic risk factors: overweight/obesity, prediabetes or T2DM, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and hypertension—excluding significant alcohol consumption (≥20 g/day for women, ≥30 g/day for men).[1,2,6] Approximately 20–30% of individuals with MASLD eventually progress to MASH, which is characterized by hepatic ballooning and inflammation with or without fibrosis.[2,7]

Cirrhosis represents the advanced stage of MASLD and is characterized by extensive fibrosis, as well as compensated or decompensated cirrhosis, the latter of which is characterized by ascites, hepatic encephalopathy (HE), jaundice, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, or variceal bleeding.[8,9] The pathogenesis of MASLD is multifactorial, with diverse metabolic influences affecting multiple organ systems and regulatory pathways, and with environmental influences, genetics, the gut microbiome, and lifestyle comorbidities as the main disease drivers.[2,10]

The circadian rhythm, regulated by a circadian "clock", coordinates both physiological and biological processes in response to daily environmental changes and influences.[11] The circadian system creates a roughly 24-h rhythm that aligns behavior and physiology with environmental cycles. Circadian rhythms modulate virtually all aspects of physiology, including body temperature, vascular tone, renal excretion, metabolism, glucose and lipid regulation, immune responses, alertness, mood, and cognition.[12] Circadian disruption contributes to a broad range of disorders beyond sleep–wake disorders, including cardiometabolic disease, inflammatory disease, cancer, mood dysfunction, and cognitive impairment.[12] Recent studies have suggested that abnormal circadian rhythms may contribute to an individual's risk of developing fatty liver disease and inflammation.[13,14] Circadian rhythms regulate key hepatic functions, including glucose metabolism and inflammatory responses, all of which are implicated in MASLD pathogenesis.[15]

This narrative review will explore not only the effects of circadian disruption on outcomes but also the bidirectional relationship between lifestyle, pharmacological treatment of MASLD, and the possible alleviation of circadian disruption. The literature search for this narrative review was conducted using PubMed/MEDLINE, Google Scholar, and the Cochrane Library. Search terms included "metabolic dysfunction–associated steatotic liver disease", "nonalcoholic fatty liver disease", "metabolic dysfunction–associated steatohepatitis", "cirrhosis", "circadian rhythm", "sleep disruption", "CLOCK", "BMAL1", "GLP-1 receptor agonists", "THR-β agonists", and "melatonin". High priority was given to guidelines and expert clinical consensus, with other works selected based on topic relevance, original research, and recently published studies directly pertaining to MASLD pathophysiology and circadian disruption, including relevant review articles and clinical trials addressing pathogenesis, lifestyle interventions or modifications, and pharmacological treatment of MASLD and circadian disruption.

Physiology of circadian rhythms and liver metabolism

The circadian system, guided by the suprachiasmatic nucleus (SCN) in the hypothalamus, creates a roughly 24-h rhythm that aligns behavior and physiology with environmental cycles. This plays a role in supporting sleep homeostasis, which tracks the buildup and dissipation of sleep debt.[12] The circadian system operates through a series of cell-autonomous oscillators known as clock genes. Clock genes generate rhythms through transcriptional–translational feedback loops in which proteins inhibit their own transcription, leading to oscillations with a near-24-h period.[12] The SCN and clock genes are modulated by several synchronization cues, with light being the most significant.[16] This is mediated by retinal ganglion cells, which absorb blue light and transmit information to the SCN. The independence of this process is well established, as individuals with blindness may still experience intact SCN regulation.[16]

With normal circadian function, the expression of genes that regulate fat metabolism, inflammatory pathways, and liver fibrosis remains relatively stable. However, when circadian rhythms are disrupted and the SCN becomes dysregulated, these effects can compound, leading to impaired detoxification, upregulated inflammatory cytokines, and increased hepatic lipid accumulation.[13] The circadian clock oscillator, a conserved negative feedback loop, is regulated by autonomous transcriptional–translational programming. Circadian rhythmicity is also present outside the SCN and is controlled by peripheral clocks, which are synchronized by the SCN.[11] Peripheral clocks exist in nearly every organ system, including the brain, heart, gastrointestinal tract, pancreas, adipose tissue, adrenal glands, lungs, skeletal muscle, kidneys, and submandibular glands.[17] In particular, circadian rhythm genes are essential for maintaining the liver's normal physiological functions. For example, CLOCK–BMAL1 initiates daily metabolic cycles specific to hepatic gene expression. REV-ERBα and REV-ERBβ also play important roles in modulating glucose and lipid metabolism by regulating transcription of metabolic genes.[18] In essence, if the liver's clock genes are not properly regulated by the SCN due to circadian disruption, metabolic disorders may arise, particularly those affecting glucose and lipid metabolism—consistent with the pathogenesis of MASLD.

Pathophysiology: Circadian disruption and MASLD

Animal models lacking circadian clock genes CLOCK and Per1 and Per2, despite having a regular, consistent diet, develop obesity, insulin resistance, metabolic syndrome, hepatic steatosis, and fibrosing steatohepatitis.[15] Mice lacking the clock genes Per1/2 and Cry1/2, or deficient in BMAL1, have a greater likelihood of developing hepatocellular carcinoma.[15] Further, CLOCK knockouts in mice deficient in ApoE or in high-fat diet (HFD) MASLD models demonstrate accelerated fibrosis, cirrhosis, and hepatocellular carcinoma development.[15] In human studies assessing additional liver pathology, such as hepatocellular carcinoma, decreased expression of clock genes has been associated with malignant tissue compared with non-tumoral tissue, with additive negative effects on cell cycle regulation and correlations with tumor size.[15] Certain forms of circadian disruption (such as social jetlag (SJL)) can induce MASLD via impairment of sleep patterns and subsequent alteration of hepatic gene transcription related to lipid metabolism.[19] For example, one study found that participants experiencing SJL demonstrated increased hemoglobin A1c (HbA1c), fasting blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and homeostatic model assessment for insulin resistance compared with control participants.[19] Regarding SJL, pituitary hormone dysregulation has also been implicated in MASLD. It was found that prolactin (PRL) levels at three distinct time points—8:00, 16:00, and 24:00—were markedly decreased in participants with more than 1 h of SJL compared with participants with less than 1 h of SJL [7.48 (5.75, 9.23) μg/L vs. 11.28 (8.53, 14.59) μg/L; 6.74 (5.48, 8.80) μg/L vs. 9.84 (7.47, 14.07) μg/L; 6.82 (5.58, 7.93) μg/L vs. 11.29 (8.81, 16.17) μg/L; $P < 0.001$].[19]

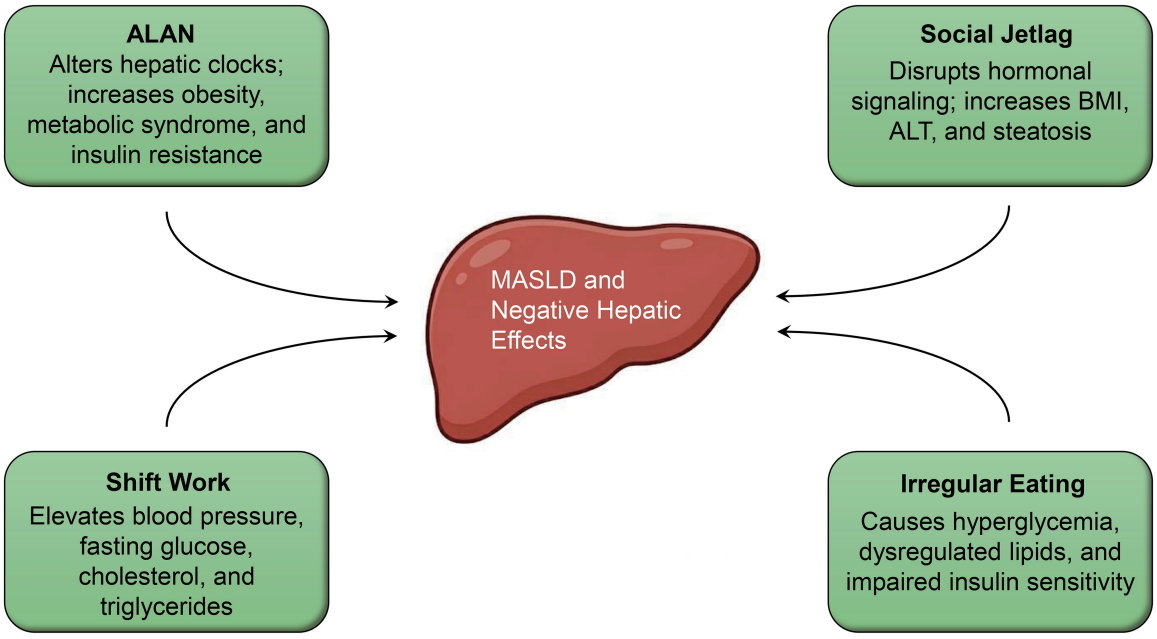

Fig. 1. Circadian misalignment as a driver of metabolic dysfunction–associated steatotic liver disease (MASLD) pathophysiology. This diagram illustrates the metabolic cascade through which diverse forms of circadian disruption converge to promote MASLD. The negative hepatic effects are initiated by four distinct pathways: artificial light at night (ALAN) alters hepatic clocks and increases metabolic risk factors; shift work elevates glucose and lipid levels; social jetlag (SJL) disrupts hormonal signaling and increases steatosis; and irregular eating patterns cause hyperglycemia and lipid dysregulation. By decoupling behavioral, dietary, and environmental cues from the master clock, these pathways jointly impair insulin sensitivity and increase metabolic stress, creating a robust pathophysiological feedback loop that drives the development and progression of MASLD. ALT, alanine aminotransferase; BMI, body mass index.

Circadian analysis also showed a lower amplitude of PRL secretion in subjects with SJL greater than one hour. Conversely, in comparatively healthy participants, higher concentrations of PRL were associated with lower levels of SJL and less severe steatosis.[19] The circadian rhythm's extensive influence on liver function and mechanisms governing cellular stress support the consideration of circadian rhythm dysfunction as a driver of MASLD development and progression. The key drivers of MASLD pathogenesis via circadian disruption are outlined below and in Figure 1.

Artificial light at night (ALAN)

ALAN is an underestimated yet significant environmental factor influencing hepatic metabolism. Animal studies consistently indicate that exposure to, and the intensity of, blue-enriched light alters circadian synchronization at both central and peripheral levels, disrupting hepatic molecular clocks.[20] In humans, observational studies align with these findings, suggesting a correlation between nighttime light exposure and increased frequency of obesity, metabolic syndrome, insulin resistance, and poor sleep quality, all of which share pathophysiological mechanisms with MASLD, supporting the hypothesis that ALAN influences MASLD disease progression.[20]

Shift work

Shift work is also associated with metabolic effects that may contribute to MASLD progression. Male workers engaged in shift work exhibit higher blood pressure and elevated levels of fasting glucose, total cholesterol, and liver enzymes. In contrast, female shift workers have lower HDL cholesterol, higher waist circumference, and higher triglyceride levels.[21] These observations support the hypothesis that non-standard work schedules may contribute to adverse metabolic profiles, ultimately increasing the risk of MASLD.[20] Studies indicate that longer duration and greater frequency of consecutive night shifts, along with prolonged shift hours, are associated with elevated risks of MASLD, with outcomes worsening as these factors intensify.[22] This correlation between night-shift work and MASLD appears noteworthy regardless of genetic predisposition.[22]

SJL

SJL is a chronic misalignment between a person's internal biological clock and their social or work obligations. This often results in insufficient rest that is "corrected" by sleeping longer on weekends or days off. The consequence of SJL is a significant misalignment of regular sleep rhythms, resulting in circadian disruption that may dampen hormonal signaling from central to peripheral organs (and their respective clocks).[19,22] One of the primary consequences of SJL is alteration in pituitary-derived PRL, a potential modulator of hepatic lipid metabolism and insulin sensitivity.[19] PRL-guided rhythms disrupted by SJL may mediate its pathogenic effects on MASLD, highlighting PRL as a pituitary hormone influenced by external factors.[19] Multiple cohort and cross-sectional studies have demonstrated a relationship between SJL and metabolic markers often associated with MASLD, including obesity, increased likelihood of metabolic syndrome, higher relative body fat, higher mean body mass index, and higher mean waist-to-hip ratio.[22] Related evidence from several large-scale population-based studies has shown that short sleep duration is linked to MASLD. For instance, sleeping fewer than five hours per night may increase the risk of MASLD.[22] This has been associated with elevated ALT levels, a positive Fatty Liver Index, and sonographic evidence of steatosis, with prevalence increasing from 35% to 70%.[22]

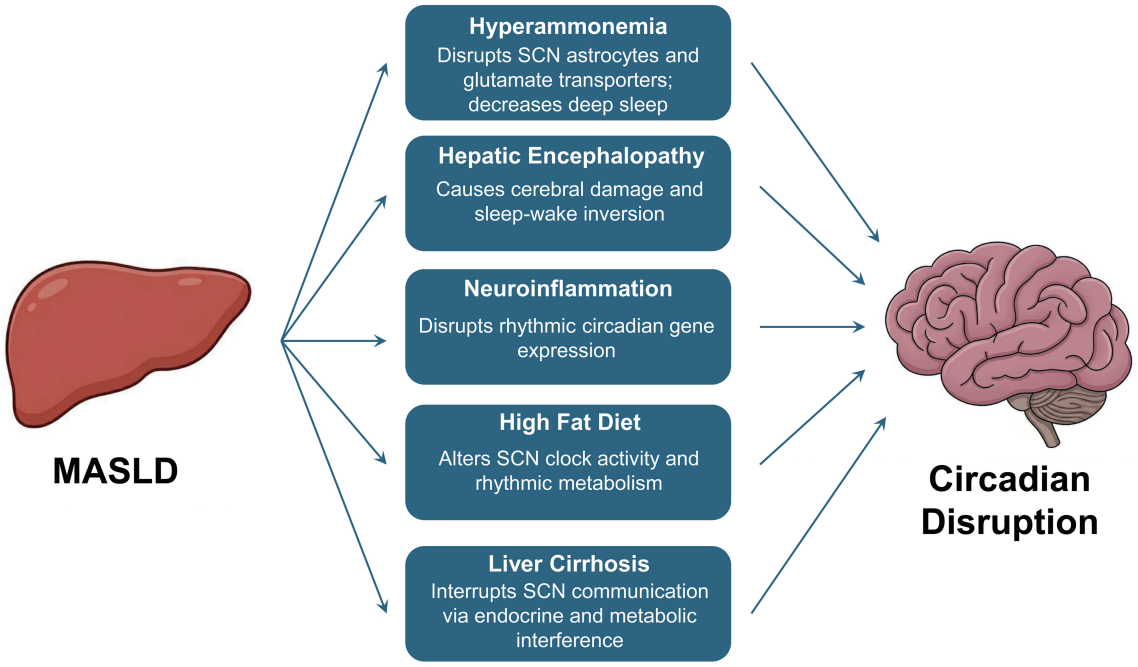

Fig. 2. The pathophysiological axis of metabolic dysfunction–associated steatotic liver disease (MASLD)-induced circadian disruption. This diagram illustrates the multi-mechanistic pathway through which MASLD impairs the central circadian clock. The progression from initial liver dysfunction to systemic circadian disruption is driven by the synergistic effects of hyperammonemia, which compromises suprachiasmatic nucleus (SCN) astrocytes and glutamate transporters, and chronic neuroinflammation, which destabilizes rhythmic gene expression. As the disease advances toward hepatic encephalopathy and cirrhosis, cerebral damage and endocrine interference further decouple the SCN from peripheral rhythms. Ultimately, the combination of a high-fat diet (HFD) and progressive liver pathology creates a "top-down" neurological insult, manifesting clinically as sleep–wake inversion, loss of deep sleep, and the breakdown of rhythmic metabolism.

Irregular eating patterns

Erratic eating habits can result in maladaptive blood glucose and lipid profiles, which are commonly linked to progression of hepatic steatosis.[21] Irregular breakfast consumption has been associated with overweight or obesity, with no significant variation between demographics.[23] These relationships fall under the concept of "chrono-nutrition", where irregular meal timing may negatively impact the body's circadian rhythms, impairing glucose metabolism, insulin sensitivity, and lipid regulation, all of which can contribute to MASLD risk.[23] Another association has been observed between late-night snacking and MASLD risk. At night, metabolism is reduced, and the body is less equipped to manage excess energy intake, leading to energy surplus and fat accumulation.[23] Moreover, increased carbohydrate consumption (particularly added sugars) contributes to elevated glycemic and lipid levels in late-night meals, ultimately disrupting feeding rhythms and further contributing to circadian imbalance.[23]

MASLD effects on circadian disruption

There is a well-established link between circadian disruption leading to metabolic dysfunction; however, more recent literature has emerged suggesting that metabolic dysfunction may also disrupt normal circadian function.[11] Sleep disorders, such as obstructive sleep apnea and insomnia, are associated with MASLD onset and are therefore considered risk factors in its progression.[24–27] A recent study utilizing actigraphy revealed that patients with MASLD had longer nocturnal wakefulness, more fragmented sleep, and lower sleep efficiency.[10] Using subjective sleep quality metrics, MASLD patients have reported significantly worse sleep experiences compared with healthy counterparts.[10] This was likely due to increased nocturnal wakefulness and reduced sleep efficiency.[10] Accordingly, some causal links between MASLD pathology and circadian disruption are worth considering. This axis is discussed below and in Figure 2.

Hyperammonemia and effects on MASLD and circadian rhythm

Based on recent medical literature, MASLD and MASH can lead to hyperammonemia primarily through urea cycle enzyme dysfunction and altered nitrogen metabolism.[28,29] Insufficient ammonia removal by the liver and increased ammonia production by gut microbiota equally contribute to hepatic ammonia accumulation in patients with steatotic liver disease.[28] A 2018 study demonstrated that both gene and protein expression of key urea cycle enzymes, ornithine transcarbamylase (OTC) and carbamoyl phosphate synthetase 1 (CPS1), are reduced in MASH.[29] This reduction occurs via hypermethylation of OTC and CPS1 promoter regions, impairing ammonia detoxification and urea synthesis.[29] As a result, it is commonly observed that patients with MASLD show reduced OTC enzyme concentration and activity, with increased ammonia concentrations, a byproduct of reduced OTC and CPS1 function. These findings are further exacerbated in patients with MASH.[29] Additionally, certain enzyme activities related to hepatic ammonia production are increased.[28] The effect is compounded by decreased ammonia elimination in more advanced forms of MASLD/MASH.[30]

Physiologically, hyperammonemia can result in significant drowsiness and an inability to achieve deep, restorative sleep.[31,32]

Evidence suggests that this mechanism likely stems from disruption of either homeostatic or circadian regulation of sleep cycles.[32,33] It is well established that hyperammonemia causes both functional and morphological astrocyte abnormalities, implicating the SCN and its regulation of clock genes.[32,34] Evidence suggests that when ammonia levels rise in the brain and serum, glutamate transporter function declines, leading to glutamate accumulation, which disrupts circadian rhythmicity and daily behavior through dysregulated SCN glutamate receptors.[32] Importantly, these findings support a clinically significant association in which normalization of ammonia levels can reverse these changes and resolve clinical pathologies such as HE and sleep–wake abnormalities.[32]

HE and circadian rhythm

Sleep–wake dysregulation, delayed sleep and wake timing, daytime drowsiness, worsening sleep latency, and nocturnal interruptions are more common in cirrhosis—the hallmark of advanced MASH—compared with other chronic diseases.[35,36] Cirrhosis, particularly decompensated cirrhosis, affects circadian rhythmicity through endocrine dysregulation, metabolic impairment, and altered sympathetic function, all of which may disrupt normal communication with central clock mechanisms in the SCN.[37–39] MASLD/MASH can further impair circadian regulation through changes in oxidative stress, cytokine release, and hypoxia. Bidirectionally, circadian disruption is also a risk factor for the pathogenesis of progressive steatotic liver disease through similar pathways.[35] This suggests that circadian dysregulation in MASLD patients is rarely a unidirectional process. An additional proposed mechanism linking hepatic pathology to brain function includes abnormal circulating factors originating from the liver in MASLD, such as those associated with irregular late-night eating, impacting both central and peripheral organ rhythmic physiology, particularly peripheral clocks.[35,40] Thus, a vicious cycle of chronometabolic decline is implicated in MASLD/MASH.

Clinically, a hallmark of progressive hepatic dysfunction is the development of hyperammonemia and impaired toxin clearance, leading to HE. This critical decompensating event is graded using the West Haven Criteria. According to the West Haven Criteria, the earliest stages of HE (minimal and Grade I) are associated with cognitive and psychomotor deficits.[41] Sleep–wake abnormalities in patients with cirrhosis have traditionally been ascribed to HE.[35] These abnormalities are consistently present in MASLD due to bidirectional communication between the central circadian clock and the liver.[35] It is worth noting that cirrhosis contributing to HE is not unique to MASLD; however, this relationship is discussed here within the context of MASLD pathology.[35]

Conversely, HE in advanced liver disease can range from minor sleep disruption, restlessness, and daytime drowsiness to more severe circadian disruption, including sleep–wake reversal, behavioral changes, confusion, and coma.[32] One of the clinical features of HE is disruption of the circadian cycle. These symptoms are consistent with liver pathologies that impair ammonia regulation, including but not limited to MASLD. Others have noted that general impairment of cognitive and sleep function in MASLD may worsen as liver disease progresses.[42] HE is one example of worsening liver dysfunction. In this context, although the decline refers to MASLD in particular, HE is not a unique consequence of MASLD alone. The relationship between declining cognitive and sleep function in liver disease likely also applies to other liver pathologies, such as alcohol–associated liver disease or chronic viral hepatitis.

Impact of diet in MASLD and circadian disruption

Research on obesity and MASLD has shown a reciprocal relationship between metabolic liver disease and circadian physiology. Animal models have demonstrated that chronic consumption of a HFD can lead to MASLD and alter circadian physiology and metabolism.[35] The SCN pacemaker and circadian entrainment are also affected by HFD consumption in mice. Locomotor activity, which is directly linked to circadian rhythmicity and serves as an output of SCN clock function, is markedly increased in HFD-fed mice.[35] Pro- and anti-inflammatory functions influenced by central clock mechanisms are closely linked to gene expression associated with synaptic plasticity. This suggests a link between immune and physiological responses in the brain and the additional stress of a high-carbohydrate or HFD (consistent with MASLD risk factors) or liver pathology.[42]

Disruption of the day–night cycle, and early MASLD rat models exhibiting these circadian disturbances, demonstrate a consistent relationship with sleep disorders in humans.[42] HFD-induced obesity leads to reprogramming of circadian physiology through variable gene expression, resulting in both gain and loss of function and ultimately dysregulating normal circadian rhythms.[43] These findings raise the possibility that circadian disruption may precede overt clinical manifestations of MASLD, although further clinical validation is needed. This suggests that an HFD, often directly linked to MASLD pathology and progression, plays a multifactorial role in central clock and circadian rhythm disruption as well as metabolic dysregulation. This may allow clinicians to assess circadian disruption in MASLD patients, which could potentially serve as an early diagnostic marker for MASLD.[42]

Pharmacologic interventions

Current treatment guidance for MASLD recommends lifestyle interventions to reduce body weight, limit alcohol use, and manage other modifiable risk factors for cardiovascular disease. The lifestyle improvements in MASLD are outlined later below and in Table 1. Glucagon-like peptide-1 (GLP-1) therapies and the thyroid hormone receptor-β (THR-β) agonist resmetirom are effective options for the treatment of obesity and MASLD.[44,45] These compounds primarily act to optimize metabolic pathways, not to restore circadian function.[46] However, there are strong diurnal patterns in the expression of many MASLD drug targets, which is a key point given that metabolic dysfunction in MASLD occurs primarily at nighttime.[43] Many of the genes controlled by these pathways are circadian clock–regulated, making these drugs strong candidates for chrono-pharmacology, a strategy in which the timing of drug delivery is informed by circadian rhythms to maximize efficacy and tolerability. Unfortunately, the application of chrono-pharmacology remains severely limited, as illustrated in a comprehensive review of ClinicalTrials.gov, which found that only a fraction (0.16%) of over 200,000 registered trials included a circadian-influenced intervention, none of which were related to hepatology.[47] The pharmacological improvements in MASLD are outlined immediately below and in Table 1.

GLP-1 receptor agonists (RAs)

GLP-1 is secreted by the gastrointestinal tract in response to food intake and exerts multiple physiological effects, such as stimulating insulin secretion, enhancing insulin sensitivity, increasing satiety signals, and slowing gastric emptying, all of which plausibly contribute to weight loss. Its secretion shows diurnal variation,

Table 1. Pharmacological and lifestyle improvements in MASLD

MASLD intervention	Effects
GLP-1 receptor agonists (e.g. semaglutide, liraglutide, dulaglutide, exenatide)	Enhanced insulin sensitivity; Weight loss; Indirect metabolic effect on hepatic clock gene expression
Thyroid hormone receptor-β agonists (e.g. resmetirom)	Increased fatty acid oxidation; Diurnal variation in expression
Melatonin	Decreased ferroptosis; Decreased lipid peroxidation; Reduced oxidative stress
Meal timing	Improved insulin sensitivity
Light therapy	Morning light exposure can realign the circadian clock; Additional daylight exposure associated with lower MASLD risk
Sleep hygiene	Improved sleep quality and decreased disruption are associated with lower MASLD risk

GLP-1, glucagon-like peptide-1; MASLD, metabolic dysfunction–associated steatotic liver disease.

with a higher response to an identical meal in the morning than in the afternoon.[48]

To preface, GLP-1 agonism has no direct action on human hepatocytes or hepatic stellate cells, nor is its receptor expressed in hepatocytes. A recent study demonstrated that GLP-1 and GIP agonists have no direct effects on human hepatocyte or hepatic stellate cell lines, suggesting that their beneficial effects in patients with liver disease are likely mediated indirectly through broad metabolic pathways.[49] A loss of circadian or diurnal coordination of GLP-1 secretion may occur in obesity and related diseases, and mounting evidence suggests that GLP-1 RAs could help re-establish metabolic circadian rhythms.[50] Physiological studies in human subjects have shown that baseline GLP-1 levels are significantly lower in normal-weight subjects, with higher amplitude and greater daily variation. Furthermore, among overweight and obese patients, daily rhythmicity in GLP-1 levels could not be restored by weight loss.[51]

Feeding is a powerful entrainment cue for peripheral clocks, and GLP-1 is secreted rapidly in response to food ingestion. In fact, prolonged fasting and omitting breakfast blunt the GLP-1 response to lunch in people with T2DM, highlighting the important role of food intake timing in GLP-1 secretion.[48,52] GLP-1 secretion is not only affected by feeding signals, but exogenous GLP-1 administration has also been shown to modulate circadian clock genes in the liver.[53] The precise mechanism of the GLP-1 system in the central nervous system and how it influences the hepatic clock remains unknown, though it is speculated to be synchronized by the hypothalamic central clock via a combination of autonomic and endocrine signals.[54]

One consideration in evaluating the timing of GLP-1 RA administration is variation between molecular backbones, as pharmacokinetics are heavily dependent on structural composition. There are two distinct molecular backbones: exendin-4 (from Gila monster venom) or modified human GLP-1, with these structural differences fundamentally determining pharmacokinetic and pharmacodynamic properties.[55] Exendin-4–based agents such as exenatide have shorter half-lives of 2–3 h, requiring twice-daily or once-daily dosing, whereas human GLP-1–based agents undergo structural modifications that resist protease degradation and extend their half-lives from 13–15 h for liraglutide to approximately 7 days for some injectable forms of semaglutide.[56] The applicability of chronobiological findings to long-acting human GLP-1 analogues remains an important area for future investigation.

In addition to aiding in weight loss, GLP-1 RAs improve liver histology in MASLD and may be more effective than lifestyle modifications in improving glucose metabolism, fasting lipid profiles, and significantly reducing *de novo* lipogenesis.[57] While some randomized controlled trials of GLP-1 RAs have failed to demonstrate significant improvement in MASH, several recent systematic reviews and meta-analyses have found that GLP-1 RA therapy is associated with increased rates of MASH resolution without worsening of fibrosis.[44,58–60] Mantovani *et al*.[44] found that GLP-1 RAs (especially semaglutide 2.4 mg/week) for up to 72 weeks were superior to placebo in achieving MASH resolution (odds ratio (OR) 3.48, 95% confidence interval (CI) 2.69–4.51; I^2 = 0%) and improving liver fibrosis (OR 1.79, 95% CI 1.37–2.35; I^2 = 0%) in individuals with MASH and moderate-to-advanced fibrosis. Furthermore, GLP-1 RAs reduced magnetic resonance–measured liver fat content (n = 9; pooled mean difference: −4.50%, 95% CI −6.60 to −2.40%).[44] Liu *et al*.[59] assessed a broader range of 32 randomized controlled trials (RCTs), finding that GLP-1 RAs were associated with resolution of MASLD without worsening of fibrosis (relative risk 3.33, 95% CI 2.38–4.66; I^2 = 12.9%) and could decrease liver fat content (weighted mean difference −4.34%, 95% CI −5.88 to −2.81). Siranart *et al*.[60] examined six RCTs with 1,555 patients with MASH and found that at 18 months of GLP-1 RA therapy, a significantly greater proportion of patients achieved MASH resolution without worsening fibrosis compared with placebo (OR 4.16, 95% CI 2.33–7.42, $P < 0.001$). Additionally, subgroup analysis excluding studies with patients with cirrhosis showed a significant benefit in fibrosis regression (OR 2.02, 95% CI 1.56–2.62, $P = 0.01$).[60]

While many early trials exhibited some heterogeneity or limited clinical benefit, more recently the phase 3 ESSENCE trial of semaglutide 2.4 mg weekly showed that 36.8% of patients achieved ≥1-stage reduction in liver fibrosis without worsening of MASH compared with 22.4% on placebo ($P < 0.001$) at 72 weeks, while 62.9% achieved MASH resolution without worsening fibrosis versus 34.3% on placebo ($P < 0.001$).[61] Notably, 32.7% achieved both MASH resolution and fibrosis reduction compared with 16.1% on placebo. These data prompted the U.S. Food and Drug Administration (FDA) accelerated approval of semaglutide (Wegovy) in August 2025 for MASH with moderate-to-advanced fibrosis (F2–F3).[9,62] Further endpoints demonstrated substantial improvements in noninvasive markers: 60% of semaglutide-treated patients achieved ≥25% reduction in liver stiffness versus 35% on placebo, with mean ALT reductions of 52% versus 8%.[61] These studies represent transformative data for a disease that previously had no

approved pharmacotherapy beyond lifestyle modification, offering patients with MASH and significant fibrosis evidence-based treatment options that address both hepatic and cardiometabolic disease.

THR-β agonists

In March 2024, the FDA announced the approval of resmetirom (Rezdiffra, Madrigal Pharmaceuticals, PA, USA) in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH and moderate-to-advanced fibrosis (stage F2–F3), with continued approval contingent upon verification and confirmation of clinical benefit in ongoing studies.[63] The MAESTRO-NASH trial formed the basis for this approval, as it demonstrated histologic improvement in steatohepatitis and fibrosis.[45] As a selective thyroid THR-β agonist, resmetirom represents the first pharmacologic agent specifically approved for MASH with fibrosis. THR-β, the predominant THR isoform in hepatic tissue, mediates most triiodothyronine (T3) actions regulating lipid metabolism, cholesterol homeostasis, and metabolic gene expression. Resmetirom operates on the mechanistic basis that THR-β function in the liver is impaired in MASLD, leading to reduced mitochondrial function and β-oxidation of fatty acids, along with an increase in fibrosis.[45]

The phase 3 MAESTRO-NASH trial enrolled 966 patients with biopsy-confirmed MASH, randomized to receive once-daily resmetirom 80 mg, 100 mg, or placebo for 52 weeks. The results showed that resmetirom achieved MASH resolution with no worsening of fibrosis in 25.9% of patients in the 80-mg group and 29.9% in the 100-mg group, compared with 9.7% in the placebo group ($P < 0.001$ for both comparisons).[45] Noninvasive markers also improved, including reductions in liver stiffness, decreased liver and spleen volumes, and improvements in the Enhanced Liver Fibrosis test score. Lipid profiles also showed significant reductions in low density lipoprotein (LDL) cholesterol (−13.6% and −16.3% vs. +0.1% with placebo; $P < 0.001$), along with improvements in triglycerides, apolipoprotein B, and lipoprotein(a). Resmetirom had neutral effects on body weight and insulin resistance, and the most common adverse events were transient diarrhea (27–33% vs. 15% placebo) and nausea (19–22% vs. 12% placebo). However, the reported improvement in liver fibrosis (i.e., approximately 10–20% more than the placebo response) after one year is still far from optimal, as over 70% of study participants did not achieve the primary treatment endpoints at week 52.[45] This limitation of resmetirom represents an area in which clinical researchers can investigate whether chrono-pharmacology could provide additional benefit.

The evidence on circadian-controlled thyroid hormone signaling and THR-β expression is mixed. Rodent hepatic THR-β1 is expressed in a diurnal pattern with peak expression at the beginning of the dark period, and this rhythmic expression partly overlaps with other T3-responsive genes.[64] However, in another experiment, this diurnal variation in liver THR-β1 mRNA expression failed to reach statistical significance in rodent models with intact suprachiasmatic nuclei, although the fluctuation was most clearly influenced by food intake. Notably, a restricted feeding schedule (one meal every 4 h) affected THR-β1 mRNA expression, but not thyroid hormone receptor α1 or α2, which remained controlled by the central clock in the SCN. This finding suggests that THR-β1 rhythmicity (like GLP-1) is primarily entrained by feeding–fasting cycles.

Previous work has demonstrated chrono-pharmacology to be beneficial in the treatment of primary hypothyroidism, with evening thyroxine (T4) replacement associated with higher thyroid hormone levels and lower thyroid-stimulating hormone (TSH) concentrations compared with morning administration, although some studies have shown conflicting results.[65–67] Thyroid hormone has time-of-day effects on metabolic transcription in hepatocytes, and these time-dependent effects differ substantially under steatotic conditions compared with normal metabolic states.[68] Additionally, TSH also displays a diurnal rhythm: plasma concentrations rise before sleep onset and reach their peak during nighttime.[69] Altogether, these data suggest that there may be an optimal time of day for resmetirom administration, given the diurnal fluctuation of its target receptor; however, additional research is needed to determine its clinical significance.

In summary, resmetirom is a first-in-class THR-β agonist with demonstrated clinical efficacy in reducing hepatic fibrosis among patients with MASH. Thyroid hormones exhibit substantial diurnal and circadian variability, and evidence supports a potential role for resmetirom in influencing circadian function.[70] Additionally, the pharmacodynamics of resmetirom show wide interindividual variability, and future research may help elucidate whether timing of administration could enhance efficacy based on circadian rhythm.[70]

Melatonin

Beginning at sunset and continuing throughout the night, the human pineal gland secretes melatonin, a pleiotropic neurohormone that plays diverse physiological roles, including regulation of the sleep–wake cycle, antioxidant activity, immunomodulation, and anti-tumor effects.[71,72] Beyond correcting a misaligned circadian clock, melatonin has a direct protective effect on the liver through antioxidant activities, including inhibition of ferroptosis, lipid peroxidation, and reduction of oxidative stress.[73] Melatonin activates receptors in the hypothalamic-pituitary-adrenal axis, which leads to downstream reduction in fat synthesis in adipocytes and promotes lipolysis.[74–76] Chief among downstream effector clock genes is Nocturnin, a deadenylase that regulates hepatic lipid metabolism. In healthy liver tissue, Nocturnin mRNA exhibits robust circadian oscillations with peak expression at zeitgeber time 12 ("lights off").[77,78] Melatonin treatment has demonstrated significant corrective effects on aberrant Nocturnin oscillations in experimental MASLD models by restoring upstream core clock gene oscillations.[79]

Clinical studies examining the effect of melatonin on MASLD have been published, and several recent landmark systematic reviews and meta-analyses highlight notable findings, though they show some discrepancies in results, possibly due to variation in study methodologies and melatonin dosages among clinical trials.

A 2021 systematic review and meta-analysis of seven clinical trials found that melatonin significantly lowered ALT levels after the fourth week ($P = 0.010$).[80] AST and alkaline phosphatase (ALP) also exhibited substantial declines overall (AST $P = 0.008$, ALP $P = 0.006$), though not after four weeks. Triglyceride ($P = 0.015$) and cholesterol levels both significantly declined ($P = 0.005$). Gamma-glutamyl transpeptidase levels were also significantly reduced following melatonin administration ($P < 0.001$). A 2024 systematic review and meta-analysis of 11 clinical trials also showed positive effects of melatonin, though with different statistically significant outcomes.[81] They found that melatonin significantly reduced cholesterol and LDL, with non-significant increases in HDL and reductions in triglycerides. Waist circumference and weight significantly decreased, as did inflammatory markers such as IL-1, IL-6, and TNF-α, suggesting that melatonin may reduce pro-inflammatory cytokines involved in fibrosis in

MASLD patients. Although both meta-analyses concluded that melatonin has beneficial effects on MASLD progression, differences in results and statistical methods suggest variation in methodology that limits interpretation. For instance, the 2021 study used "NAFLD" as its primary search term, whereas the 2024 study used "MASLD". Finally, a 2025 comprehensive meta-analysis of 63 RCTs across multiple conditions (*not* specific to MASLD) concluded that melatonin significantly improves cardiovascular risk factors.[82] Several markers were significantly improved, including C-reactive protein, TNF-α, IL-6, total cholesterol, LDL cholesterol, HDL cholesterol, fasting glucose, and ALT.[82] Interestingly, this review found no significant effects of melatonin on triglycerides, AST, gamma-glutamyl transferase, and HbA1c.[82] These heterogeneous conclusions may be explained by discrepancies such as dosage variability (ranging from 3–20 mg/day, with most studies using 6–10 mg/day), treatment duration, and timing of administration (most studies administered melatonin 1 h before bedtime, but timing relative to meals and circadian phase varied). Nonetheless, there is compelling rationale to investigate melatonin for MASLD, as it reinforces circadian periodicity and may help re-align the clock with meaningful effects on metabolic profiles implicated in MASLD pathogenesis.

Lifestyle interventions

Meal timing

Chrono-nutrition, also known as time-restricted eating (or colloquially referred to as intermittent fasting), is a circadian-informed dietary strategy for the prevention and management of not only MASLD but also cardiometabolic disease more broadly.[83] Most studies compare time-restricted eating as an adjunct dietary intervention to calorie restriction. Time-restricted eating may ameliorate MASLD progression and improve symptom severity, though it may not be more effective than eating without time restriction at a caloric deficit.[84,85] For example, individuals with MASLD who tend to perform their daily activities later in the day (having a late chronotype, or colloquially known as being a night owl) are at increased risk for hepatic fibrosis, with late chronotype independently associated with higher liver stiffness and advanced fibrosis scores.[86] Late chronotypes are also associated with low adherence to the recommended Mediterranean diet.[87]

Evaluating cardiometabolic and weight loss efficacy in time-restricted eating, implementation of a hypocaloric Mediterranean-type diet with no eating time restrictions (control), an early schedule (8 a.m. to 6 p.m.), or a late window (12 p.m. to 10 p.m.) found that an early eating schedule indeed reduced HbA1c and insulin resistance levels.[88] Interestingly, late feeding was associated with decreased total cholesterol, which differs from other studies in MASLD patients that support early-time feeding for reducing lipid markers. The researchers postulated that these differences may be due to the prolonged fasting period, which may contribute to re-esterification of triglycerides after lipolysis and increased hepatic and intramuscular triglyceride storage.[84] However, late eating on a Mediterranean diet did not impair glucose metabolism or cardiometabolic profiles, suggesting that caloric deficit may play a larger role than meal timing.[84]

Comparing caloric restriction to time-restricted eating, a recent RCT assigned patients to standard of care (500 kcal/day reduction plus monthly text message support from a dietician), calorie restriction (intensive nutritional monitoring and guidance), or time-restricted eating.[89] Results showed that time-restricted eating offered clear advantages over standard of care in terms of hepatic fat reduction, weight loss, cardiometabolic improvements, and visceral fat reduction, but it did not affect glucose homeostasis, body fat and muscle distribution, cardiometabolic risk, or changes in circadian rhythms.[85] Specifically, hepatic steatosis significantly decreased in the time-restricted eating group compared with the standard-of-care group ($P < 0.001$), with no significant difference between time-restricted eating and calorie restriction ($P > 0.999$). Additionally, the time-restricted eating group showed greater reductions in body weight, waist circumference, and body fat mass compared with the standard-of-care group, while these changes were comparable to those in the calorie restriction group. Finally, liver stiffness, glucose homeostasis, and sleep quality were similar between the time-restricted eating and calorie restriction groups.[85] In the study population, the largest meal was in the evening, and the majority of participants chose a late eating window (12 p.m. to 8 p.m.) as the default protocol. No significant differences were observed in weight, hepatic fat, fasting glucose, or insulin levels between an early eating window and a late eating window, although this result should be interpreted in the context of a small sample size. In addition to various metabolic and hepatic markers, tools such as smartwatches and surveys have been used to assess the effect of time-restricted feeding on circadian clocks and sleep quality; however, total sleep time, sleep onset time, wake time during sleep, and insomnia scores were not affected.[90,91]

It is important to clarify the relationship between meal timing and MASLD, as meal disruption, such as skipping breakfast, disrupts the circadian clock.[92] In murine models, chronic breakfast skipping may also disrupt sleep homeostasis, reducing wakefulness and increasing REM sleep duration, while impairing hippocampal memory-related gene expression.[93] One study of "breakfast skippers" and/or late dinner consumption found that the prevalence of MASLD was higher among "breakfast skippers" compared with those who ate breakfast regularly, and similarly higher among late dinner eaters compared with those with regular dinner times.[94] In a combined analysis, MASLD prevalence was positively correlated with the severity of irregular eating. Additional work has established that late-night dinner consumption is associated with increased total calorie intake, which may explain why participants with both behaviors (breakfast skipping and late-night dinner eating) showed the highest disease severity, representing a "double metabolic hit" of circadian disruption plus evening caloric excess.[95] Recent work has found that eating from 9 a.m. to 6 p.m. at a caloric deficit, combined with calorie restriction, may restore insulin sensitivity in patients with MASLD compared with calorie restriction alone.[96]

In conclusion, while time-restricted eating provides significant metabolic benefits over standard care, its efficacy appears comparable to simple calorie restriction, with the specific timing of the eating window—particularly avoiding a double metabolic hit of breakfast skipping and late-night eating—playing a crucial role in enhancing insulin sensitivity and circadian alignment. Additionally, the benefits of time-restricted eating may be primarily driven by the underlying caloric deficit it facilitates, though early eating windows may offer additional advantages for glucose metabolism and liver health.

Light therapy

As highlighted previously, light exposure and circadian misalignment are linked to MASLD. In particular, ALAN, especially blue light, can disrupt circadian physiology.[97] ALAN suppresses melatonin secretion, delays its onset, and shifts the internal timing of

the circadian clock, thereby affecting sleep initiation and downstream effector genes of the central clock. The American Heart Association's 2025 scientific statement emphasizes that morning bright light exposure (traditionally ≥10,000 lux, though lower intensities enriched with blue-green wavelengths may suffice) advances circadian phase, improves mood and energy levels, and is associated with lower body fat, body mass, and appetite.[83]

It is established that ALAN promotes hepatic lipid accumulation through uptake of circulating free fatty acids by the liver and alteration of circulating adipokines such as leptin and adiponectin.[20] ALAN also disrupts the normal circadian rhythmicity of glucose metabolism in the liver through significant changes in hepatic gene expression, affecting hepatocyte glucose uptake, glycolysis, and gluconeogenesis.[98] Finally, experimental models have shown that ALAN may affect the gut microbiome through increased intestinal mucosal permeability, which may contribute to hepatic disease via progressive inflammatory effects within the portal system.[99]

Circadian misalignment, rather than sleep duration alone, is a predominant risk factor for steatosis and fibrosis, with evidence supporting up to a twofold increase in MASLD compared with controls.[100] While this may be affected by shift work, one study that excluded participants with a history of shift work found that increased daylight exposure corresponded to lower MASLD risk, while increased ALAN exposure corresponded to higher MASLD risk in a dose-dependent manner.[101] The rest–activity rhythm, a measure of daytime versus nighttime activity, is associated with substantially lower MASLD risk, with higher daytime activity decreasing MASLD risk and higher nighttime activity increasing MASLD risk.[101]

Sleep

To preface, the relationship between sleep patterns and MASLD is complex. Sleep patterns vary naturally between individuals, creating physiological variation in sleep, but pathological circadian misalignment also causes sleep disturbances, and it is difficult to differentiate these using sleep duration alone.[102–104] Secondly, numerous psychosocioeconomic factors contribute to the pathogenesis of obesity and metabolic diseases, and there is a plausible overlap in populations at higher risk of chronic disease and those more likely to experience poor sleep, such as individuals working in shift work occupations, especially night shifts.[105,106]

Short sleep duration is known to be associated with obesity and metabolic syndrome. Previous work characterizing sleep patterns in individuals with MASLD has noted shorter sleep duration, prolonged sleep onset latency, poorer sleep quality, and associated changes in psychological affective state.[24] Interestingly, daytime sleepiness significantly correlates with liver enzymes and insulin resistance independently of cirrhosis in MASLD patients but not in healthy individuals.[24] More recent evidence has suggested a nonlinear association between sleep duration and MASLD risk, with risk increasing at sleep durations <7.5 h or >9.5 h.[25] Other sleep dysfunctions, including snoring, sleep apnea, insomnia, self-reported sleep disorders, and daytime sleepiness, are also associated with increased risk of MASLD.[25–27]

The evidence supports a complex, multisystem, multidimensional relationship between sleep patterns and MASLD risk, and it is difficult to extrapolate a universal recommendation for sleep and meal timing for patients based on current literature. Approaches that minimize interference with daily life, such as sleep hygiene counseling and avoiding nighttime eating, may improve adherence. Strategies such as light therapy (morning blue light exposure), limiting ALAN, and increasing morning activity may also be effective.

Synthesis and perspectives

Given the high prevalence, strong association with cardiometabolic disease, risk of progression to advanced liver disease, and growing burden alongside rising obesity and diabetes rates, MASLD represents a critical target for early identification, risk stratification, and integrated lifestyle and pharmacologic intervention. Circadian homeostasis is essential for synchronizing hepatic glucose, lipid, inflammatory, and fibrotic pathways with environmental light–dark cycles. Disruption of this system destabilizes peripheral hepatic clocks, promotes insulin resistance, dyslipidemia, cytokine upregulation, and excess lipid deposition, which are hallmarks of MASLD pathogenesis.

Experimental models demonstrate that circadian disruption precipitates steatosis and fibrosing steatohepatitis even under standard dietary conditions, while environmental and behavioral disruptors including ALAN, shift work, SJL, short sleep duration, and chrononutritional misalignment exacerbate adverse metabolic phenotypes closely aligned with MASLD risk. Importantly, this relationship is bidirectional: progressive MASLD and MASH impair circadian regulation through hyperammonemia, astrocyte dysfunction, altered glutamatergic signaling within the SCN, neuroinflammation, endocrine dysregulation, and HE, thereby reinforcing sleep–wake fragmentation and chronobiologic instability. High-fat dietary patterns further reprogram central clock activity and peripheral gene expression, compounding metabolic and inflammatory stress. Collectively, these data support a self-perpetuating chronometabolic cycle in which circadian disruption both drives and is amplified by MASLD, positioning circadian integrity as a mechanistically central and potentially modifiable axis in disease progression.

Pharmaceutical interventions are currently limited to the GLP-1 RA semaglutide and the THR-β agonist resmetirom, both of which have shown significant clinical benefit leading to FDA approval for the treatment of MASLD with fibrosis.[44,63] While most of these benefits are directly related to metabolic changes, there are considerations regarding their impact on circadian rhythm and the potential role of chrono-pharmacology as a future research target to enhance medication efficacy. Melatonin is an over-the-counter supplement that, while not FDA-approved, has shown clinical benefit in small RCTs using noninvasive endpoints such as liver enzymes, imaging-based fatty liver grading, and metabolic parameters.[81,82] Lifestyle interventions remain the mainstay of treatment for both MASLD and sleep disorders. Meal timing, sleep hygiene, and light exposure should all be considered in clinical context when counseling patients.

Limitations

Although accumulating evidence supports a bidirectional relationship between MASLD and circadian disruption, the underlying mechanisms remain incompletely defined. In particular, it remains unclear how liver-derived signals such as hepatokines, cytokines, and metabolic intermediates affect central and extrahepatic peripheral clocks, and whether these pathways are causal or merely associative. Further mechanistic and clinical studies are needed to validate these relationships.

In addition to the above limitations in current knowledge, inherent biases in this review include selection bias due to continually evolving terminology related to liver disease, limitations in the selected search criteria, and publication bias in the included literature when evaluating clinical associations and mechanistic findings.

Conclusions

The relationship between MASLD and circadian disruption is bi-directional. Various forms of circadian disruption, such as ALAN, shift work, SJL, irregular eating patterns, and irregular sleeping patterns, all contribute to MASLD progression. Conversely, MASLD risk factors and associated sequelae, including hyperammonemia, HE, high-fat diet, and cirrhosis, all dysregulate circadian rhythms. Several pharmacological (GLP-1 RAs, THR-β agonists, and melatonin) and lifestyle (meal timing, light therapy, and sleep hygiene) interventions are promising for the treatment of MASLD and circadian disruption.

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Conflict of interest

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Author contributions

Study concept and design (WKS, AVH, SMD, ECO, DAJ), acquisition of data (WKS, AVH), analysis and interpretation of content (SMD, ECO, DAJ), drafting of the manuscript (WKS, AVH, SMD, ECO), critical revision of the manuscript for important intellectual content (SMD, ECO, DAJ), administrative, technical, or material support (SMD, ECO), and study supervision (SMD, ECO, DAJ). All authors have made significant contributions to this study and have approved the final manuscript.

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