A Bidirectional Association Between Obstructive Sleep Apnea and Metabolic-Associated Fatty Liver Disease

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KEYWORDS

• Metabolic-associated fatty liver disease • Obstructive sleep apnea
• Chronic intermittent hypoxia • Insulin resistance • Steatosis • Fibrosis • CPAP

KEY POINTS

- There is a strong association between metabolic-associated fatty liver disease (MAFLD) and obstructive sleep apnea (OSA).
- OSA is associated with a twofold increased risk of steatosis, steatohepatitis, and fibrosis, independent of obesity.
- OSA-induced insulin resistance, oxidative stress, gut dysbiosis, and molecular changes are all considered to contribute to the pathogenesis of MAFLD.

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing.[1] OSA is characterized by ventilatory disruptions from repetitive upper respiratory airway collapse during sleep. This triggers periodic apnea, hypopneas, intra-thoracic pressure changes, derangements of gas exchange, sleep fragmentations, and repetitive intermittent hypoxia sequence (i.e., chronic intermittent hypoxia [CIH]).[2]

The presence of hepatic steatosis and signs of metabolic dysfunction, obesity, or diabetes defines metabolic-associated fatty liver disease (MAFLD).[3] In time, a certain proportion of patients develop inflammatory infiltration and hepatocyte ballooning, progressing to steatohepatitis and eventually progressing to liver cell injury and fibrosis. Emerging research indicates that MAFLD is a multi-system disease. The mechanism by which MAFLD progresses into non-alcoholic steatohepatitis (NASH)

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Endocrinol Metab Clin N Am 52 (2023) 509–520
https://doi.org/10.1016/j.ecl.2023.01.006
0889-8529/23/

endo.theclinics.com

is not entirely understood. Multiple mechanisms causing lipotoxicity, inflammation, and fibrosis have been postulated.

Although multiple pieces of literature explore the relationship between OSA and MAFLD, a complied literature review is lacking. This comprehensive review aims to compile, interlink, and delineate the available evidence to understand the pathophysiological, diagnostic, and management aspects of patients with OSA and MAFLD.

EPIDEMIOLOGY

Prevalence data from 17 epidemiological studies report that approximately 21% of the global population is estimated to have OSA.[4] The OSA prevalence increases with obesity, older age, male sex, and upper airway abnormalities.[4] OSA is associated with various metabolic complications, such as type 2 diabetes mellitus (T2DM) and MAFLD.

MAFLD has become the most common cause of chronic liver disease globally in recent years, paralleling the obesity epidemic worldwide. Current trends suggest that MAFLD may be present in about one-third of the global population.[5] NASH is projected to be the leading indication for liver transplantation in the future.[6]

A recent individual data meta-analysis from France has demonstrated that the prevalence of steatosis in severe OSA patients is 85%, among which 26% have signs of liver fibrosis.[7] A meta-analysis by Musso and colleagues[8] has conferred a twofold increase in the risk of steatosis, steatohepatitis, and fibrosis in OSA patients, independent of obesity. An OSA–MAFLD association has also been noted in the pediatric population, where 44% of non-obese and 68% of obese children with OSA were observed to have MAFLD.[9]

DIAGNOSTIC APPROACH

The gold standard diagnostic test for OSA is the attended in-laboratory polysomnography to estimate the apnea-hypopnea index (AHI).[10] Testing is currently recommended for patients with excessive daytime sleepiness, fatigue, and unrested sleep and should be considered in individuals with snoring, nocturnal awakenings, and gastroesophageal reflux.[11] The classification of OSA severity is based on the AHI; an AHI of 5 to 15 events per hour of sleep is classified as mild OSA, 15 to 30 events per hour as moderate, and $\geq$ 30 events per hour as severe.[12]

New guidelines for diagnosing MAFLD are based on radiological, histological, or non-invasive biomarkers for steatosis coupled with one or more of the following: (1) raised body mass index, (2) T2DM, or (3) two or more signs of metabolic risk abnormalities, including hypertension, increased glucose levels, insulin resistance (IR), high c-reactive protein, elevated waist circumference, and dyslipidemia.[3] The gold standard for MAFLD diagnosis remains to be a liver biopsy. However, given the invasive nature of a biopsy, ultrasound is recommended as the first-line test for detecting steatosis.[3] Ultrasound and vibration-controlled elastography are widely used in clinical practice, with computerised tomography (CT) or magnetic resonance imaging (MRI) being used to diagnose moderate to severe steatosis.[3] Upon confirming the diagnosis of MAFLD, the presence and extent of fibrosis can be detected using non-invasive biomarkers and liver stiffness markers. A definitive, reliable non-invasive scoring system is yet to be established.[13] However, a meta-analysis by Moze and colleagues[14] has established an algorithm sequentially combining non-invasive test cut-offs (Fibrosis-4 Index [FIB-4] and MAFLD fibrosis score [NFS]) with vibration-controlled transient elastography (fibroscan) to either rule out fibrosis or positively diagnose cirrhosis. Ideally, serum biomarkers combined with elastography could potentially replace the need for biopsy and imaging modalities in the future.

OBSTRUCTIVE SLEEP APNEA AND METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Association Obesity on Obstructive Sleep Apnea and Metabolic-Associated Fatty Liver Disease

OSA leads to metabolic dysfunction via OSA-induced CIH and its downstream effects. These include sympathetic overactivity, oxidative stress, low-grade inflammation, dyslipidemia, and IR. Obesity and its consequent anatomical obstruction is a significant cause of sleep apnea.[15] The pathophysiology of OSA goes beyond the theory of anatomical obstruction. The physiological components of obesity, such as IR, elevated leptin levels, and glycemic control, can all contribute to the development of OSA.[16] Obesity may lead to sleep-disordered breathing and central sleep apnea through reduced respiratory mechano-receptor sensitivity via sympathetic overactivity and reduced pharyngeal muscle tone due to chronically increased muscle activity through inflammatory cascades (**Fig. 1**).[16]

A recent meta-analysis estimates the prevalence of obesity in MAFLD individuals at 50% and 80% for steatohepatitis.[17] In addition, prolonged exposure to CIH causing liver injury in diet-induced obese mice is similar to MAFLD in obese individuals with OSA.[18]

Risk of Metabolic-Associated Fatty Liver Disease in Obstructive Sleep Apnea

CIH and the repetitive desaturation and reoxygenation sequence is the most explored pathophysiological feature for the progression of metabolic dysfunction and subsequent MAFLD. The exact mechanism by which OSA causes hepato-metabolic alteration is unclear, but numerous studies (**Table 1**) support an association between MAFLD and OSA via both obesity-dependent and independent factors. There is emerging evidence in human studies affirming the degree of nocturnal hypoxemia in OSA being linked to the OSA–MAFLD association.[19]

Risk of Obstructive Sleep Apnea in Metabolic-Associated Fatty Liver Disease

There is a direct association between MAFLD and OSA. Recent studies suggest that MAFLD, defined by fatty liver index (FLI), independently increases the risk of OSA.[22,23] A US-based population study showed elevated liver enzyme-defined MAFLD was associated with sleep disorders.[24] The mechanism for this is unclear, and further randomized controlled trials (RCTs) are required to confirm the association. **Table 2** shows the studies showing MAFLD–OSA association.

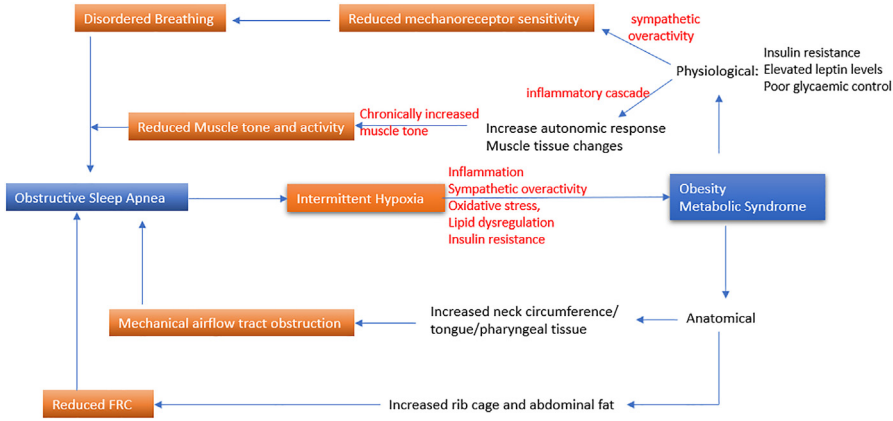

Fig. 1. OSA and obesity.

Table 1
Meta-analysis studies on obstructive sleep apnea–metabolic-associated fatty liver disease association

Study	Subjects (n)	Key Findings
Musso et al,[8] 2013	N = 2183	OSA is associated with a twofold increased risk of steatosis, steatohepatitis, and fibrosis, independent of obesity.
Jin et al,[20] 2018	N = 2272	OSA was significantly correlated with the development and progression of steatosis, ballooning degeneration, and fibrosis.
Jullian-Desayes et al,[7] 2020	N = 2120	There is a strong association between steatosis and OSA severity; 85% of severe OSA patients (AHI > 30 events/h) have steatosis. Risk factors for steatosis include AHI >5/h, male sex, higher age, excess body mass index (BMI), and diabetes.
Chen et al,[21] 2021	N = 1133	OSA was significantly associated with elevated liver transaminases and fibrosis in the pediatric population.

PATHOPHYSIOLOGY

No human studies have confirmed the tissue-specific effects of CIH. Multiple studies using experimental mice models show insight into the potential effects of CIH on the pathogenesis of MAFLD. Initially, a "two-hit" mechanism was hypothesized, where (1) hepatic lipid accumulation and IR followed by (2) inflammatory insults with oxidative stress resulting in steatohepatitis and fibrosis.[27] More recently, a "multi-parallel hit" process has been suggested, acting synergistically through various mechanisms.[27] CIH-induced IR and metabolic health, oxidative stress, gut dysbiosis, and molecular changes are all considered to contribute to the pathogenesis of MAFLD.

Chronic Intermittent Hypoxia, Insulin Resistance, and Metabolic Health

Multiple mechanisms are proposed by which CIH is an intermediate to IR, T2DM, and impaired glucose metabolism, independently of obesity (**Fig. 2**). CIH-induced systemic inflammation via nuclear factor kappa B (*NF-KB*) activation seems to be a key process in the pathogenesis of cardio-metabolic dysfunction. Activation of NF-KB leads to the

Table 2
Observational studies on metabolic-associated fatty liver disease-obstructive sleep apnea association

Study	Subjects (n)	Key Findings
Mir et al,[24] 2013 (population data)	N = 10,541	Individuals with MAFLD had a higher prevalence of sleep disorders.
Petta et al,[25] 2015	N = 126	OSA was highly prevalent in individuals with MAFLD, and severity was associated with the severity of liver fibrosis.
Cakmak et al,[26] 2015	N = 137	AHI and oxygen saturation indices were significantly higher in MAFLD compared to the non-MAFLD population.
Kim et al,[22] 2022 (population cohort)	N = 334,334	MAFLD is independently associated with OSA in the Korean population.
Chung et al,[23] 2021 (population cohort)	N = 8,116,524	The risk of OSA was significantly greater in patients with a higher FLI.

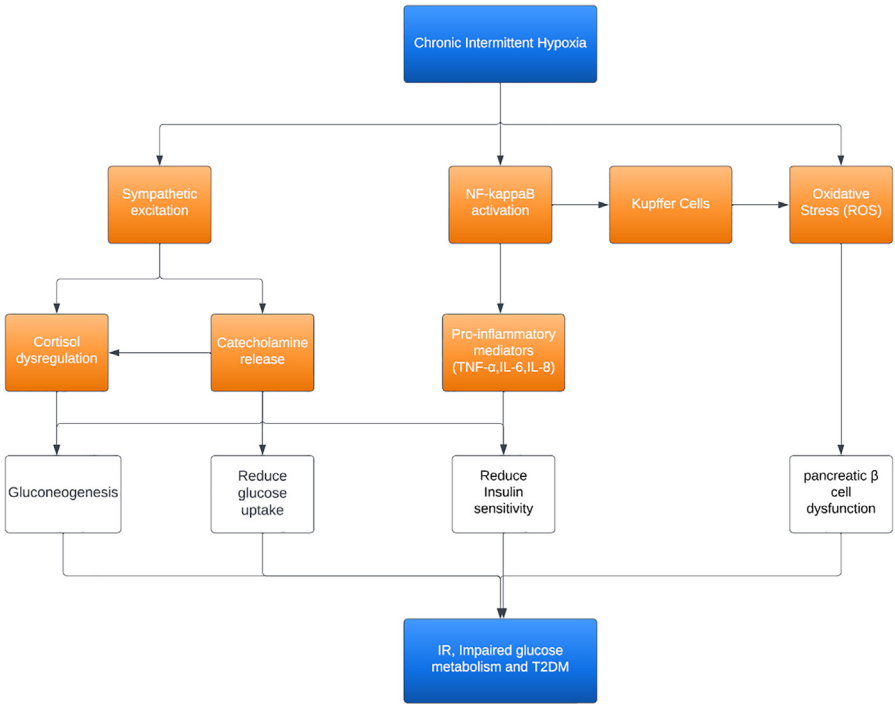

Fig. 2. *CIH and IR*. IL, interleukin; IR, insulin resistance; ROS, reactive oxidative species; T2DM, type 2 diabetes mellitus; TNF α, tumor necrosis factor-alpha.

production of numerous pro-inflammatory mediators.[28] Hypoxia and hypercapnia are found to stimulate the peripheral chemoreceptors triggering autonomic dysfunction and sympathetic hyperactivity.[29] There is an increased risk for liver steatosis secondary to CIH-induced sympathetic excitation and autonomic imbalance.[30] The underlying mechanisms postulated involve catecholamine and cortisol release secondary to sympathetic overactivity, resulting in reduced insulin sensitivity, glucose uptake, and increased gluconeogenesis.[28,31] Additionally, CIH is associated with increased production of reactive oxidative species (ROS) directly and indirectly through the activation of Kupffer cells and recruitment of activated phagocytes into the liver.[32,33]

Hypoxia induced by adipose tissue expansion also increases adipocyte dysfunction, proliferation, and subsequently lipolysis, leading to adipocyte inflammation, which results in an acute rise of plasma-free fatty acids (FFAs). Increased FFAs lead to lipid accumulation and gluconeogenesis, causing impaired insulin signaling and increased IR.[28] IR, via the various mechanisms mentioned above, leads to an increase of the sterol regulatory element-binding protein 1c (SREBP-1c) gene through (1) the downregulation of insulin receptor substrate 2 (IRS-2), (2) suppression of FFA β-oxidation, (3) the inhibition of lipolysis, and (4) stimulation of phosphatidylinositol-3 kinase (PI3K).[27,34] Increase of SREBP-1c results in de novo lipogenesis and, consequently, steatosis. Elevated insulin levels also directly stimulate PI3K resulting in apoptosis and inflammation of hepatocytes leading to steatohepatitis.[34]

Molecular Consequence of Chronic Intermittent Hypoxia

Previous studies have explored the role of activation of hypoxia-inducible factors (HIFs). These induce lipid accumulation in hepatocytes resulting in the development

of MAFLD and further progression to steatohepatitis and fibrosis.[35] The cellular mechanisms of the human body are highly dependent on oxygen. Even a mild reduction in oxygen initiates a rapid adaptive oxygen response, after which activation of both the HIF and NF-KB pathways are significant to the development of MAFLD.[32] Sleep fragmentation/CIH exposure upregulates the expression of HIF1α complexes, which interact with hypoxic response elements to induce target genes with downstream effects on glucose and lipid metabolism, angiogenesis, and epithelial-mesenchymal transition, thereby, activating pro-inflammatory cascades.[32,35] Recent research demonstrated the role of CIH in the imbalance of Treg/Th17 cells (regulatory T cell/T helper cell 17) through the expression of the HIF1α subunit and subsequent activation of the mTOR-HIF1α-TLR4-IL-6 (mammalian target of rapamycin-HIF1α-toll-like receptor 4-interleukin-6) inflammatory pathway.[36] This exacerbates oxidative stress and induces hypoxia, accelerating the progression of steatohepatitis and liver fibrosis.

There is growing evidence that hypoxia-induced HIF2α activation, in addition to HIF1α activation, leads to the upregulation of genes involved in FFA uptake and hepatocyte lipid accumulation while suppressing lipid synthesis and β-oxidation.[37] An increase of HIF2α in hypoxic HepG2 cells also was shown to increase adipose differentiation-related protein expression, which results in further FFA uptake and steatosis.[38] An upregulation of HIF2α can also activate the NF-KB pathway and exacerbate steatohepatitis.[39] HIF2α may be a potential therapeutic target, given its implied role in the progression of steatosis to severe steatohepatitis and fibrosis.

Chronic Intermittent Hypoxia-Induced Oxidative Stress and Chronic Inflammation

Previous studies have demonstrated that prolonged exposure to CIH induces increased lipid peroxidation, independently of obesity.[40] Under hypoxic conditions, NF-KB activates Kupffer cells and generates ROS. An increase in ROS interacts with FFAs to induce lipid peroxidation and causes mitochondrial dysfunction and subsequent liver damage.[41] Recurrent sleep fragmentation and arousals may also incite endothelial dysfunction and increased inflammatory cytokine recruitment (such as interleukin (IL)-6).[42] In addition, Kupffer cells release inflammatory cytokines [IL-6, tumor necrosis factor-alpha (TNF-a)], which have been suggested to promote the development of MAFLD and progression into NASH.[32] A recent study on a mouse model explored the effect of CIH on MAFLD development and progression via the nuclear factor erythroid 2–related factor 2 (Nrf2)/NF-KB signaling pathway, modulated by the receptor-interacting serine/threonine-protein kinase 3 (RIPK3)-dependent necroptosis.[43] When RIPK3 is downregulated, hepatocyte necroptosis and subsequent inflammation and oxidative stress are ameliorated.[43] This opens new doors to exploring therapeutic strategies in OSA-induced MAFLD.

Chronic Intermittent Hypoxia and Alterations in Gut Microbiota

The association between OSA-induced alterations in gut microbiota and its effect on the liver has been explored in the pediatric population. In a mouse model, Nobili and colleagues[44] and Barcelo and colleagues[45] have suggested that OSA is associated with impaired gut permeability and intestinal damage resulting in elevated levels of lipopolysaccharide and endotoxins. This leads to low-grade inflammation and hepatocyte injury via upregulation of the hepatocyte Toll-like receptor 4 (TLR4).[44,45] Thus, OSA-induced gut–liver axis impairment contributes to MAFLD progression.

MANAGEMENT ALGORITHM

A clear management guideline to mitigate liver injury and prevent the complications of OSA and MAFLD is lacking. The aim should be to optimize metabolic sequelae and cardiovascular risk with early screening to prevent long-term complications of OSA and MAFLD. The cornerstone therapies for OSA and MAFLD continue to be behavioural and lifestyle modifications.

Behavioral/lifestyle changes

Multiple studies have shown good results in improving MAFLD and OSA with weight loss through exercise and diet control. Vilare-Gomez et al have demonstrated significant improvement in steatohepatitis in 90% of individuals with 7% to 10% weight loss (BW), with similar studies in Asia supporting this evidence.[46,47] Similarly, OSA patients with >10 kg weight loss have been shown to have a greater reduction in AHI of at least nine events/hour.[48] Exercise, independent of weight loss and diet, is also associated with a 20% reduction in OSA severity and intrahepatic triglycerides, hepatic steatosis, and liver stiffness.[49,50] Achieving and maintaining weight loss is challenging; hence an individualized, multi-disciplinary approach is required to assist and ensure motivation and continued participation.

Pharmacological management

There are multiple anti-diabetic medications reported to reduce weight, improve AHI, and protect against MAFLD, including glucagon-like peptide-1 receptor agonists .[51] Previous RCTs have demonstrated that Liraglutide is well tolerated and effective in reducing AHI and improving liver enzymes.[52,53] Other pharmacological agents reported to benefit MAFLD and OSA are antioxidants, such as vitamin E. However, evidence is lacking in MAFLD.[54] There are no FDA-approved drugs for MAFLD at this stage, but a few drugs (obeticholic acid, elafibranor, and selonsertib) have progressed to phase 3 development, showing evidence in reducing hepatic inflammation and fibrosis.[55] There are also emerging studies into novel therapeutic strategies targeting hypoxia and HIF factors.[56]

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) remains the gold standard therapy for OSA. Although the associations between OSA and MAFLD have been proven, large-scale RCTs on CPAP use in OSA and MAFLD have yet to demonstrate significant benefits on glucose levels, IR, or inflammatory markers, except in the improvement of blood pressure.[57–60] This questions a true association between the two conditions. The lack of evidence may be due to limited CPAP trials, poor CPAP compliance, or the multi-hit mode of MAFLD pathogenesis, in which CPAP only targets the CIH. Without targeting the other factors (among which especially obesity), a positive impact of CPAP on liver function may be challenging to establish. Furthermore, data on CPAP studies are predominately short-term. A more extended observational period in studies will be required to show the true effect of CPAP on MAFLD.

Metabolic/Bariatric Surgery

Among individuals who underwent bariatric surgery, MAFLD is present in the majority of patients (>90%) and OSA in 71% of patients.[61,62] Multiple studies have explored the effect of bariatric surgery on OSA and MAFLD, showing a resolution of steatosis in >75% of patients, and even suggesting a regression in fibrosis.[62] A meta-analysis on the effects of bariatric surgery on OSA reported that over 75% of patients had

improved OSA outcomes and demonstrated more significant improvement in AHI than non-surgical interventions.[63] Bariatric surgery is considered the most efficacious management for obesity, although current guidelines still consider it premature to be offered as a first-line therapy.[64] This may be due to the lack of RCTs comparing bariatric surgery to other interventions (such as CPAP), making it difficult to assess the benefit and harm. However, in light of the evidence above, bariatric surgery should be considered for obese patients (BMI >35) with MAFLD and severe OSA.

CLINICS CARE POINTS

- The degree of OSA is linked to the MAFLD severity (A1)
- Patients with moderate to severe OSA should be routinely screened for MAFLD, with/without obesity (A2)
- Patients with MAFLD should be considered for OSA screening (B2)
- Sequentially combining non-invasive test cut-offs (FIB-4 and NFS) with vibration-controlled transient elastography (fibroscan) can rule out fibrosis and rule in cirrhosis (A2)
- Behavioral and lifestyle changes toward a healthy diet and exercise should be recommended in obese and non-obese individuals with MAFLD and OSA (B2)
- Weight loss of approximately 10% should be the target for improvement of OSA and MAFLD (B1)
- Liraglutide is well tolerated and is effective in reducing AHI and improving liver function tests (B1)
- CPAP alone does not provide any significant benefit in MAFLD (A2)
- Bariatric surgery should be considered for obese patients (BMI >35) with MAFLD and severe OSA (B1)

SUMMARY

In conclusion, the exact mechanisms for OSA causing MAFLD and vice versa are unclear, despite the well-established association between OSA and MAFLD. Previous research studies have shown a direct relationship between the severity of OSA and the degree of MAFLD. There is also a relationship between nocturnal hypoxemia and MAFLD severity. This may be due to the CIH burden of OSA. We can confirm that CIH-induced sympathetic overactivity, oxidative stress, low-grade inflammation, dyslipidemia, and IR are involved, but more in-depth studies are required to clarify the causal relationship between these factors and MAFLD. Additional long-term CPAP studies need to be designed and be more reflective of clinical practice to evaluate the liver's response to OSA treatment. A multimodal management plan is required as combined therapies, including weight loss and exercise in combination with pharmacological and CPAP management, have been shown to improve IR and triglyceride levels, influencing MAFLD and OSA outcomes.

DISCLOSURE

All authors have nil commercial or financial conflicts of interest.

ACKNOWLEDGMENTS

Nil.

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