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Obstructive Sleep Apnea and the Liver

Malav P. Parikh[a], **Niyati M. Gupta**[a], and **Arthur J. McCullough**[a,b,*]

[a]Department of Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Cleveland Clinic Foundation, Cleveland, OH 44114, USA;

[b]Department of Inflammation and Immunity, Cleveland Clinic Lerner College of Medicine, Case Western University, Cleveland, OH 44195, USA

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver disorders, including the initial stage of simple fat accumulation (hepatic steatosis); followed by inflammatory changes leading to nonalcoholic steatohepatitis (NASH); and, finally, fibrosis and scaring resulting in liver cirrhosis and its consequences.[1]

The current prevalence of NAFLD is estimated to be 20% to 30%,[2,3] and it has become the second most common indication for liver transplantation in the United States, after chronic hepatitis C.[4] It is projected that over the next 15 years, NASH will become the most common disease cause for liver transplantation.[5] This exponential increase in the incidence and progression of NASH is attributed to the worldwide epidemic of obesity,[6] which has also resulted in an increase in the prevalence of other obesity-related disorders, including metabolic syndrome, type 2 diabetes mellitus (DM), cardiovascular disease, and obstructive sleep apnea (OSA).[7]

OSA is caused by complete or partial obstruction of the upper airway. This results in repetitive episodes of shallow or paused breathing during sleep and causes a reduction in blood oxygen saturation. This nocturnal hypoxia, or chronic intermittent hypoxia (CIH), is the most important factor linking OSA and NAFLD.[8–10] Recent studies have conclusively shown the role of OSA in the development and progression of NAFLD in terms of liver enzyme elevation and histologic alterations (steatosis, lobular inflammation, ballooning degeneration, and fibrosis).[11–19] This article discusses the pathologic mechanisms associating OSA with NAFLD and the impact of OSA treatment on NAFLD outcomes.

*Corresponding author. mcculla@ccf.org.

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OBSTRUCTIVE SLEEP APNEA

OSA is a common clinical condition in which the throat narrows or collapses repeatedly during sleep, resulting in episodes of intermittent oxygen desaturations and nocturnal awakenings.[20,21] It is estimated to be present in 4% to 5% of the general population and is seen twice as commonly in men as in women. Advancing age, male gender, obesity, neck thickness, craniofacial changes, and upper airway soft tissue abnormalities are important risk factors for OSA.[20–22]

The direct consequences of airway collapse are snoring; increased respiratory efforts; hypercapnia; and, most importantly, CIH. This hypoxemia is sensed by carotid body receptors, leading to sympathetic activation; arousal; clearing of the airway; and, eventually, reoxygenation. The cycle of deoxygenation and reoxygenation is repeated several times every night and results in increased catecholamine release, reactive oxygen species (ROS) generation, oxidative stress, and a state of systemic inflammation. Lack of a restorative night sleep also results in excessive daytime sleepiness; morning headaches; concentration difficulties; anxiety; depression; road-traffic accidents; and, in general, a poor quality of life.[20,21,23] OSA is also associated with hypertension, atherosclerosis, coronary artery disease, stroke, insulin resistance, and NAFLD.[24–27]

Polysomnography is the gold standard test for diagnosing OSA and involves recording of several physiologic parameters, including electroencephalogram, electrooculogram, and electromyogram, along with nasal and oral airflow measurements.[28] An episode of apnea is defined by cessation of airflow for greater than 10 seconds despite ongoing inspiratory effort; whereas an episode of hypopnea is defined by greater than 50% reduction in airflow or moderate airflow reduction (<50%) along with either desaturation or electroencephalographic evidence of awakening. The severity of sleep apnea is characterized by the apnea-hypopnea index (AHI), which is simply calculated by dividing the number of events by number of hours of sleep. Accordingly, OSA can be classified as mild (AHI: 5–15), moderate (15–30), and severe (>30).[29] Continuous positive airway pressure (CPAP) is the first-line treatment for OSA. It results in more restful sleep, reduced daytime symptoms, and improved quality of life.[30] However, the effect of CPAP therapy on other chronic conditions, including metabolic syndrome and NAFLD, is less clear (see later discussion).

PATHOGENESIS OF NONALCOHOLIC STEATOHEPATITIS

Two-Hit Hypothesis

Berson and colleagues[31] conducted a pivotal study, during which rat liver mitochondria and rat hepatocytes were exposed to a hepatotoxic drug 4,4′-diethylaminoethoxyhexestrol. This resulted in hepatic steatosis and inhibition of mitochondrial β-oxidation. Inhibition of mitochondrial respiration caused reduced adenosine triphosphate (ATP) levels and raised levels of ROS. The increased oxidative stress resulted in lipid peroxidation and subsequent cell death.

Day and James[32] proposed the popular 2-hit hypothesis (Fig. 1) of steatohepatitis based on this study.[31] The first hit represents hepatic steatosis, which could be related to factors such

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as excess caloric intake, obesity, or insulin resistance. A subsequent second hit, in the form of an oxidative stress, increased lipid peroxidation, and activation of inflammatory cascade, causes progression to steatohepatitis and fibrosis.

Multiple-hit hypothesis—Although the 2-hit hypothesis remains extremely popular and is often cited, emerging data show that it is too simplistic to explain the complex interplay of the multiple factors involved in the development of NASH. An alternative a multiple-hit hypothesis has been proposed that attempts to take into account several of the underlying mechanisms that may contribute to the pathogenesis of NASH.[33,34]

Genetic predisposition, environmental factors, and dietary habits lead to development of obesity, metabolic syndrome, and insulin resistance. Insulin resistance is a key factor in the progression of NAFLD because it not only leads to increased peripheral lipolysis with increased flux of free fatty acids (FFAs) but also to hepatic de novo lipogenesis (DNL). It also causes adipose tissue dysfunction with altered secretion of adipokines and increased levels of inflammatory cytokines, interleukin (IL)-6, and tumor necrosis factor (TNF)-α.[35] Alteration of gut microbiome causes increased gut permeability, systemic levels of lipopolysaccharides, and absorption of FFAs.[17]

All of these factors cause an increased flux of FFAs into the liver. This results in excess triglyceride (TG) deposition in the liver (hepatic steatosis) that parallels the generation of lipotoxic metabolites of FFAs. Further, these toxic metabolites cause mitochondrial dysfunction with increased oxidative stress, generation of ROS, and endoplasmic reticulum stress, which manifests in the form of hepatocyte injury and inflammation. Hence, TG accumulation in the hepatocyte is just an innocent bystander or an epiphenomenon in NAFLD pathogenesis, with the toxic metabolites of FFAs being the major mechanism for hepatotoxicity.[33,34]

LINK BETWEEN OBSTRUCTIVE SLEEP APNEA AND NONALCOHOLIC FATTY LIVER DISEASE

Several studies have firmly established the relationship between OSA and NAFLD in adult and pediatric populations (Table 1). The severity of sleep apnea and, particularly, its manifestation, CIH, is the most important trigger for increased oxidative stress, generation of ROS, and release of inflammatory cytokines, resulting systemic inflammation that drives the exacerbation of NAFLD and progression to liver fibrosis.[10] CIH causes reduced oxygen tension in the liver, particularly in the hepatocytes surrounding the central vein (zone 3) and results in the expression of hypoxia inducible factors (HIFs), which are the key oxygen sensors that mediate the ability of the cell to respond to a hypoxic environment. HIFs are implicated in the development of dyslipidemia, hepatic steatosis, insulin resistance, and liver fibrosis, and are a key link in the association of OSA and NAFLD.[10,50]

Obstructive Sleep Apnea and Dyslipidemia

Increased de novo lipogenesis—Entry of lipid substrates in the liver occurs through 1 of the following 3 mechanisms:(1) dietary intake of lipids and carbohydrates, (2) de novo

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lipogenesis, or (3) flux of FFAs from peripheral lipolysis, whereas liver disposes lipids through (1) storage as TGs, (2) oxidation of FAAs, or (3) export of TGs as very-low density lipoproteins (VLDLs) in the peripheral blood (Fig. 2).[51] Studies have identified several regulators that control hepatic lipid metabolism. Sterol receptor element-binding protein (SREBP) is a transcription factor that plays a vital role in hepatic DNL.[51,52] It consists of 3 isoforms, of which SREBP-1_c is predominantly expressed in liver. It mediates the expression of lipogenic genes such as fatty acid synthase and acyl-CoA carboxylase and thereby promotes de novo FFAs and TG synthesis.[55] It also increases stearoylcoenzyme-A desaturase (SCD)-1 activity that is responsible for converting polyun-saturated fatty acids into monounsaturated fatty acids (MUFAs). MUFAs are converted into cholesterol esters and TGs, which are incorporated into secreted particles.[53]

CIH, a major component of OSA, is independently associated with dyslipidemia in NAFLD.[53,54] Studies in mice have shown that exposure to CIH results in enhanced expression of previously mentioned lipogenic genes, resulting in higher TG content in the liver.[55] On the contrary, interruption of SREBP-1 signaling and depletion of SCD-1 prevents hyperlipidemia during CIH.[56,57] In a study by Li and colleagues,[58] under hypoxic conditions, protein levels of nuclear isoforms of SREBP-1 and SCD-1 were significantly lower in mice with partial deficiency of HIF-1α compared with wild-type mice. As a result, mice with partial deficiency of HIF-1α were protected against hypertriglyceridemia and hepatic fat accumulation during CIH. HIF-1α is a master regulator of metabolic responses to hypoxia and these data confirm that CIH increases lipogenesis through the mediation of HIF-1α.

Enhanced peripheral lipolysis and reduced lipoprotein clearance—CIH raises sympathetic activity and induces a state of insulin resistance. This promotes lipolysis in the adipose tissue and increased flux of FFAs in the liver. Under normoxia conditions, FFAs are metabolized by oxygen-dependent mitochondrial combustion through β-oxidation. Hence hypoxia creates a condition of excess FFAs and its reduced utilization through mitochondrial β-oxidation. More FFAs become available for TG and cholesterol synthesis, which eventually results in fatty liver, liver injury through oxidative stress, and NASH. CIH has also been shown to selectively inactivate the adipose tissue lipoprotein lipase and reduce the clearance of VLDL from circulation.[59] In summary, CIH can cause dyslipidemia by upregulating DNL and lipoprotein secretion, and reducing lipoprotein clearance, along with enhanced peripheral lipolysis and influx of FFAs in the liver.

Obstructive Sleep Apnea and Insulin Resistance

OSA is associated with CIH and sleep fragmentation, and an increasing pool of evidence now points toward an association between OSA, insulin resistance, and predisposition to type 2 DM (Fig. 3). In a study by Stamatakis and Punjabi,[60] sleep was experimentally fragmented across all stages using auditory and mechanical stimuli in healthy normal volunteers. After 2 nights of sleep fragmentation, they were noted to have reduced insulin sensitivity and glucose effectiveness with an elevated morning cortisol level and increased sympathetic tone. Increase in cortisol levels[61] and raised sympathetic tone[62,63] are well known to promote insulin resistance by reduction of insulin secretion from the pancreas,

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inhibition of insulin-mediated glucose uptake, and increased hepatic gluconeogenesis. In another study, selective suppression of slow-wave sleep in young healthy adults showed similar results. Sensitivity to insulin was markedly reduced without adequate compensatory increase in insulin release, leading to reduced glucose tolerance and increased DM risk.[64] In a study by Ip and colleagues,[65] 270 consecutive subjects referred for suspected sleep apnea and no underlying type 2 DM were included and tested for insulin resistance. OSA was associated with insulin resistance as measured by HOMA-IR, independent of body mass index, and progressive increase in insulin resistance was noted per each additional apnea or hypopnea per sleep hour. Mouse models of OSA have further implicated the role of ROS,[66] pancreatic beta cell apoptosis,[67] and inflammation[68] in the development of insulin resistance and predisposition to type 2 DM.[60] Hence, several human and animal studies establish a robust association between OSA and insulin resistance.

Insulin resistance is known to play a crucial role in the pathogenesis of NAFLD. Studies have shown increased adipose tissue and hepatic insulin resistance, and reduced whole-body sensitivity to insulin in NAFLD patients. These are manifested by increased peripheral lipolysis, impaired inhibition of hepatic gluconeogenesis, and reduced glucose disposal, respectively. Further, inability of the insulin to suppress peripheral lipolysis results in increased flux of FFAs to liver and contributes to hepatic DNL. Insulin resistance leads to a state of hyperinsulinemia, which stimulates lipogenic genes via SREBP-1c and further contributes to hepatic steatosis. Overall, hepatic DNL, increased flux of FFAs, and impaired mitochondrial oxidation of FFAs creates a perfect milieu for development and progression of NAFLD.

Obstructive Sleep Apnea and Adipose Tissue Dysfunction

Traditionally considered an inert tissue for pure energy storage, it now clear that adi-pose tissue is a major endocrine and a signaling organ. During obesity, hypertrophied adipocytes mediate inflammation and harbor an increased proportion of proinflammatory macrophages compared with the antiinflammatory type. Secretion of adiponectin, which mediates a protective role in NAFLD by improving insulin sensitivity and regulating fatty acid oxidation, is reduced. In contrast, the release of proinflammatory cytokines such as TNF-α and IL-6 is increased, which reduces hepatic insulin sensitivity. Peripheral lipolysis is also increased, along with the flux of FFAs to the liver, which further potentiates hepatic and muscle insulin resistance.[69–71] It has been conclusively proven in animal models that during obesity adipose tissue is hypoxic and the local adipose tissue hypoxia is responsible for the dysregulated production of adipokines and metabolic syndrome.[69]

Because inflammation and hypoxia play crucial roles in obesity-mediated adipose tissue dysfunction, CIH, as it occurs in OSA, can be postulated to further intensify adipose tissue dysfunction. To this effect, various animal studies and models have conclusively established the role of intermittent hypoxia (IH) in inducing adipose tissue inflammation and dysfunction, even in the absence of obesity.[70,72] In a recent study by Taylor and colleagues,[73] human adipocytes exposed to IH showed increase in nuclear factor-κβ DNA-binding activity compared with controls. There was also a significant increase in the secretion of inflammatory cytokines such as IL-8, IL-6, and TNF-α with IH in adipocytes. Hence, it was

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concluded that human adipocytes are sensitive to IH, which enhances the expression of inflammatory genes and the release of inflammatory cytokines. Overall, these data provide evidence that IH can mediate adipose tissue dysfunction and the release of proinflammatory adipokines, which are known to be involved in pathogenesis of NAFLD. However, further studies are required in humans to understand the exact underlying mechanisms of IH, especially the impact of obesity.

Obstructive Sleep Apnea and Mitochondrial Dysfunction

Mitochondria are responsible for the production of 95% the cellular energy source, ATP. Under aerobic conditions, mitochondria produce ATP via 3 main biochemical pathways: the tricarboxylic acid cycle or Krebs cycle, oxidative phosphorylation, and fatty acid β-oxidation.[74] In OSA, hypoxia, along with an increased oxidative stress and flux of FAAs, overwhelm these normal mechanisms and result in structural and functional alteration of the mitochondria. Structural alteration is characterized by depletion of mitochondrial DNA[75] and upregulated transcriptional and replication machinery of mitochondrial biogenesis.[76] Increased levels of TNF-α, ROS, and lipid peroxidation products alter the mitochondrial respiratory chain, block the flow of electrons in the respiratory chain, and increase the mitochondrial ROS formation. The resultant oxidative stress further activates inflammatory pathways, contributing to hepatocytes inflammation and the diverse hepatic lesions of NASH.[77]

Obstructive Sleep Apnea and Liver Fibrosis

Stellate cells and portal fibroblasts are important sources of fibrillar collagen and lysyl oxidase (LOX) enzymes in the normal liver and after early hepatic injury (Fig. 4).[78] Hypoxia is a potent stimulator of LOX activity, which in turn plays an important role in the covalent cross-linking of collagen and elastin, increasing liver stiffness.[79] This increased stiffness causes increased mechanical tension that is crucial for the differentiation of hepatic stellate cell and portal fibroblasts into myofibroblasts, which are responsible for deposition of extracellular collagen and, eventually, the development of fibrosis.[78] Mesarwi and colleagues[80] have recently demonstrated that serum LOX is elevated in patients with NAFLD-associated hepatic fibrosis, relative to those without fibrosis. These same investigators also proposed the potential role of serum LOX as a biomarker of liver fibrosis in patients with severe obesity and OSA. HIF-1α has also been independently implicated in the development of liver fibrosis in a mouse model of NAFLD.[81] Hence, it can be concluded that hypoxia induces HIF-1α, which in turn induces the expression of LOX enzyme and the subsequent development of fibrosis.

Continuous positive airway pressure treatment and impact on nonalcoholic fatty liver disease—CPAP was originally described in 1983 by Sullivan and colleagues[82] and is considered the gold standard therapy for moderate to severe OSA. CPAP therapy acts as a pneumatic support, causing the pharyngeal intraluminal pressure to exceed the surrounding pressure. It also stabilizes the upper airway by increasing the end-expiratory lung volume, thereby preventing the hypoxic events related to the upper airway collapse.[83] Studies have conclusively established the benefits CPAP therapy in decreasing the hypoxic events and daytime sleepiness, lowering the risk of motor-vehicle accidents, and improving

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hypertension and a better quality of life in general.[84] However, studies have yielded conflicting results about the efficacy of CPAP therapy on metabolic syndrome, including insulin resistance, lipid profile, and body fat composition.[85,86]

Given that CIH plays a vital role in mediation of NAFLD in OSA, treatment with CPAP would be expected to yield unequivocal benefits in NAFLD patients. However, the available studies have yielded mixed results and are listed in Table 2 and Table 3.[80,87–102] In these studies, the impact of CPAP therapy on NAFLD was assessed by means of improvements in liver enzymes, hepatic adiposity, or fibrosis. Importantly, the observational studies that demonstrated the benefits of CPAP (see Table 2) were of longer duration than the randomized controlled trials that did not show CPAP to be beneficial (see Table 3). Progression of liver fibrosis from 1 stage to another takes an average of 7 years in patients with NASH and 14 years in those with NAFLD.[103] Hence it is likely that studies of longer duration will be required to demonstrate the importance of OSA in the pathogenesis of NAFLD and the benefits of CPAP in its treatment. Increasing data indicate that CPAP should be considered as an integral component in the management off NAFLD patients with moderate to severe OSA and that more than 3 months of treatment with appropriate compliance is needed to notice any significant improvements in NAFLD parameters (see Table 2). As mentioned earlier, development of NAFLD requires multiple-hits and aberrations in multiple metabolic pathways. Hence, its effective management also needs a multi-modal approach with paramount emphasis on diet and lifestyle modification, and weight loss, with CPAP being an essential element in those with NAFLD and moderate to severe OSA.[104]

SUMMARY

CIH is an important risk factor in the pathogenesis of NAFLD in patients with moderate to severe OSA. Reduced oxygen tension induces HIFs, which are implicated in the development of dyslipidemia, hepatic steatosis, insulin resistance, and liver fibrosis, and are a key link in the association of OSA and NAFLD. Given that several metabolic pathways are involved in its pathogenesis, a multipronged approach to NAFLD management is required, with emphasis on weight loss and lifestyle modification. The role of CPAP in the management of NAFLD is yet to be established firmly; however, adequate duration of CPAP therapy with appropriate compliance are important to notice any significant improvements in NAFLD parameters.

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KEY POINTS

- Chronic intermittent hypoxia (CIH) is the most important factor linking obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD).
- CIH results in a state of systemic inflammation, increased oxidative stress, insulin resistance, and dyslipidemia, predisposing to various manifestations on NAFLD.
- Even though the 2-hit theory has been a popular hypothesis to explain the pathogenesis of NAFLD, current evidence points toward a multiple-hit hypothesis involving complex interplay of environmental and dietary factors, role of insulin resistance, adipose tissue dysfunction, and altered gut microbiota in genetically predisposed subjects.
- The role of continuous positive airway pressure (CPAP) in the management of NAFLD is yet to be established firmly.
- In general, a multifaceted approach to NAFLD with emphasis on diet, life style modification, and weight loss is required, along with sufficiently longer duration of CPAP therapy and appropriate compliance in those with NAFLD and moderate to severe OSA.

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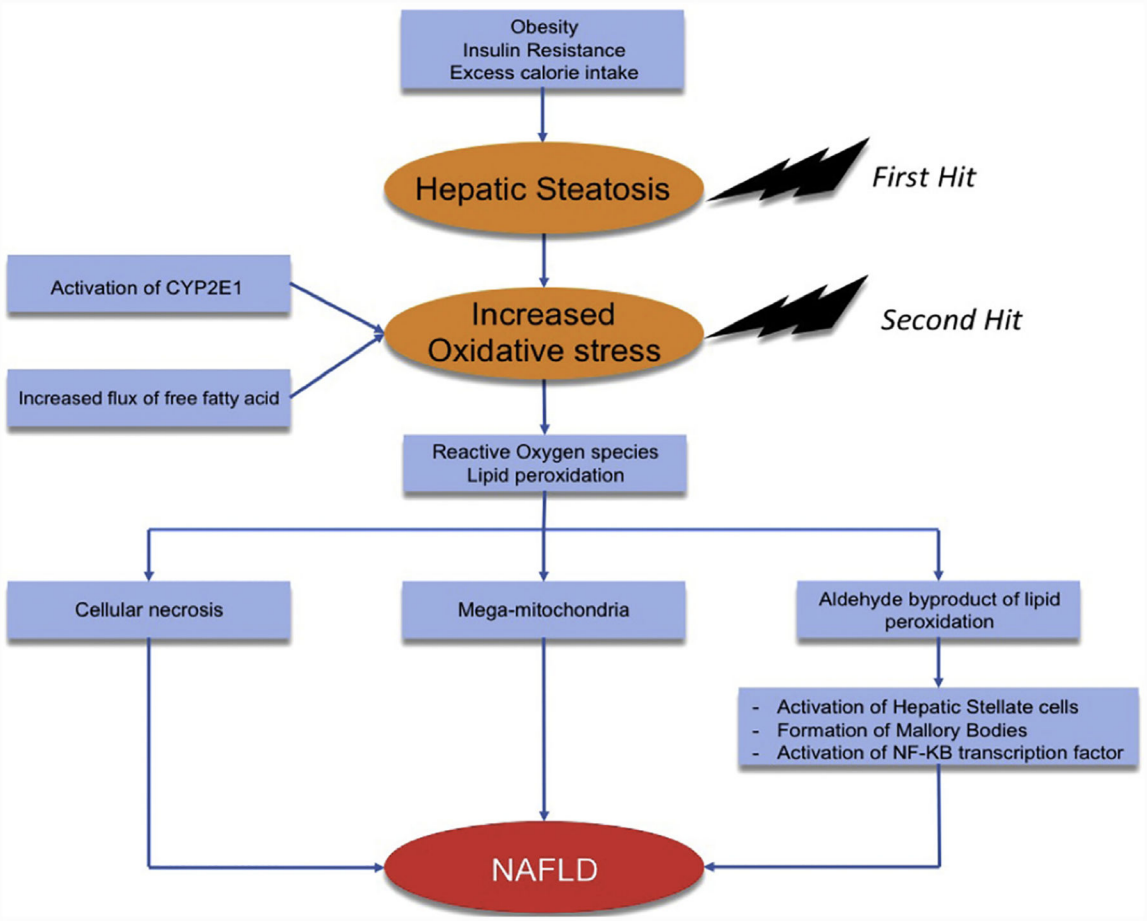

Fig. 1.
Two-hit hypothesis. CYP2E1, cytochrome P450 2E1; NF-κB, in nuclear factor-κβ.

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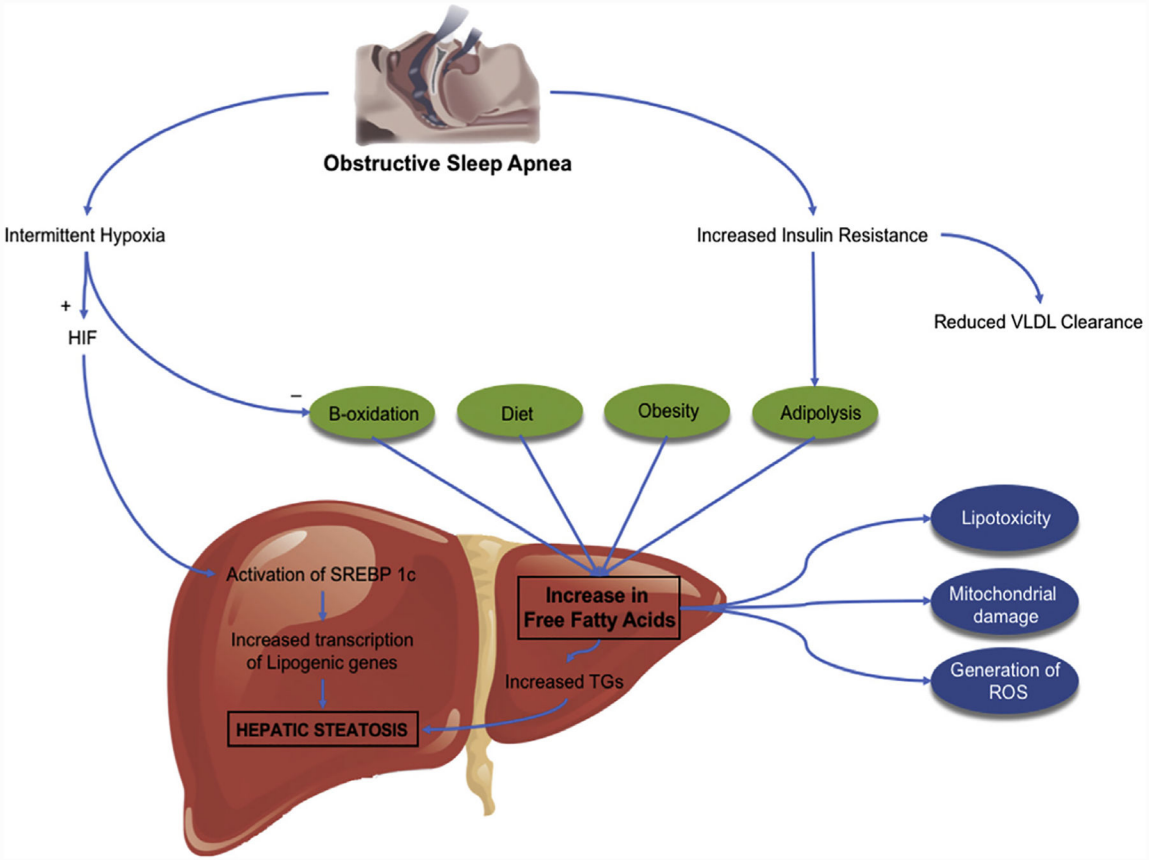

Fig. 2.

Increased de novo lipogenesis. SREBP, sterol receptor element-binding protein.

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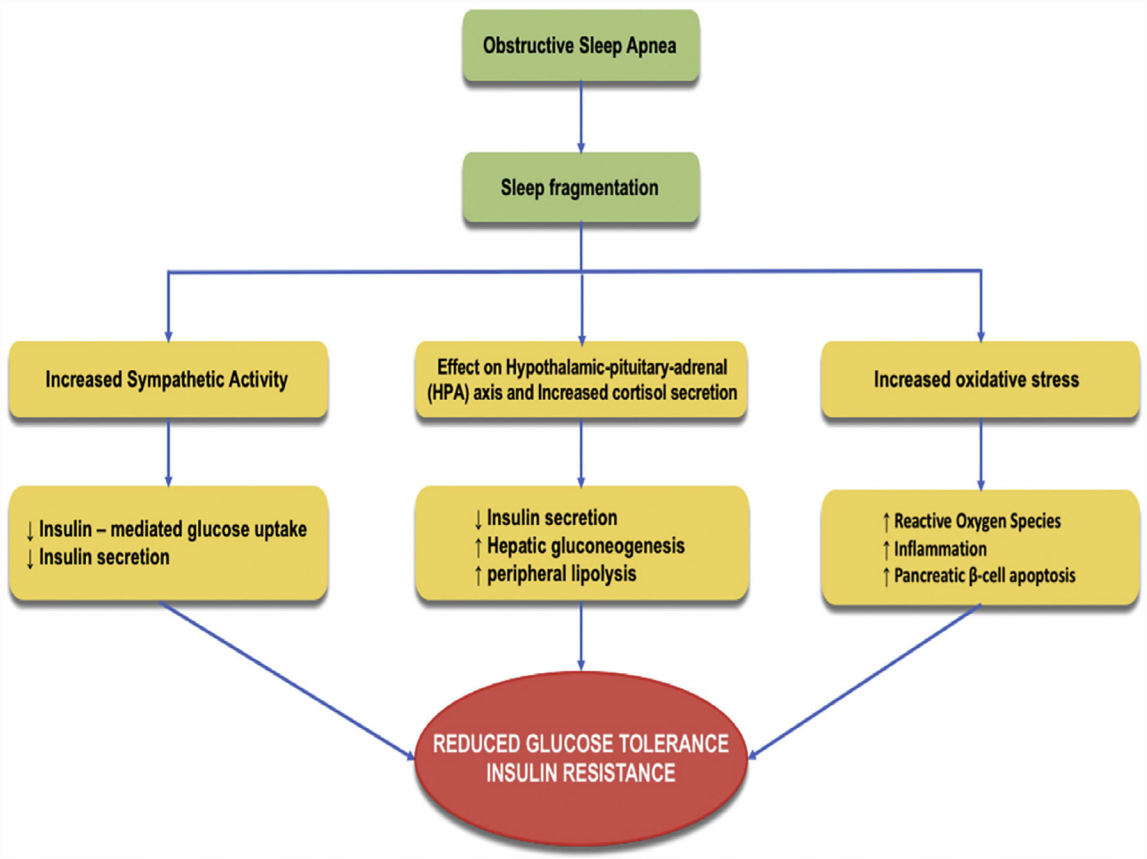

Fig. 3.
OSA and insulin resistance.

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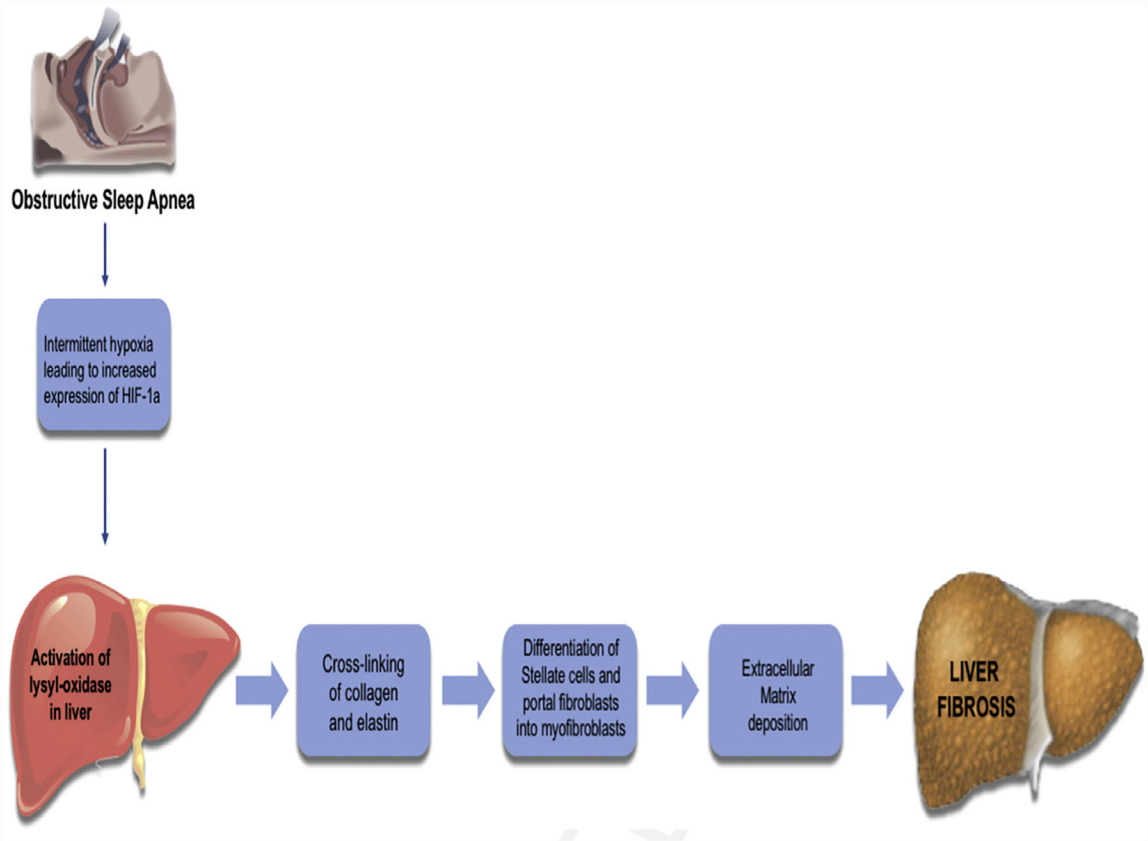

Fig. 4.
OSA and liver fibrosis.

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Table 1

Human studies assessing the correlation between obstructive sleep apnea and nonalcoholic fatty liver disease

Reference	Type of Study (Subject Population [n]); Country	NAFLD Assessment	OSA Diagnosis	Important Findings
Tanne et al,[36] 2005	PSG (163); France	LFT or liver biopsy	PSG	Severe OSA is associated with elevation of liver enzymes, insulin resistance, and steatohepatitis.
Kallwitz et al,[37] 2007	Bariatric surgery (85); USA	Liver biopsy	PSG (AHI ≥15/h)	OSA was associated with elevated ALT levels and a trend toward histologic evidence of progressive liver disease (inflammation and fibrosis).
Polotsky et al,[18] 2009	Bariatric surgery (90); USA	LFT or liver biopsy	PSG	Oxygen desaturation >4.6% was associated with 1.5-fold increase in insulin resistance. Significant desaturations may predispose to steatohepatitis.
Daltro et al,[15] 2010	Bariatric surgery (40); Brazil	Liver biopsy	PSG	OSA (AHI ≥15/h) was associated with insulin resistance but not with the severity of NASH.
Aron-Wisnewsky et al,[8] 2012	Bariatric surgery (101); France	Liver biopsy	ODI by nocturnal oximetry	CIH was independently associated with hepatic fibrosis, fibroinflammation, and NAFLD activity score.
Turkay et al,[27] 2012	PSG (71); Turkey	LFT, ultrasound	PSG	AHI, ODI, lowest desaturation values, and percentage of sleep duration with SpO2 <90% were independent predictors of NAFLD.
Corey et al,[38] 2013	Bariatric surgery (159); USA	Liver biopsy	Electronic medical record	Absence of OSA was associated with normal liver histology in subjects undergoing bariatric surgery.
Mir et al,[39] 2013	Population-based study, NHANES database. (NAFLD cases = 1572, controls = 8969); USA	LFT	Sleep Disorders Questionnaire	NAFLD was associated with sleep apnea (OR = 1.39, 0.98–1.97)
Minville et al,[40] 2014	PSG (226); France	SteatoTest, Nash Test, and FibroTest	PSG	On multivariate analysis, nocturnal cumulative time spent at <90% of oxygen saturation was associated with hepatic steatosis but not with NASH.
Sundaram et al,[41] 2014	Obese children aged 10–18 y (25); USA	Liver biopsy or LFT	PSG	Severity of hypoxemia and OSA were associated with transaminitis and advanced liver histology.
Nobili et al,[17] 2014	Children with NAFLD undergoing PSG (65); Italy	LFT or liver biopsy	PSG	Severity of OSA was independently associated with presence of NASH, significant fibrosis, and NAFLD activity score.
Lin et al,[42] 2015	NAFLD subjects undergoing sleep apnea assessment (85); China	Ultrasound	PSG	ODI and average O_2 saturation were independently associated with elevated ALT and AST, respectively.
Agrawal et al,[43] 2015	Subjects from liver clinic with NAFLD and chest clinic with OSA (123); India	Ultrasound, Fibroscan	PSG	OSA severity was an independent predictor of significant hepatic fibrosis in NAFLD subjects.
Corey et al,[14] 2015	Bariatric surgery (213); USA	Liver biopsy	PSG	OSA was independently associated with transaminitis, NASH, and advanced liver histology.

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Reference	Type of Study (Subject Population [n]); Country	NAFLD Assessment	OSA Diagnosis	Important Findings
Alkhouri et al,[44] 2015	Obese children evaluated for OSA (58); USA	Circulating markers of hepatic apoptosis or inflammation	PSG	Circulating markers of apoptosis and macrophage activation were significantly increased in obese children with OSA. Treatment reduced markers of macrophage activation.
Petta et al,[45] 2015	NAFLD subjects with elevated ALT, undergoing OSA assessment (126); Italy	LFT, liver biopsy	Cardiorespiratory polygraph	Prevalence of OSA was higher in subjects with F2–F4 fibrosis. Significant fibrosis was associated with nocturnal oxygen saturation (SaO_2) <95%.
Cakmak et al,[46] 2015	NAFLD subject undergoing OSA assessment (137); Turkey	Ultrasound	PSG	AHI and ODI were significantly higher in subjects with moderate and severe NAFLD. A strong association was noted between reduction in lowest O_2 saturation and increase in NAFLD severity.
Benotti et al,[13] 2016	Bariatric surgery (362); USA	Liver biopsy	PSG	Severity of OSA was associated with NAFLD liver histology.
Qi et al,[47] 2016	Nonobese subjects undergoing PSG and abdominal ultrasound (175); China	Ultrasound	PSG	In nonobese subjects, lowest oxygen saturation was independently associated with NAFLD.
Trzepizur et al,[19] 2016	Multisite cross-sectional study (1285); France	Hepatic steatosis index, LFT, FibroMeter	PSG or home sleep test	Risk of hepatic steatosis increased with severity of OSA and sleep-related hypoxemia.
Asfari et al,[48] 2017	Cross-sectional study using NIS database (OSA subjects = 1490150, non-OSA = 29,222 374); USA	ICD-9-CM	ICD-9-CM	OSA subjects were 3 times more likely to have NASH compared with subjects without OSA.
Ding et al,[49] 2018	Subjects with suspected apnea undergoing OSA and NAFLD assessment (415); China	LFT and ultrasound	PSG	Percentage of total sleep time spent with oxygen saturation of <90%, lowest oxygen saturation, and insulin resistance were associated with NAFLD.

Abbreviations: ICD-9-CM, international classification of diseases, ninth revision, clinical modification; LFT, liver function test; NHANES, National Health And Nutrition Examination Survey; NIS, national inpatient sample; ODI, oxygen desaturation index; PSG, polysomnography.

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Table 2

Studies showing beneficial impact of continuous positive airway pressure in subjects with obstructive sleep apnea and nonalcoholic fatty liver disease

Reference	Study Design	Study Population; Country	Duration of CPAP Therapy	Findings
Impact on liver enzymes				
Chin et al,[87] 2003	Prospective cohort study	40 men; Japan	6 mo	CPAP therapy had beneficial effects on serum aminotransferase abnormalities in obese OSA subjects.
Shpirer et al,[88] 2010	Prospective cohort study	11 subjects; Israel	3 y	Significant reduction in liver enzyme levels and improvement in the mean liver attenuation index in CPAP subjects (n = 6) compared with control group (n = 5).
Hobzova et al,[89] 2015	Prospective cohort study	179 subjects; Czech Republic	13 mo	Significant positive effect on liver enzymes in subjects with moderate to severe OSA.
Kim et al,[90] 2018[a]	Retrospective cohort study	351 subjects; California	6 mo	CPAP treatment was associated with significant biochemical improvement in liver enzymes.
Chen et al,[93,101] 2018	Prospective cohort study	160 subjects; China	3 mo	CPAP therapy was significantly associated with improvement of ALT and AST levels.
Sundaram et al,[100] 2018	Prospective cohort study	9 subjects; USA	3 mo	CPAP treatment reduces alanine aminotransferase, metabolic syndrome markers, and F (2)-isoprostanes.
Chen et al,[93,101] 2018	Meta-analysis	5 studies	—	CPAP was associated with a statistically significant decrease in the liver enzyme levels in OSA subjects.
Impact on liver steatosis				
Yoshiro et al,[94] 2014	Retrospective cohort study	61 male subjects; Japan	31 mo	In male OSA subjects with abdominal obesity, significant decrease in liver fat content was observed after long-term CPAP therapy, only when fatty liver was present at baseline.
Buttacavoli et al,[95] 2016	Observational study	15 subjects (3 at 6 mo and 15 at 12 mo follow-up)	6 and/or 12 mo	Long-term CPAP treatment may improve liver steatosis.
Impact on fibrosis				
Mesarwi et al,[80] 2015	Prospective cohort study	35 subjects; Brazil	3 mo	A reduction in serum LOX (an enzyme that cross-links collagen and can serve as a biomarker of hepatic fibrosis) was seen in OSA subjects on CPAP.
Hang et al,[99] 2017	Retrospective cohort study	Propensity-matched 5214 subjects; Taiwan	2–10 y	CPAP plays an important role in the delay of the progression of liver disease in OSA subjects and decreases the incidence of liver disease among these groups of subjects.
Kim et al,[90] 2018[a]	Retrospective cohort study	351 subjects; California	6 mo	CPAP treatment was associated with reduction in NAFLD-related fibrosis.

[a]Represents same study with findings in 2 different headings.

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Table 3

Studies showing no significant impact of continuous positive airway pressure in subjects with obstructive sleep apnea and nonalcoholic fatty liver disease

Reference	Study Design	Study Population; Country	Duration of CPAP	Findings
Impact on liver enzymes				
Kohler et al,[91] 2009	Randomized controlled trial	94 subjects; United Kingdom	1 mo	CPAP therapy did not improve biochemical markers of potential NAFLD in OSA subjects.
Sivam et al,[92] 2012[a]	Randomized controlled trial	27 subjects; Australia	2 mo	No significant differences were observed in liver enzymes except ALP.
Impact on liver steatosis				
Sivam et al,[92] 2012[a]	Randomized controlled trial	27 subjects; Australia	2 mo	CPAP treatment did not change the adipose tissue distribution in the liver.
Hoyos et al,[96] 2012	Randomized controlled trial	65 men; Australia	12 wk	No significant reduction in liver adiposity was observed with CPAP therapy.
Kritikou et al,[97] 2013	Randomized controlled trial	42 subjects; USA	2 mo	Short-term CPAP treatment did not affect intrahepatic adiposity.
Impact on fibrosis				
Jullian-Desayes et al,[98] 2016	Randomized controlled trial	103 subjects; France	6–12 wk	CPAP therapy did not demonstrate any significant impact on reduction of steatosis, NASH and liver fibrosis.
Labarca et al,[102] 2018	Meta-analysis	5 randomized controlled trials	—	CPAP treatment did not significantly contribute to the improvement in liver histology, liver steatosis, liver fibrosis, and aminotransferase levels.

[a]Represents same study with findings in 2 different headings.