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Obstructive Sleep Apnea, Hypoxia, and Nonalcoholic Fatty Liver Disease

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Abstract

Recent studies have demonstrated that obstructive sleep apnea (OSA) is associated with the development and evolution of nonalcoholic fatty liver disease (NAFLD), independent of obesity or other shared risk factors. Like OSA, NAFLD is a prevalent disorder associated with major adverse health outcomes: Patients with NAFLD may develop cirrhosis, liver failure, and hepatocellular carcinoma. One major finding that has emerged from these studies is that the OSA–NAFLD association is related to the degree of nocturnal hypoxemia in OSA. Animal models have therefore largely focused on intermittent hypoxia, a key manifestation of OSA, to shed light on the mechanisms by which OSA may give rise to the complex metabolic disturbances that are seen in NAFLD. Intermittent hypoxia leads to tissue hypoxia and can result in oxidative stress, mitochondrial dysfunction,

inflammation, and overactivation of the sympathetic nervous system, among many other maladaptive effects. In such models, intermittent hypoxia has been shown to cause insulin resistance, dysfunction of key steps in hepatic lipid metabolism, atherosclerosis, and hepatic steatosis and fibrosis, each of which is pertinent to the development and/or progression of NAFLD. However, many intriguing questions remain unanswered: Principally, how aggressively should the clinician screen for NAFLD in patients with OSA, and vice versa? In this review, we attempt to apply the best evidence from animal and human studies to highlight the relationship between these two disorders and to advocate for further trials aimed at defining these relationships more precisely.

Keywords: metabolic syndrome; sleep disordered breathing; insulin resistance; dyslipidemia; intermittent hypoxia

Obstructive sleep apnea (OSA) is a highly prevalent disorder that has been associated with multiple adverse health outcomes; among these are a variety of metabolic disorders or illnesses under the umbrella term of “metabolic syndrome,” such as hypertension, glucose dysregulation and insulin resistance, atherosclerosis, and alterations in lipid metabolism (1). It may therefore be unsurprising that OSA also is associated with nonalcoholic fatty liver disease (NAFLD) (2).

NAFLD is common in the general population, affecting up to 75% of obese individuals and 1 in 4 people worldwide (3, 4). It can be broadly subdivided into two categories: 1) nonalcoholic fatty liver (NAFL), which is characterized by

hepatic steatosis without important inflammation, ballooning, or fibrosis, and which is believed to be the nonprogressive form of NAFLD, and 2) nonalcoholic steatohepatitis (NASH), which is typically characterized by hepatic steatosis, lobular inflammation, and ballooning with or without perisinusoidal fibrosis and which is believed to be the progressive form of NAFLD. Some patients with NASH subsequently develop cirrhosis, hepatocellular carcinoma, need for liver transplant, or liver-related death; indeed, NASH is the fastest growing cause of cirrhosis and hepatocellular carcinoma (5). The pathogenesis of NAFLD and the means by which some patients will

progress to NASH are not completely understood, but many suggest a “multihit” model whereby some with hepatic steatosis are subsequently exposed to a variety of insults that may trigger the development of NASH (6). There are currently no U.S. Food and Drug Administration–approved agents to treat NAFLD, although several promising drugs may be on the horizon. Weight reduction is universally recommended, however, because successful and sustained weight loss may improve not only hepatic steatosis but also liver fibrosis and liver inflammation (7).

Starting in the mid-2000s, a series of reports was published that associated OSA severity with the development and

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progression of NAFLD. Since then, this association has been fairly well established with more than 20 studies in a variety of patient populations, both pediatric and adult. In this review, we describe the putative relationship between OSA and metabolic dysfunction in NAFLD, and we delineate both clinical and animal studies that have provided insight into this link. We end with a series of unanswered questions in the field, for which we advocate further investigation.

Sleep-disordered Breathing and Hypoxia

Animal Models of OSA

OSA is characterized by recurrent closure of the upper airway during sleep. In turn, these events have several physiological effects that are believed to be hallmarks of OSA and that may lead to further adverse outcomes (8, 9):

- *Intrathoracic pressure swings:* Negative intrathoracic pressure during inspiration may be greatly accentuated in the presence of apneas, because the patient attempts to inspire against a collapsed oropharynx.
- *Sleep fragmentation:* With many disordered breathing events, there is transient electroencephalographic evidence of arousals from sleep. Recurrent arousals are believed to be the major contributor to daytime sleepiness in OSA.
- *Hypercapnia:* With each disordered breathing event, there may be an elevation in PaCO₂. CO₂ monitoring in OSA is not routinely performed but can generally be accomplished via transcutaneous or end-tidal CO₂ detectors. This CO₂ elevation may be more profound in patients with underlying lung diseases such as chronic obstructive pulmonary disease or interstitial lung disease.
- *Intermittent hypoxia (IH):* The pattern of nocturnal hypoxia may vary considerably among patients with OSA. Some may have a very high apnea-hypopnea index (AHI) with relatively mild desaturations, and others could have few, prolonged events resulting in marked hypoxemia.

Few animals naturally exhibit OSA, so instead this illness historically has been

modeled by way of mechanical obstruction of the upper airway, such as by intermittent occlusion of an endotracheal tube or tracheostomy. However, a more targeted approach, affecting one of the above-described physiological effects of OSA, is useful and has provided considerable insight into the mechanisms that link OSA to a variety of adverse outcomes (10). For instance, animals exposed to IH have elevated blood pressure (11) and develop sympathetic overactivation (12), atherosclerosis (13), and glucose and lipid dysregulation (14–16). IH may be modeled with or without intermittent hypercapnia, although data are mixed with respect to the relative physiological effects of IH versus intermittent hypercapnia in the development of disease (17–20). Sleep fragmentation can be modeled by way of a mechanical apparatus to disrupt sleep (8); this model has been shown to induce insulin resistance and increased food intake (21), tumorigenesis (22), adipose tissue inflammation (23), elevated systemic cytokine concentrations (24), and endothelial dysfunction (25). The remainder of this review is focused on the link between IH and metabolic dysfunction in NAFLD.

Unique Aspects of IH

Since reliable IH systems were first developed in the early 1990s, multiple studies have demonstrated clear differences in the physiological impact of IH versus sustained hypoxia (SH) (26–28). Chronic IH and SH have very different effects on the hypoxic ventilatory response (ventilatory sensitivity to acute hypoxia), depending on the paradigm of IH that is used (29, 30). Also relevant to the pathogenesis of OSA, IH appears to have a more profound effect than SH on weakening upper airway dilator muscle responsiveness (31). Chronic IH and SH result in dissimilar gene expression profiles in rat lungs (32), and IH but not SH appears to induce hypertension in a variety of rodent models, perhaps via sympathetic activation (33). IH and SH produce differences in cardiovascular function (34) and in various metabolic markers, including body weight, insulin resistance, and changes in the relative content of white versus brown adipose tissue (35). In rodent models, IH and SH also cause epigenetic differences (28). Although these data are still nascent, epigenetic changes may account for a major portion

of the phenotypic differences between IH and SH. Thus, IH as encountered in OSA is a unique phenomenon that is associated with distinct, often maladaptive, outcomes.

Downstream Effects of IH in OSA

OSA causes IH by recurrent collapse of the upper airway during sleep, as measured by peripheral oxyhemoglobin saturation. It may seem intuitive that arterial desaturation would result in intermittent tissue hypoxia as well. However, no study has examined the tissue-specific effects of recurrent airway closure in humans. A few studies have shown that liver enzymes may be acutely elevated in OSA and are lowered with continuous positive airway pressure (CPAP) (36), and at least one study has shown that serum creatine phosphokinase similarly may be elevated in OSA and reduced by CPAP (37). One explanation of these findings is that OSA might induce mild tissue ischemia resulting from recurrent hypoxemia, but in any case, these studies only provide inferential data about the tissue-specific effects of OSA. Because of the relative lack of insight human studies provide in this context, we must look at experimental data in animal models for clues about the tissue-specific hypoxic effects of OSA. Reinke and colleagues looked at tissue effects of IH and SH in a murine model, exposing animals to one of four profiles: SH (10% F_IO₂), “mild” IH (12 cycles/h), “severe” IH (60 cycles/h), and room air (38). Experiments were performed in both lean and obese mice, and tissue oxygen tension was measured in anesthetized mice under each condition by use of an oxygen microelectrode. The oxygen tension in each exposure type was reduced in obese versus lean mice, and superimposed IH caused a cyclic reduction in oxygen tension in liver, fat, and muscle tissue. This finding suggests that the IH of OSA likely causes recurrent hypoxia and reoxygenation not just in the circulation but at the tissue level as well.

As might be expected, these cycles of recurrent hypoxia and reoxygenation, both in experimental IH and in OSA, are associated with further molecular and cellular disruption. Reactive oxygen species, molecules containing one or more unpaired electrons, are highly unstable and may interfere with normal cell signaling and function, leading to oxidative stress. Oxidative stress may manifest as genetic

mutations, alterations in protein function, or disruption of the cell membrane. Oxidative stress normally is countered by endogenous antioxidant systems. Several studies have demonstrated that patients with OSA have elevated markers of oxidative stress in various tissues (39, 40). Likewise, in experimental models, IH in rodents has been linked to oxidative stress in the brain, heart, and pancreas (41–43). Whether oxidative stress leads to further injury in OSA is unclear, however, because there are only scant data supporting the use of antioxidants in OSA (44, 45).

OSA and experimental IH both have been shown to increase output of the sympathetic nervous system (46–48). Muscle sympathetic nerve activity and catecholamine concentrations are both increased in OSA and are reduced to near-normal levels again with CPAP use. In fact, sympathetic nerve activity is increased in OSA not just during sleep but during wakefulness as well (49). Rodent studies have shown that IH increases carotid body chemoreflex, driving an excess of sympathetic tone (50, 51), and that IH also increases catecholamine release by the adrenal medulla (52, 53). These findings have important repercussions for a variety of metabolic conditions, including hypertension, NAFLD, and insulin resistance.

Mechanisms of Hypoxia-induced Metabolic Dysfunction in OSA

OSA, Hypoxia, and Obesity

Obesity is a clear precipitating factor in the development of NAFLD, and the development of OSA is undoubtedly related to obesity. Around 70% of patients with OSA are obese (54), although this statistic may represent somewhat of a referral bias because clinicians may not consider the diagnosis routinely in lean individuals. Weight reduction in obese individuals with OSA is associated with an improvement in OSA severity and reduced upper airway collapsibility (55, 56). Given this relationship, it is natural to wonder whether OSA itself is associated with weight gain. Interestingly, OSA *treatment* appears to be associated with a slight increase in body weight, refuting this paradigm (57), although one study has shown that CPAP may reduce visceral body fat even if overall weight is unchanged (58). There have been no studies of long-term IH exposure in

humans. However, one study examined the impact on a variety of metabolic parameters of aerobic exercise in a hypoxic environment versus normoxia and found that hypoxia did not impact weight, blood pressure, fasting glucose, or hemoglobin A1c (59). It is well characterized that individuals at altitude (hypobaric hypoxia) lose weight (60); however, altitude is a model of chronic SH. By contrast, experimental chronic IH in rodent models that mimic severe OSA causes less weight gain, and perhaps weight loss, relative to control conditions. This observation is made in animals fed a normal chow diet or a variety of high-fat diets (61, 62).

Glucose Dysregulation in Hypoxia

OSA has been associated with insulin resistance and glucose intolerance using a variety of clinically relevant outcomes (hemoglobin A1c, fasting glucose, homeostatic model assessment of insulin resistance, glucose tolerance testing, and the hyperinsulinemic euglycemic clamp) (63). Data are mixed about whether treating OSA with CPAP improves markers of glucose dysregulation. Other expert reviews have provided insight about such studies. There are relatively few studies in humans investigating the distinct impact of IH on glucose handling. One such study by Newhouse and colleagues placed healthy volunteers in cyclic normoxia or IH (25 s of 5% $F_{I_{O_2}}$, followed by 2 min of normoxia, at a frequency of 25 events/h for 3 h). Subjects in IH had increased fasting glucose concentrations but no change in insulin sensitivity (64). These findings echo earlier findings by Louis and Punjabi, who applied a similar 8-hour protocol and found reduced insulin sensitivity and glucose effectiveness in the hypoxic arm, as measured by intravenous glucose tolerance test (65). In this study, sympathetic tone was also increased in hypoxic subjects. Experimental data in rodent models have been more consistent in their outcomes. Universally, severe chronic IH is associated with an increase in fasting glucose, marked insulin resistance, and poor glucose handling (14, 66). Recent data have implicated sympathetic nervous system function in these outcomes: One study showed that IH effects of hyperglycemia, glucose intolerance, and insulin resistance could be abrogated by adrenal medullectomy or by administration of an α -adrenergic antagonist (67). Other studies

have demonstrated that IH causes pancreatic β -cell apoptosis, resulting in glucose intolerance and a reduction in insulin sensitivity (68, 69) (Figure 1).

OSA, Hypoxia, and Lipid Metabolism

Over the last 15 years, dozens of studies have attempted to determine the effect of OSA on lipid metabolism. A recent, large meta-analysis that analyzed 107 datasets encompassing over 18,000 patients showed that OSA is associated with higher triglyceride, low-density lipoprotein, and total cholesterol concentrations, as well as lower high-density lipoprotein concentrations (70), with a correlation between AHI and lower high-density lipoprotein and higher triglyceride concentrations. Accordingly, several studies have examined the effect of CPAP on lipid profiles in patients with OSA, although results have mainly been negative. The first randomized, placebo-controlled crossover trial measuring the effect of CPAP versus sham CPAP on fasting lipids showed minor differences in triglyceride and total cholesterol concentrations after 2 months of treatment (71). This study was notable for fairly rigorous methodology: Authors sampled blood for lipid profiles at seven time points during both wake and sleep and compared the area under the 24-hour concentration curve between groups as endpoints. Other studies, including a meta-analysis, have shown some modest effect of CPAP in improving lipid profiles in OSA (72). In one intriguing study, investigators examined the effect of CPAP withdrawal from CPAP-adherent subjects with severe OSA on nighttime free fatty acid, insulin, glucose, and cortisol concentrations. The authors showed that untreated OSA quickly increased nocturnal glucose and free fatty acid concentrations (73).

There are considerable data in rodent models suggesting that the hypoxic burden of OSA may be a critical factor in the development of dysfunctional lipid metabolism in OSA. Chronic IH in obese mice increases liver triglyceride content (74), upregulates pathways of hepatic liver biosynthesis (74), elevates total cholesterol and low-density lipoprotein concentrations in lean mice (16), and induces atherosclerosis (13, 75, 76) (Figure 1). The effect of IH to increase free fatty acid concentrations is reversible by pretreatment with a β -adrenergic antagonist (67), suggesting that these ill effects of hypoxia in

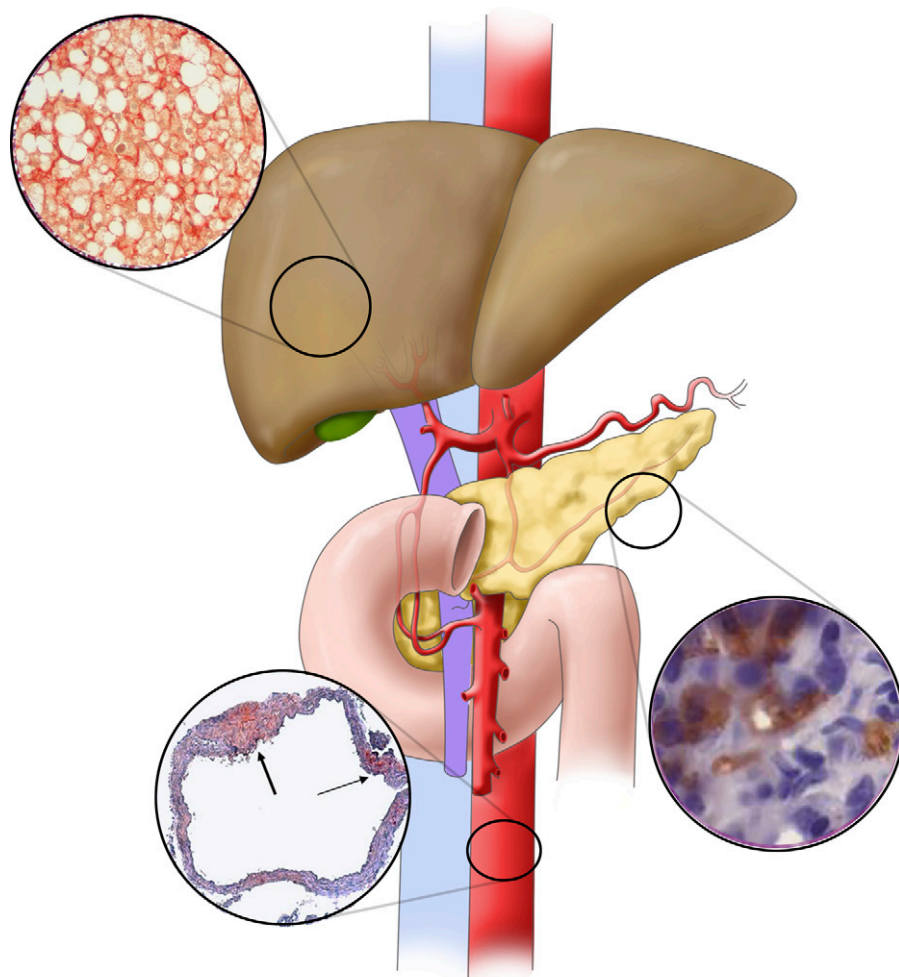


Figure 1. Mechanisms by which intermittent hypoxia in obstructive sleep apnea may result in metabolic dysfunction in nonalcoholic fatty liver disease. In rodent models, intermittent hypoxia has been linked to pancreatic apoptosis (cells in inset stained for active caspase 3), resulting in insulin resistance. Intermittent hypoxia-mediated overactivation of the sympathetic nervous system is also implicated in the development of glucose dysregulation predisposing to nonalcoholic fatty liver disease. In the vasculature, intermittent hypoxia causes atherosclerosis, among many other effects on lipid metabolism. The thick arrow in the bottom inset points to atherosclerotic plaque with a necrotic core. The thin arrow points to a fatty streak. Intermittent hypoxia has been shown to directly cause hepatic steatosis and fibrosis, possibly owing to oxidative stress and mitochondrial dysfunction. Insets are adapted with permission from References 13 and 68, as well as our unpublished data.

OSA might be mitigated by pharmacologic targeting. This concept has not yet been tested in humans, however. To our knowledge, there is only one study of the isolated effect of IH on lipid concentrations in humans. Healthy subjects were exposed to normoxia or IH for 6 hours, with hypoxic gas flow sufficient to target nadir peripheral oxyhemoglobin saturations of 85%, 17 times per hour. Consistent with data obtained from subjects with OSA, free fatty acid concentrations were elevated in those exposed to IH (77). These data

collectively suggest that hypoxia is likely a driver of alterations in lipid metabolism in OSA.

OSA, Hypoxia, and Hepatic Steatosis

With all the preceding data, it may come as no surprise that OSA has been independently associated with the development of NAFLD and with its progression to NASH and liver fibrosis. NAFLD is considered a hepatic manifestation of the metabolic syndrome. Therefore, glucose and lipid dysregulation are critical antecedent events in NAFLD development (78). There are now over 20

studies associating OSA with NAFLD in adult subjects (Table 1). Many early studies examined bariatric surgery cohorts because liver biopsy is widely performed at the time of surgery and because most such patients have at least NAFL. However, more recent studies have documented the link between OSA and NAFLD in those of normal weight, and even in children, and studies in obese individuals have generally been careful to examine the independent effect of OSA on NAFLD. Comparatively few studies have sought to determine the effect of CPAP on NAFLD progression, and this line of inquiry is inherently challenging for a few reasons: 1) Most patients with NAFLD do not have elevated liver aminotransferases, and diagnosis of NAFLD in the absence of liver biopsy is a rapidly evolving field, often requiring technical expertise; 2) the time scale of NAFLD progression and regression may require lengthy CPAP trials, which are difficult and costly; and 3) patients with the highest pretest probability for OSA and NAFLD are those who are morbidly obese, but this group may not represent the diversity of these illnesses.

The link between hypoxia and steatosis in NAFLD has been examined in several studies. Drager and colleagues (79) determined that chronic IH in obese mice causes elevations in hepatic triglyceride content and histological evidence of hepatic steatosis (Figure 1). In humans, many associative studies have examined the effect of OSA on hepatic steatosis, with results seemingly supportive of the role of OSA in modulating this early NAFLD phenotype. In fact, several markers of OSA severity have been linked to liver fat content, including AHI (80–82), time with oxyhemoglobin saturation less than 90% (83), oxyhemoglobin desaturation index (84), and mean (81) and nadir (85) nocturnal oxyhemoglobin saturation. Although some earlier studies were not adjusted for common covariates such as obesity (80), careful multivariate analysis has been performed in larger recent studies.

By contrast, results of studies investigating the impact of CPAP on hepatic steatosis have been largely negative. In a crossover study design of 2 months of CPAP versus sham CPAP in 27 subjects with moderate to severe OSA, Sivam and colleagues showed no change in intrahepatic lipid content, based on magnetic resonance imaging/spectroscopy (86). Similarly negative results were observed in other

Table 1. Studies of Obstructive Sleep Apnea and Nonalcoholic Fatty Liver Disease in Adult Human Subjects, Including Interventional Trials

Study	Subjects (n), Background	NAFLD Diagnosis	NAFLD Prevalence	OSA Diagnosis	Key Findings
Tanné <i>et al.</i> , 2005 (80)	163 subjects with suspected OSA, mean BMI <30 kg/m ²	LFTs, biopsy in a small subset	Elevated LFTs in 20%, 13 of 18 subjects with biopsy showed steatosis	PSG	Severe OSA independently associated with elevated LFTs, insulin resistance, liver necrosis, and fibrosis
Jouët <i>et al.</i> , 2007 (101)	62 morbidly obese bariatric surgery patients, mean BMI 47.8 kg/m ²	LFTs, biopsy	LFTs increased in 47%, NASH in 34%	Polygraphy	OSA an independent risk factor for elevated LFTs but not for NASH
Kallwitz <i>et al.</i> , 2007 (102)	85 subjects undergoing bariatric surgery, mean BMI 55.0 kg/m ²	LFTs, biopsy	99% with NAFLD, 19% with fibrosis	PSG	Subjects with OSA more likely to have elevated ALT. Trend toward increase in OSA prevalence in those with inflammatory injury and fibrosis
Campos <i>et al.</i> , 2008 (103)	200 subjects undergoing bariatric surgery, mean BMI 48.0 kg/m ²	LFTs, biopsy	32% with NASH	PSG	Previously diagnosed OSA associated with a fourfold increased risk for the presence of NASH
Mishra <i>et al.</i> , 2008 (91)	101 subjects undergoing bariatric surgery with biopsy-proven NAFLD, BMI 52.6 kg/m ² (NASH), 47.3 kg/m ² (no NASH)	Biopsy	78% with NASH	PSG	Subjects with NASH had lower nadir and mean O ₂ saturations, higher AHI, and higher ALT/AST ratio. Nadir O ₂ saturation was an independent predictor of NASH. Nadir and mean O ₂ saturations were lower in those with fibrosis
Polotsky <i>et al.</i> , 2009 (92)	90 subjects with severe obesity, mean BMI 49.0 kg/m ²	LFTs, biopsy in a subset	70% of those with biopsy	PSG	Desaturations in >4.6% and respiratory disturbance index >15 independently associated with lobular inflammation, balloon degeneration, and fibrosis
Kohler <i>et al.</i> , 2009 (104)	94 subjects with moderate to severe OSA, mean BMI 35.0 kg/m ²	LFTs	N/A (only LFTs used as outcome measure)	Nocturnal oximetry	Both therapeutic CPAP and subtherapeutic CPAP (1 mo) reduced LFTs, but there was no between-group difference
Daltro <i>et al.</i> , 2010 (105)	40 subjects undergoing bariatric surgery, mean BMI 41.6 kg/m ²	LFTs, biopsy	NAFLD in 83%, NASH in 80%	PSG	Moderate to severe OSA associated with insulin resistance, but no relationship between AHI and NASH, or T84 and NASH
Ulitsky <i>et al.</i> , 2010 (106)	253 subjects undergoing bariatric surgery, mean BMI 48.2 kg/m ²	LFTs, biopsy	46% with steatosis, 21% with NASH	Prior diagnosis or sleep study in chart	Trend toward OSA as an independent predictor of NASH

(Continued)

Table 1. (Continued)

Study	Subjects (n), Background	NAFLD Diagnosis	NAFLD Prevalence	OSA Diagnosis	Key Findings
Türkay <i>et al.</i> , 2012 (107)	106 subjects who underwent PSG for possible OSA, BMI 29.2 kg/m ² (no NAFLD), 33.1 kg/m ² (NAFLD)	Ultrasound, no biopsy	67%	PSG	AHI, ODI, nadir O ₂ saturation, T90 all independent predictors of NAFLD. Duration of hypoxic events was most significant predictor of NAFLD severity.
Aron-Wisniewsky <i>et al.</i> , 2012 (93)	101 subjects undergoing bariatric surgery, 91% women, mean BMI 46.9 kg/m ²	LFTs, biopsy	8% with NASH	Nocturnal oximetry	No difference in LFTs between tertiles of ODI. Lobular inflammation, balloon degeneration, NAFLD activity score, and fibrosis were all more severe in those with highest ODI tertile. Hypoxic burden was independently predictive of liver fibrosis and NAFLD activity score.
Sivam <i>et al.</i> , 2012 (86)	27 subjects with AHI ≥25, ODI ≥20, naive to CPAP, mean BMI 31.3 kg/m ²	LFTs, abdominal MRI	Undefined	PSG	No difference in intrahepatic lipid content or in any LFTs except alkaline phosphatase with CPAP vs. sham CPAP (2 mo).
Corey <i>et al.</i> , 2013 (108)	159 subjects undergoing bariatric surgery, BMI 47.5 kg/m ² (NAFLD), 45.7 kg/m ² (no NAFLD)	ALT, biopsy	69% with NAFLD	Prior diagnosis of OSA	Absence of OSA was strongly associated with normal liver histology (OR, 5.6).
Minville <i>et al.</i> , 2014 (83)	226 referred to sleep clinic for possible OSA, mean BMI 34.5 kg/m ²	Biomarker panels (SteatoTest, NashTest, FibroTest [BioPredictive]), no biopsy	62%	PSG	T90 independent risk factor for hepatic steatosis in multivariate analysis, and possible NASH in univariate analysis. Severity of hypoxia associated with worsened liver injury only in obese subjects.
Pulixi <i>et al.</i> , 2014 (109)	159 subjects with histologic NAFLD, 80 age-, sex-, and BMI-matched control subjects, BMI <30 kg/m ²	Biopsy	67% (predefined)	Berlin questionnaire, Epworth Sleepiness Scale score	In sleepy subjects with risk for OSA, increased prevalence of NASH and significant fibrosis.
Lin <i>et al.</i> , 2015 (110)	85 subjects with NAFLD diagnosed by ultrasound, mean BMI 27.3 kg/m ²	Ultrasound, no biopsy	100% (only subjects with NAFLD enrolled)	PSG	ODI predicted elevated ALT; average O ₂ saturation predicted elevated AST. OSA severity associated with increase in LFTs, cholesterol, fasting glucose.

(Continued)

Table 1. (Continued)

Study	Subjects (n), Background	NAFLD Diagnosis	NAFLD Prevalence	OSA Diagnosis	Key Findings
Agrawal <i>et al.</i> , 2015 (111)	100 subjects with NAFLD from liver clinic (BMI, 28.3 kg/m ²), 23 OSA subjects from pulmonary clinic (BMI, 32.2 kg/m ²)	Ultrasound, FibroScan (Echosens), no biopsy	91% of subjects with OSA	PSG	Among those with OSA, AHI was an independent predictor of liver fibrosis in NAFLD
Petta <i>et al.</i> , 2015 (94)	126 subjects with elevated ALT and NAFLD, BMI 29.0 kg/m ² (no OSA), 33.5 kg/m ² (OSA)	LFTs, biopsy	100% (only subjects with NAFLD enrolled)	STOP-Bang, polygraphy in subset of 50	OSA prevalence higher in patients with F2–F4 fibrosis on biopsy. Liver fibrosis associated with T95 on polygraphy
Mesarwi <i>et al.</i> , 2015 (95)	35 subjects undergoing bariatric surgery, mean BMI 50.2 kg/m ² (liver fibrosis), 46.7 kg/m ² (no fibrosis)	Biopsy	36% with hepatic fibrosis	PSG	AHI higher in those with fibrosis, and severe OSA more prevalent among those with fibrosis
Cakmak <i>et al.</i> , 2015 (84)	137 subjects who underwent PSG for suspected OSA, mean BMI 34.4 kg/m ²	Ultrasound	83% with NAFLD	PSG	AHI and ODI higher in those with moderate to severe steatosis than in those without fatty liver. Nadir O ₂ saturation lower in those with NAFLD
Qi <i>et al.</i> , 2016 (85)	175 nonobese subjects	Ultrasound, no biopsy	61%	PSG	No differences in TG, LFTs, CRP, HOMA-IR with worsening OSA. Nadir O ₂ saturation predicted NAFLD presence
Trzepizur <i>et al.</i> , 2016 (81)	1,285 subjects without excessive alcohol intake, suspected of having OSA, mean BMI 30.7 kg/m ²	LFTs, hepatic steatosis index, FibroMeter (Echosens) NAFLD score	73% with steatosis	PSG or home sleep testing	OSA severity and mean nocturnal O ₂ saturation both associated with increased risk of hepatic steatosis. Severe OSA associated with 2.5-fold higher risk of liver fibrosis but only in univariate modeling
Buttacavoli <i>et al.</i> , 2016 (87)	15 subjects with severe OSA, mean BMI 35.4 kg/m ²	Ultrasound, FibroScan	87% with steatosis	Polygraphy	No significant change in hepatic steatosis or fibrosis after 6–12 mo of therapeutic CPAP
Jullian-Desayes <i>et al.</i> , 2016 (88)	103 subjects with moderate to severe OSA, mean BMI 28.3 kg/m ²	LFTs, FibroMax (SteatoTest, NashTest, FibroTest)	44% with moderate to severe steatosis, 44% with fibrosis	PSG	No difference in steatosis, NASH, or liver fibrosis between those who got 6–12 wk of CPAP vs. sham CPAP
Trzepizur <i>et al.</i> , 2018 (112)	124 subjects with at least one criterion for metabolic syndrome, suspected of having OSA	FibroScan	27% with significant fibrosis	PSG	Dose–response relationship between OSA severity and liver stiffness. Severe OSA was independently associated with significant fibrosis

(Continued)

Table 1. (Continued)

Study	Subjects (n), Background	NAFLD Diagnosis	NAFLD Prevalence	OSA Diagnosis	Key Findings
Chen <i>et al.</i> , 2018 (82)	160 subjects who underwent PSG for OSA symptoms, mean BMI 28.0 kg/m ²	LFTs, ultrasound, acoustic radiation force impulse ultrasound	64% with steatosis	PSG	LFTs and liver steatosis severity increased with increasing OSA severity. AST and ALT both reduced with 3 mo of CPAP therapy
Toyama <i>et al.</i> , 2018 (113)	61 male subjects with OSA on CPAP, abdominal adiposity, mean BMI <30 kg/m ²	Abdominal CT (hepatic steatosis)	41% with steatosis	PSG	AHI and T90 were greater in subjects with fatty liver than in those without. Liver fat content did not change after a mean 31 mo of therapy, but among those with fatty liver at baseline, CPAP reduced liver fat content

Definition of abbreviations: AHI = apnea-hypopnea index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CPAP = continuous positive airway pressure; CRP = C-reactive protein; CT = computed tomography; HOMA-IR = homeostatic model assessment of insulin resistance; LFT = liver function test (aminotransferase level unless otherwise indicated); MRI = magnetic resonance imaging; N/A = not applicable; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; ODI = oxygen desaturation index; OR = odds ratio; OSA = obstructive sleep apnea; PSG = polysomnogram; STOP-Bang = snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference, and male sex questionnaire; TG = triglycerides; Tx = percentage of total sleep time with oxyhemoglobin saturation less than x%.

cohorts (87, 88). Though discouraging, these studies to date have been limited either by small cohorts studied or by limited time on CPAP. Large-scale studies of the impact of CPAP on a variety of markers of lipid metabolism, including hepatic steatosis, are forthcoming.

OSA, Hypoxia, and Hepatic Inflammation and Fibrosis in NAFLD

Although glucose and lipid dysregulation and hepatic steatosis are critical features of early NAFLD, well-designed studies have now convincingly demonstrated that liver fibrosis is the only pathologic feature of NAFLD that is associated with death or need for liver transplant (89, 90). As such, the most critical questions in evaluating the disease-modifying potential of OSA in NAFLD are whether OSA is associated with more severe liver fibrosis in NAFLD and whether CPAP may mitigate the progression of fibrosis. The majority of studies to date that have looked at markers of liver fibrosis as an outcome have shown that OSA is associated with increased fibrosis (Table 1), and a few studies have linked the hypoxic burden of OSA to worsened fibrosis as well (91–93). Some of these studies have used inflammatory markers (cytokine or aminotransferase concentrations) as outcomes, and several biopsy-based studies have found associations

between OSA and histologic NASH. However, these studies are not definitive, and one negative study merits particular attention, given its sample size: Trzepizur and colleagues examined a cohort of nearly 1,300 subjects with suspected OSA. Those with severe OSA were found to have a 2.5-fold higher risk for liver fibrosis, but this association did not hold after multivariate adjustment (81). A few studies have examined the prevalence of OSA in patients with NAFLD and liver fibrosis (94, 95), but these studies are lacking either in sample size or in definitive OSA diagnosis. In general, results of CPAP trials that have examined liver fibrosis as an outcome in subjects with OSA and NAFLD have been negative (87, 88), but studies of surrogates of NASH progression such as aminotransferase concentrations have appeared more promising.

Interestingly, despite mixed results in humans, the available data do suggest that rodents exposed to IH develop liver fibrosis, oxidative damage, and hepatic inflammatory injury, and when exposed to IH plus another hepatic insult (e.g., acetaminophen), they may also exhibit marked hepatocellular inflammation and necrosis (96–98). Modeling hypoxia in OSA and NAFLD is problematic, however, because IH generally causes weight

reduction in mice with diet-induced obesity. Moon and colleagues have described a possible link between hypoxia-inducible factor 1 and liver fibrosis (99), and our group has shown that deletion of hypoxia-inducible factor 1 α in hepatocytes reduces hepatic expression of lipogenic genes and protects against the development of liver fibrosis in a mouse model of NAFLD (100). It therefore seems biologically plausible that the IH of OSA may accentuate liver injury in NAFLD, leading to a shift in the phenotype toward NASH and liver fibrosis. Additional studies are clearly needed to elucidate further the nature of this relationship.

Future Directions

Open Questions for Clinical Research

As clinicians, our primary task is to determine ways to diagnose and treat illness, and this goal can occasionally be lost in the jungle of available trial and bench research data. Practical questions remain for the clinician:

1. Should patients with NAFLD routinely be screened for OSA, and vice versa? To answer this question, we need an accurate estimate of the prevalence of NAFL, NASH, and advanced fibrosis in

patients with OSA, as well as of the prevalence of OSA in patients with NAFLD. Prospective studies are needed to fill this gap and to assess the impact of early interventions.

2. There are few hard indications to treat patients with mild OSA in the absence of sleep-related symptoms, so if a patient has NAFLD and mild OSA, should this nudge the clinician toward recommending CPAP?
3. There are no currently available U.S. Food and Drug Administration–approved drugs for NAFLD. Weight loss and dietary discretion are mainstays of therapy. If a patient with NAFLD is found to have OSA, should this prompt more aggressive treatment of NAFLD (e.g., early referral for bariatric surgery)?
4. Why have results of CPAP trials in subjects with OSA and NAFLD been largely negative? How can we design better trials to evaluate response to OSA treatment? Should OSA treatment aside from CPAP be considered? What outcomes would be most appropriate in trial design? How can we identify high-risk patients to enroll in clinical trials?

It is our view that patients with NAFLD, particularly those who are obese and even those without specific sleep-related symptoms, should be screened for OSA, because a large percentage of those with OSA are relatively asymptomatic. However, at this time, we do not recommend that those with mild OSA be treated in the absence of other sleep-related symptoms or major comorbidities. We advocate aggressive attempts at weight reduction in patients with NAFLD as with any other manifestation of metabolic syndrome.

Trial design will likely require considerable multicenter efforts to recruit sufficient subjects to demonstrate the effect of OSA therapy on NAFLD progression, and in light of poor CPAP adherence inherent to most clinical trials in OSA, we advocate that trials be more reflective of clinical practice and that alternative therapies, such as an oral appliance, might be considered in CPAP-nonadherent subjects.

Open Questions for Laboratory-based Research

Research in animal models has the potential to elucidate mechanisms that might tie together OSA and NAFLD, and considerable progress is being made. Ongoing issues for bench researchers include the following:

1. In light of the often disparate results afforded by laboratory research and clinical trials, is IH an acceptable model of OSA? In focusing on IH, are we neglecting other aspects of OSA that might themselves worsen NAFLD progression, such as sympathetic overactivation, mitochondrial dysfunction, and the balance of the microbiome?
2. Several studies have now demonstrated that low-intensity IH (low frequency or higher-nadir oxygen saturation as measured by pulse oximetry target) may actually be beneficial in a variety of outcomes. Might this be the case in NAFLD? Similarly, if hypoxic burden is clinically relevant for NAFLD progression, what feature of IH is most critical (e.g., nadir saturation, time with saturation <85% or <90%,

oxyhemoglobin desaturation index, slope of the desaturation)?

3. What model of NAFLD should be used? Several models recapitulate the histologic and genomic effects of human NAFLD, but are there advantages of diet-based approaches over other models?

Conclusions

NAFLD and OSA are exceedingly common in the general population, and OSA is associated with the development of key injurious stimuli that give rise to NAFLD as well as the progression of NAFLD to NASH and liver fibrosis. This association may be due to the hypoxic burden of OSA, although OSA is an enormously heterogeneous disease state that results in a variety of physiological changes aside from IH. There is experimental evidence linking IH with a variety of key features of NAFLD, including glucose and lipid dysregulation, and hepatic inflammation, oxidative stress, and fibrosis. Further studies are needed to investigate this relationship, and several key questions remain for the clinician and trialist alike. High-quality evidence is required to provide data on screening for OSA in NAFLD and vice versa so that an optimal approach to the management of OSA and NAFLD can be realized. ■

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