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Authors

Corey, Kathleen E
Misdraji, Joseph
Gelrud, Lou
et al.

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ORIGINAL ARTICLE

Obstructive Sleep Apnea Is Associated with Nonalcoholic Steatohepatitis and Advanced Liver Histology

Kathleen E. Corey[1,6] · Joseph Misdraji[2,6] · Lou Gelrud[3] · Lindsay Y. King[1] · Hui Zheng[4,6] · Atul Malhotra[5] · Raymond T. Chung[1,6]

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Abstract
Background and Aims Nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA) are growing in prevalence in the USA. Existing data on the relationship between OSA and NAFLD are conflicting and limited by the use of various histologic definitions of nonalcoholic steatohepatitis (NASH). Using a robust definition of NASH in a large, well-characterized cohort, we sought to evaluate whether OSA was associated with NASH and advanced fibrosis.
Methods Two hundred and thirteen subjects undergoing weight loss surgery were queried for OSA and then underwent liver biopsy. NASH was defined, as recommended by the American Association for the Study of Liver Disease, by the presence of all of the following: >5 % macrovesicular steatosis, lobular inflammation, and hepatocyte ballooning. NAFLD activity score (NAS) was also determined for each subject.
Results Subjects with OSA had significantly higher alanine and aspartate aminotransferase levels than subjects without OSA (ALT 54.1 vs. 37.7 U/L, $P = 0.0007$; AST 31.7 vs. 20.5 U/L, $P = 0.0007$). OSA was associated with the presence of NASH, and this remained significant after adjusting for age, gender, race, and diabetes mellitus ($P = 0.03$ OR 2.01; 95 %, 1.05–3.87). Steatosis grade, lobular inflammation grade, NAS score, and fibrosis stage were all significantly associated with the presence of OSA and remained so after adjustment.
Conclusions OSA is associated with elevated aminotransferase levels, the presence of NASH, and advanced NASH histology. Further studies are needed to evaluate the impact of OSA treatment on NASH.

Keywords Obstructive sleep apnea · Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Fibrosis

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
OSA	Obstructive sleep apnea
NASH	Nonalcoholic steatohepatitis
NAS	NAFLD activity score
WLS	Weight loss surgery
BMI	Body Mass Index
AASLD	American Association for the Study of Liver Disease

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the USA and is growing in prevalence worldwide. Nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD, can lead to

✉ Kathleen E. Corey
kcorey@partners.org

1 Gastrointestinal Unit, Massachusetts General Hospital, Warren 1007, 55 Fruit Street, Boston, MA 02114, USA

2 Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

3 Department of Internal Medicine, Bon Secours Richmond Health System, Richmond, VA, USA

4 MGH Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA

5 Department of Pulmonary and Critical Care Medicine, University of California San Diego, San Diego, CA, USA

6 Harvard Medical School, Boston, MA, USA

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cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. By 2020, NASH cirrhosis is predicted to be the leading indication for liver transplantation in the USA [1]. Unfortunately, current therapies for NASH are limited to weight reduction and, in select patients, vitamin E. However, these therapies have significant limitations. Weight loss and weight maintenance are difficult to achieve, and only a proportion of individuals (41 %) have a histologic response to vitamin E [2]. Therefore, there is a pressing need to better understand the pathogenesis of NAFLD and NASH and to develop novel treatments for NASH.

Like NAFLD, obstructive sleep apnea (OSA) is a growing problem worldwide [3]. OSA is associated with the development of hypertension and the metabolic syndrome [4–6]. Further treatment of OSA has been associated with improvements in cardiometabolic risk markers [7, 8]. Emerging data suggest that an important association may exist between OSA and NAFLD. Animal models have demonstrated that lean mice exposed to chronic intermittent hypoxia (CIH) develop hepatocyte ballooning and hepatocellular glycogen accumulation and lipid peroxidation [9]. Induction of CIH in mice on a high-fat, high-cholesterol diet produces more pronounced liver injury with increased zone 3 steatosis, lobular inflammation, and collagen deposition consistent with NASH [10]. These findings suggest that OSA may play an important role in the development and progression of NASH.

A number of human studies have demonstrated an association between elevated aminotransferase levels and the presence of OSA in adults [11–13]. However, the existing literature on the relationship between OSA and histologically defined NASH is conflicting. Two studies have failed to show a relationship between OSA and NASH, while other studies have demonstrated a more robust association [14–22]. However, several of these studies have been limited by the omission of race, an important potential confounder, in their final analysis and, most importantly, by the use of varying and unconventional definitions of NASH. These studies have generally relied on the NAFLD activity score (NAS) to define NASH or use definitions of NASH that do not require the presence of hepatocyte ballooning. The present study seeks to address the limitations of prior studies by using a robust and well-accepted definition of NASH in a large, well-phenotyped cohort that includes comprehensive data on patient race [23].

Materials and Methods

This cohort study included consecutively enrolled patients who underwent weight loss surgery (WLS) in the form of Roux-en-Y gastric bypass or sleeve gastrectomy at a single center in the Bon Secours Health System between 2010 and 2012. One hundred and fifty-nine subjects had been included in a previous publication evaluating predictors of normal liver histology in individuals undergoing weight loss surgery [24]. Criteria for WLS included (1) body mass index (BMI) $\geq$35 kg/m^2 with major co-morbid disease or BMI $\geq$40 kg/m^2; (2) previous unsuccessful weight loss efforts; and (3) ability to understand the risks and benefits of WLS and postoperative lifestyle changes.

Subjects were assessed by a treating physician for weight, height, BMI, and co-morbid disease including diabetes mellitus, hypertension, obstructive sleep apnea (OSA), and dyslipidemia. Diabetes mellitus was defined by a fasting glucose $\geq$126 mg/dL, HbA1C $>$ 6.5 %, or known diagnosis of diabetes. Dyslipidemia was defined as total cholesterol $>$200 mg/dL, low-density lipoprotein $>$130 mg/dL, triglycerides $>$130 mg/dL, or high-density lipoprotein $<$40 mg/dL [25]. Hypertension was defined by a blood pressure $\geq$135/85 or ongoing treatment for hypertension. The presence of OSA was defined by patient report of a positive sleep study (polysomnography, PSG) in the past. When possible, the diagnosis of OSA was confirmed by medical record review. All diagnoses of OSA were made prior to weight loss surgery. The patients in this cohort do not undergo routine diet-induced weight loss prior to surgery.

All subjects undergoing WLS had a standard of care wedge liver biopsy at the time of surgery. Liver biopsies were reviewed by single-blinded hepatopathologist (JM) and assigned a score for grade of steatosis (grade 0 $\leq$ 5 % steatosis; 1 = 5–33 %; 2 = 33–66 %; 3 $\geq$ 66 %), hepatocyte ballooning (0 = no ballooning; 1 = few; 2 = many), and lobular inflammation per 200 $\times$ (0 = no foci; 1 $\leq$ 2 foci; 2 = 2–4 foci; 3 $\geq$ 4 foci), as described by Kleiner et al. [26]. NAFLD activity score (NAS) is a sum of the scores for steatosis grade, lobular inflammation, and hepatocyte ballooning and ranges from 0 to 8. Fibrosis stage was assigned according to the modified Brunt stage (stage 0, 1a, 1b, 1c, 2, 3, or 4) [26]. NAFLD was defined by the presence of grade 1 or greater steatosis not meeting criteria for NASH. NASH was defined as lobular inflammation $\geq$1, hepatocyte ballooning $\geq$1, and zone 3 macrovesicular steatosis grade $\geq$1 as recommended by the American Association for the Study of Liver Disease (AASLD) [27]. Advanced fibrosis was defined as stage 3 or 4 fibrosis.

All statistical analyses were performed using SAS software, version V.9.2 (SAS Institute, Cary, NC). Continuous variables were analyzed using a Student's *t* test for normally distributed variables and a Wilcoxon rank sum test for variables that were not normally distributed. Categorical variables were analyzed using a Chi-square test or Fisher's exact test as appropriate. Multivariable

regression modeling was used to assess the independent association of OSA with liver histology.

All subjects provided informed consent for this study. This study was approved by the Partners' Health Care Human Research Committee.

Results

Baseline Characteristics

Two hundred and thirteen patients were included in this study. The majority of subjects were women (82.2 %) with a mean age of 48 years and mean BMI of 46.7 kg/m^2. Thirty-one percent of subjects were black, and 65.7 % of subjects were white. NAFLD was present in 157 individuals (73.7 %), of whom 83 subjects had NASH (39.0 % of all subjects and 53 % of NAFLD patients). Eighty-two individuals (38.5 %) had fibrosis of any stage, and seven subjects (3.3 %) had advanced fibrosis (stages 3–4).

Individuals With and Without Self-Reported Obstructive Sleep Apnea

Patients with clinical OSA were significantly older than patients without OSA (51.0 vs. 43.8 years, $P < 0.0001$). In addition, subjects with OSA were more frequently men than those without OSA (29.5 vs. 5.0 %, $P < 000.1$) and more frequently of white race (75.0 vs. 55.5 %, $P < 0.0001$). Diabetes was more common in the OSA group (49.6 vs. 18.2 %, $P < 0.0001$). There was no difference in BMI, prevalence of CAD, or dyslipidemia (Table 1).

Aminotransferase Levels by OSA Status

Subjects with OSA had significantly higher aminotransferase levels than subjects without OSA. Mean ALT was 37.7 U/L in subjects without OSA and 54.1 U/L in subjects with OSA ($P = 0.0007$). Mean AST was 20.5 U/L in those without OSA and 31.7 U/L in those with OSA ($P = 0.0007$). Total bilirubin was also significantly higher in those with OSA than those without OSA (0.51 vs. 0.43 U/L, $P = 0.006$).

Liver Histology by OSA Status

OSA was associated with the presence of NASH ($P = 0.0009$, OR 2.64, 95 % CI 1.49–4.70). After adjusting for age, gender, race, and the presence of diabetes mellitus, an independent association between OSA and NASH persisted ($P = 0.03$ OR 2.01; 95 %, 1.05–3.87). The presence of OSA also positively correlated with the NAFLD activity score ($P = 0.0002$). The presence of OSA was associated with an increased odds of elevated NAFLD activity score and remained significant after adjusting for age, race, gender, and diabetes mellitus ($P = 0.01$; OR 2.1; 95 % CI 1.2–3.4).

The grade of hepatic steatosis was assessed by OSA status (Table 2). Steatosis (grade 1–3) was significantly more frequent in subjects with OSA than those without OSA (84.8 vs. 61.4 %, $P = 0.0001$). The presence of OSA was associated with steatosis in individuals on univariate analysis ($P < 0.001$; OR 3.2; 95 % CI 1.9–5.4). Even after adjusting for age, gender, race, and the presence of diabetes mellitus, an independent association between OSA and steatosis persisted ($P = 0.004$ OR 2.3; 95 % CI 1.3–4.1).

Table 1 Baseline characteristics of subjects with and without OSA

	No OSA reported ($n = 101$)	OSA reported ($n = 112$)	P value
Men [n (%)]	5 (5.0)	33 (29.5)	<0.0001
Age (years)[a]	43.8 (12.0)	51.0 (10.3)	<0.0001
Ethnicity [n (%)]			0.009
Black	43 (42.5)	24 (21.4)	
Hispanic	2 (2.0)	3 (2.7)	
White	56 (55.5)	84 (75.0)	
Other	0 (0)	1 (0.9)	
Body mass index (kg/m^2)	45.8 (6.5)	47.5 (8.1)	0.11
Coronary artery disease [n (%)]	3 (3.0)	9 (8.1)	0.14
Diabetes mellitus [n (%)]	18 (18.2)	55 (49.6)	<0.0001
Dyslipidemia [n (%)]	86 (85.1)	99 (88.4)	0.55
Low-density lipoprotein (mg/dL)	100.3 (27.4)	93.3 (33.7)	0.10
Total cholesterol (mg/dL)	171.5 (34.7)	164.9 (40.1)	0.20
Glucose (mg/dL)	115.6 (42.1)	121.7 (43.4)	0.30
Insulin (μU/mL)	29.0 (31.6)	35.8 (33.5)	0.13

[a] Continuous variables are expressed as mean (SD)

Table 2 Histology by OSA status

	No OSA reported	OSA reported	*P* value
Steatosis			
Grade 0	39 (38.6 %)	17 (15.2 %)	
Grade 1–3	62 (61.4 %)	95 (84.8 %)	0.0001
Hepatocyte ballooning			
Grade 0	49 (48.5 %)	33 (29.5 %)	
Grade 1–2	52 (51.5 %)	79 (70.5 %)	0.0043
Lobular inflammation			
Grade 0	65 (64.4 %)	43 (38.4 %)	
Grade 1–3	36 (35.6 %)	69 (61.6 %)	0.0002
Fibrosis			
Stage 0	76 (75.3 %)	53 (48.2 %)	
Stages 1–4	25 (24.7 %)	57 (51.8 %)	<0.0001
NAS			
0–2	70 (69.3 %)	46 (41.1 %)	
3–4	18 (17.8 %)	40 (35.7 %)	
5–8	13 (12.9 %)	26 (23.2 %)	0.0002

NAS NAFLD activity score

Lobular inflammation also differed by OSA status. Any lobular inflammation (grade 1–3) was found in 35.6 % ($n = 36$) of subjects without OSA and 61.6 % ($n = 69$) of patients with OSA. The presence of OSA was positively correlated with lobular inflammation ($P = 0.0002$; OR 2.90; 95 % CI 1.66–5.06). This finding remained significant after adjustment for age, race, gender, and diabetes mellitus ($P = 0.02$; OR 2.06 95 % CI 1.10–3.88).

Hepatocyte ballooning was also more commonly found in individuals with OSA. The prevalence of any hepatocyte ballooning was 51.5 % ($n = 52$) in individuals without OSA and 70.5 % ($n = 79$) in patients with OSA ($P = 0.004$). After adjustment for gender, race, and DM, a trend toward increased risk of hepatocyte ballooning was seen, but this was not statistically significant ($P = 0.07$; OR = 1.80; 95 % CI, 0.96–3.40).

Fibrosis of any stage was more frequent among patients with OSA than those without OSA. Fibrosis stages 1–4 were found in 24.7 % ($n = 25$) of individuals without OSA and 51.8 % ($n = 57$) of patients with OSA ($P < 0.0001$). The presence of OSA was significantly associated with fibrosis ($P < 0.0001$; OR 3.27; 95 % CI 1.82–5.88) and remained significant on multivariate analysis ($P = 0.04$; OR 2.01; 95 % CI 1.02–4.00). It is worth noting that advanced fibrosis (stages 3–4) was found only in subjects with OSA.

Discussion

The present study demonstrates that clinical OSA is associated with increased aminotransferase levels. In addition, OSA was found to be associated with robustly defined NASH as well as the NAFLD activity score. Further, the presence of OSA correlated with greater degrees of steatosis and lobular inflammation grade and fibrosis stage. In the present study, advanced fibrosis was found only in individuals with OSA. These observations confirm the findings of previous studies and bolster these studies by the use of a large, racially diverse cohort with clearly defined NASH by AASLD criteria. In addition, we add to the existing literature by demonstrating that not only is OSA associated with NASH but that the individual components of NASH including steatosis, inflammation, and fibrosis are increased in the presence of OSA [18].

The existing literature on the relationship between OSA and NASH is conflicting. Two studies by Jouet et al. [14] and Ulitsky et al. [15] failed to show an association between OSA and NASH. The study by Jouet was limited by small sample size, and both studies were limited by their use of nonstandard definitions of NASH. Several studies have suggested a relationship between OSA and NASH [16–22]. Each of these studies has contributed to the literature on this topic but is hampered by several limitations. Several studies fail to include information of subject race and to incorporate this information into predictive models of NASH. As NASH and OSA are both strongly impacted by race, the absence of these data fails to incorporate a potential confounding variable [16, 17, 19]. Further several studies are limited by their varying definitions of NASH. The definition of NASH has changed over time, and the current accepted histologic definition of NASH requires a minimum of the presence of each of the following: (1) >5 % macrovesicular Steatosis, (2) hepatocyte ballooning, and (3) inflammation [27]. A diagnosis of *definite* NASH

requires zone 3 macrovesicular steatosis of any degree, lobular inflammation, and hepatocyte ballooning. Previous studies largely used a NAS $\geq$ 5 to define NASH or did not require the presence of hepatocyte ballooning for the definition of NASH [14–17, 19–22]. The use of the NAS score to define NASH or the absence of the inclusion of hepatocyte ballooning may result in significant misclassification, causing patients with simple steatosis to be misclassified as NASH and is not recommended [23]. Our study addresses this limitation by using the specific definition of definite steatohepatitis as recommended by the American Association for the Study of Liver Disease while using the NAS to quantify disease activity rather than define NASH [27].

A single study by Mishra et al. [18] evaluating OSA and NASH did use the AASLD accepted definition of NASH. However, this study did not evaluate the relationship between the individual histologic characteristics of NASH (i.e., steatosis, ballooning, lobular inflammation, and fibrosis) and OSA. Our study confirms the findings of Mishra et al. and adds to these findings by evaluating, in a significantly larger cohort, the relationship between OSA and steatosis grade, lobular inflammation, hepatocyte ballooning, and fibrosis.

Two recent meta-analyses suggest a relationship between NAFLD, NASH, and OSA. Musso et al. [28] evaluated 18 studies and found that the presence of OSA was associated with the presence of NASH, fibrosis of any stage, and advanced fibrosis. This meta-analysis does demonstrate an important relationship between OSA, NASH, and fibrosis but was not able to evaluate the relationship between individual components of the NASH activity score including lobular inflammation or hepatocyte ballooning. In addition, the majority of studies included in this paper did not use the accepted definition of NASH that was used in our study. Sookoian et al. [29] performed a similar meta-analysis from 11 studies. They also confirmed that fatty liver and fibrosis were associated with the presence of OSA. This study was also unable to provide data about the relationship between steatosis grade and hepatocyte ballooning and OSA. Thus, while human studies have suggested a relationship between OSA and NAFLD, the data regarding the impact of OSA on individual components of NASH, including hepatocyte ballooning and lobular inflammation, are limited. Our study, which included a high proportion of subjects both with and without OSA and with and without NASH, was able to evaluate all histologic parameters of NASH and the relationship with OSA.

The present study has several limitations. Importantly, the diagnosis of OSA was based on patient self-report of OSA from formal PSG. While patients reported having a positive PSG indicating OSA, we did not have access to PSG reports for the majority of patients. Limited analysis on patients with only PSG data available was limited by insufficient power and lack of detail on OSA severity from PSG reports. We did not have information about why patients were referred for PSG but presume that this was the result of symptoms of possible OSA. Patients who did not report OSA may in fact have undiagnosed OSA but with less compelling symptoms and perhaps less severe disease than those referred for PSG that could account for the differences in histology. Further prospective studies are needed in patients with documented PSG results to better evaluate the relationship between OSA and the individual histologic components of NASH. Another limitation of the present study is the absence of data on continuous positive airway pressure (CPAP) adherence for those with diagnosed OSA were not available and will need to be evaluated in future studies to determine whether patients with OSA using CPAP have less severe liver injury than those with OSA not using CPAP. The population studied was also a group referred for weight loss surgery and therefore a distinct sample from the general population. Further studies are needed to assess the relationship between NASH and OSA in the non-WLS population.

At present, the management of NAFLD includes treatment of associated co-morbidities including dyslipidemia and diabetes mellitus [30]. However, routine assessment and treatment of OSA are not currently recommended. Based on its cross-sectional design, the present study cannot conclude causality in the relationship between OSA and NAFLD. However, these findings suggest an important association between NAFLD and OSA and highlight the need for prospective studies to further assess this relationship and to determine the benefit of OSA treatment on NASH histology.

In conclusion, our data indicate that OSA is associated with NASH and increased NAFLD activity score as well as a greater degree of steatosis, hepatocyte ballooning, and fibrosis in patients undergoing weight loss surgery. These findings strongly support an important role for OSA in NASH development and progression. Additional studies are warranted to further evaluate this relationship and the impact of OSA treatment on NASH histology.

Key Points

- Obstructive sleep apnea (OSA) is a growing problem worldwide.
- OSA is associated with NASH and NAFLD activity score.
- OSA is associated with increased steatosis and lobular inflammation.

- Fibrosis is more common in patients with OSA and NAFLD than in those with NAFLD alone.

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Conflict of interest The authors have no conflict to report.

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