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The Association of Nonalcoholic Steatohepatitis and Obstructive Sleep Apnea

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Abstract

Background and Aims—The association between obstructive sleep apnea (OSA) and abnormal liver enzymes has been reported in multiple studies. The existing literature regarding the relationship between OSA and nonalcoholic steatohepatitis (NASH) is conflicting. Thus we aimed to determine the relationship between OSA and NASH from a large database.

Methods—A cross-sectional study was performed using the 2012 Nationwide Inpatient Sample. We identified adult patients (18–90 year) who had a diagnosis of OSA using the International Classification of Diseases ICD-9 codes. The control group was comprised of adult individuals with no discharge records of OSA. NASH diagnosis was also identified using the ICD-9 codes. The association between OSA and NASH was calculated using univariable and multivariable logistic regression.

Results—30,712,524 hospitalizations were included. The OSA group included 1,490,150 patients versus 29,222,374 in the control non-OSA group. The OSA group average age was 61.8±0.07 years (44.2% females) compared to 57.0±0.11 years (60.1% females) in the non-OSA group. NASH prevalence was significantly higher in the OSA group compared to the non-OSA group [2% (95% CI: 1.9, 2.1) versus 0.65% (0.63, 0.66), $p<0.001$]. After adjusting for obesity, diabetes, hypertension, dyslipidemia, the metabolic syndrome and Charlson comorbidity index, OSA patients were 3 times more likely to have NASH [adjusted OR:3.1 (95% CI: 3.0 – 3.3), $p<0.001$].

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Authors Contribution:

Mohammad Maysara Asfari, MD: Study concept, data interpretation, manuscript writing and editing.

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Arthur J McCullough MD: Study concept, data interpretation, manuscript editing.

Conclusions—Patients with OSA are three times more likely to have NASH compared to patients without OSA after controlling for other confounders. These data indicate that OSA should be considered as an independent risk factor for developing NASH.

Keywords

Obstructive sleep apnea; nonalcoholic steatohepatitis; national inpatient sample

INTRODUCTION

Chronic liver disease is the twelfth leading cause of death in the United States (US) according to the national vital statistics report¹ and nonalcoholic fatty liver disease (NAFLD) is considered the most common cause of abnormal liver function tests among adult population in the US.² NAFLD includes nonalcoholic fatty liver (NAFL) which is predominantly a benign non-progressive condition caused by fat accumulation in the liver with a prevalence of approximately 30 % in the US.³ Nonalcoholic steatohepatitis (NASH) is the more serious type caused by fat accumulation associated with hepatic necro-inflammation.^{4,5} Biopsy proven NASH has prevalence as high as 22% in the US⁶ with a progression to cirrhosis in up to 15% of patients.^{7,8}

NASH is also considered the most rapidly growing indication for liver transplantation in the US with nearly fourfold increase since 2002.⁹ It is known to be associated with insulin resistance and various metabolic factors such as type 2 diabetes, dyslipidemia, and obesity.^{4,10} Emerging data are conflicting regarding the association between OSA and NASH. While some studies have reported an association between OSA and NASH in patients undergoing bariatric weight loss surgery,^{11,12} the results of other studies have been inconsistent.^{13–16} Consequently, the certainty of OSA being an independent risk factor for the development of NASH remains unclear. Summary of recent clinical trials with their findings are shown in table 1.

Giving this controversy in the literature, we aimed to use a large national database to investigate the association between OSA and NASH.

PATIENTS AND METHODS

Data Source

This cross sectional study was conducted using the 2012 National Inpatient Sample (NIS). The NIS is the largest all-payer inpatient database in the US and contains a sample of over 7 million inpatient admissions, which represent an approximately 20 percent sample of discharges from all community hospitals participating in the Healthcare Cost and Utilization Project (HCUP). It excludes rehabilitation and long-term acute care hospitals. The data includes primary and secondary diagnoses up to 25 and primary and secondary procedures up to 15. In addition, it contains the patient demographics, discharge status, length of stay, disease severity and comorbidity measures.

The principal diagnosis in these patients is defined, according to HCUPnet, as “the condition established after study to be chiefly responsible for occasioning the admission of the patient

to the hospital for care. The principal diagnosis is always the reason for admission". Hence, the diagnosis of OSA and NASH should be reliable in this study.

Study Population, Inclusion and Exclusion Criteria

Data on hospital admissions of all adult patients 18 to 90 years old was extracted from the 2012 NIS. We divided discharges into two groups. The study group was identified using the International Classification of Diseases 9th version (ICD-9) code for OSA. The rest of patients with no discharge diagnosis of OSA were considered the control group. ICD-9 codes were also used to identify all patients with a diagnosis of NASH in both the control and study groups. Comorbidities of interest were defined by querying all diagnostic and procedural fields for the corresponding ICD-9 codes. Table 2 shows all ICD-9 diagnostic codes used for patient selection.

Study Variables

The HCUP comorbidity software was used to generate Elixhauser comorbidities from ICD-9 diagnosis codes. The Deyo modification of the Charlson Comorbidity Index (CCI) was used to define severity of co-morbid conditions. CCI ranges from 0 to 17, with higher numbers representing a greater comorbidity burden. Comorbid conditions were recorded if they were listed among the diagnoses for the hospitalization. All available demographic data, patients' age, gender, race, CCI, Elixhauser's comorbidities and the other relevant comorbidities were extracted (Table 3). Of the included variables, race was the factor with most missing data (5%) as certain states do not document race in the discharge information; we included this as a separate category under said variable. In addition, gender was missing for 0.007% of subjects; these observations were dropped from the final multivariable analysis if said variables were included.

Statistical Analysis

Data are presented as mean $\pm$ standard error for continuous variables or weighted frequency (percent) for categorical factors. A univariable analysis was performed to assess differences between subjects with and without OSA; continuous variables were compared using t-tests and categorical variables were compared using Rao-Scott chi-square tests. In addition, univariable and multivariable logistic regression analysis was performed to assess the association between OSA and NASH; NASH was modeled as the outcome with OSA as the independent variable. The following variables were also included as independent predictors in the multivariable model: obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome and CCI. All analyses were performed using SAS survey procedures (version 9.4, The SAS Institute, Cary, NC), which account for the complex sampling design of NIS and appropriately weight participants in statistical models. A $p < 0.05$ was considered statistically significant.

Results

Our study nationwide cohort included 30,712,524 hospitalizations. Of these, 1,490,150 patients were identified in the OSA group (the study group) and 29,222,374 in the control non-OSA group.

Univariable Comparison

As shown in table 3, the OSA group patients were significantly older (61.8 ± 0.07 years) and were more likely to be male (55.8% males) as compared to the non-OSA control group patients who were younger (57.0 ± 0.11 years) and more likely to be female (60.1% females), $P < 0.001$. The prevalence of obesity and the metabolic syndrome were also higher in the OSA group compared to the non-OSA control group ($P < 0.001$); as 50% of the patients in the OSA group were obese and 0.8% had a diagnosis of metabolic syndrome compared to 9.8% obese patients and 0.1% patients with metabolic syndrome in the control non-OSA group. The OSA group had a higher prevalence of diabetes and hypertension compared to non-OSA control group [49.2% versus 23.2%, $P < 0.001$] and [53.3% versus 38.1%, $P < 0.001$] respectively. Dyslipidemia was present in 41.7% of OSA patients compared to 23.1% of control non-OSA patients ($P < 0.001$). The prevalence of NASH in subjects with OSA was 2% (95% CI: 1.9, 2.1) compared to 0.65% (0.63, 0.66) in subjects without OSA ($p < 0.001$) (Figure 1). The control non-OSA patients had higher prevalence of esophageal varices (EV) compared to OSA group [0.45% versus 0.29%, $P < 0.001$]. The same results were found when comparing the prevalence of hepatic encephalopathy between non-OSA and OSA patients [0.46% vs 0.40%, $P < 0.001$]. The prevalence of thrombocytopenia and ascites was higher in the non-OSA control group compared to the OSA group [0.68% versus 0.60%, $P < 0.001$] and [1.2% versus 0.88%, $P < 0.001$] respectively. OSA patients had a significant higher prevalence of NASH compared to non-OSA group [OR: 1.55, (95% CI: 1.4 – 1.5), $P < 0.001$].

Multivariable Comparison

After adjusting for obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome and CCI, patients with OSA were 3 times more likely to have NASH than those without OSA [adjusted OR: 3.1, (95% CI: 3.0 – 3.3), $P < 0.001$] (Figure 2).

DISCUSSION

Our study from a large national inpatient database showed that OSA patients are three times more likely to have NASH compared to patients without OSA after controlling for other confounding factors including obesity, hypertension, diabetes, dyslipidemia, metabolic syndrome, and the CCI.

OSA is a growing concern; particularly in regards to the ongoing debate as to OSA being an independent risk factor for developing NASH. Only a few prior trials have reported OSA as a risk factor for developing NASH.^{11,12} In contrast, a few studies reported this association as a coincident rather than a significant correlation^{13–16}. Of note, another study suggested that severe OSA might be a risk factor for NASH regardless of the patients' body weight, which is similar to our study finding.¹⁷

The rationale behind the progression of NAFLD to NASH is not completely understood as only a percentage of hepatic steatosis cases progress to NASH,¹⁸ whereas other cases of steatosis progress to end stage liver disease.¹⁹ Recent studies have suggested that OSA may influence the progression of hepatic steatosis to NASH. Induced Chronic Intermittent

Hypoxia (CIH) resembling OSA in both animal and human studies showed evidence of hepatocyte injury.^{20,21} CIH increases lipolysis, oxidative stress, and up regulates hypoxia inducible factor 1, which may increase hepatic steatosis, induce necro-inflammation and fibrogenesis. Likewise, many cases of ischemic hepatitis have been reported in OSA patients, in whom the liver hypoxia was felt to be caused by underlying OSA.^{22,23} Nonetheless, OSA treatment with nasal continuous positive airway pressure showed a decrease in the serum levels of aminotransferases.²⁴ Additional study reported association between CIH and NAFLD activity score (NAS) after adjustment for age, obesity, and insulin resistance.²⁵ One study reported that there is no correlation between the severity of OSA and NASH severity.¹⁵ Our study could not confirm or contradict this concept due to the limitation in the ICD-9 codes which is considered one of our study limitations.

Multiple therapies have been studied for the treatment of NASH²⁴, weight loss has shown histologic improvement in NASH patients.²⁶ One study showed that CPAP therapy for OSA has shown evidence of improvement in blood pressure and partial reversal of other metabolic factors.²⁷ The administrative nature of our study database lacks the ability to determine the effect of OSA treatment on NASH regression which is considered one of the weaknesses in this study; further studies are needed to investigate the effect of OSA treatment in preventing NASH and even reversing it.

There are several strengths of the current study. Our data are obtained from a very large database, which represents a large segment of the US population. This allowed us to determine that OSA is an independent risk factor for NASH, which is important since OSA and NASH share multiple co-morbidities. Our study also has some limitations. NIS cannot specify if the diagnosis of NASH was biopsy proven or based on imaging studies. NIS cannot provide clinical information about specific medication use or laboratory results for each individual. In addition, NIS relies on the accuracy of clinical data and validity of medical diagnoses, which might be different between individuals and facilities. In addition, the outpatients' exclusion and inpatients' inclusion could lead to more sick individuals in the data, which might affect the generalizability of the results. On the other hand, exclusion of academic hospitals by the database could potentially exclude patients with more complex disease. Our like most published studies could not determine the severity of OSA, which has been suggested to be an important that impact the severity of liver injury.

In conclusion, this large nationwide database study strongly supports the role of OSA as an independent risk factor for NASH with a threefold higher prevalence of NASH in patients with OSA. Further studies are needed to explore the possible etiologies and determine if OSA is a modifiable treatment that could both decrease the progression and possibly reverse disease severity in patients with nonalcoholic fatty liver disease.

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Figure 1.
Prevalence of NASH in adult subjects with and without OSA

Figure 2.

Association between OSA and NASH in adult subjects

*Adjusted for obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome and CCI

Table 1

Recent trials with summarized findings

Author/ year	Sample size	Population	Findings	Ref #
Corey/2015	213	Bariatric Surgery	OSA correlated with ALT, AST and histology Adjusted for age, gender, race and diabetes	11
Weingarten/2012	218	Bariatric Surgery	Neither the presence or severity of OSA correlated with ALT or histology Not adjusted for co-morbidities	15
Ulitsky/2010	253	Bariatric Surgery	OSA did not correlate with histology in a Clinical scoring system Adjusted for diabetes, ALT and triglycerides	13
Daltro/2010	40	Bariatric Surgery	OSA correlated with insulin resistance (HOMA) but not with histology	16
Campos/2008	200	Bariatric Surgery	OSA correlated with histologic NASH 23% in NASH vs 9% in non-Nash Not adjusted for co-morbidities	12
Jouët /2007	262	Bariatric Surgery	OSA correlated with ALT but not NASH 33% in Nash vs 44% in non-NASH	14

Table 2

ICD-9 Codes Used

Description	ICD-9
NASH	571.8
OSA	327.23
Smoking	305.1, V158.2
Alcohol	303.00–303.93
Hemochromatosis	275.03
Obesity	278.00–278.03, 278.1–278.8
Diabetes	250.00–250.93
HTN	401.0–401.9, 405.01–405.99
Dyslipidemia	272.4
Metabolic Syndrome	277.7
Hepatic Encephalopathy	572.2
Esophageal Varices	456.0, 456.1, 456.2, 456.20, 456.21
Thrombocytopenia	287.4, 287.49
Ascites	789.5, 789.59

Table 3

Patient Characteristics

Factor	Total N=30,712,524	No OSA N=29,222,374	OSA N=1,490,150	p-value
Age (years), mean±SE	57.3±0.10	57.0±0.11	61.8±0.07	<0.001
Age (years)				<0.001
. 18–44	8,996,393 (29.3)	8,836,658 (30.2)	159,735 (10.7)	
. 45–64	9,011,427 (29.3)	8,342,632 (28.5)	668,795 (44.9)	
. 65+	12,704,704 (41.4)	12,043,084 (41.2)	661,620 (44.4)	
Gender				<0.001
. Male	12,484,972 (40.7)	11,653,182 (39.9)	831,790 (55.8)	
. Female	18,225,407 (59.3)	17,567,102 (60.1)	658,305 (44.2)	
Race				<0.001
. White	19,999,604 (65.1)	18,943,145 (64.8)	1,056,460 (70.9)	
. Black	4,265,509 (13.9)	4,047,504 (13.9)	218,005 (14.6)	
. Hispanic	2,985,302 (9.7)	2,905,302 (9.9)	80,000 (5.4)	
. Other	1,860,951 (6.1)	1,807,071 (6.2)	53,880 (3.6)	
. Unknown	1,601,158 (5.2)	1,519,353 (5.2)	81,805 (5.5)	
Obesity	3,612,511 (11.8)	2,854,451 (9.8)	758,060 (50.9)	<0.001
Smoking	7,582,482 (24.7)	7,109,512 (24.3)	472,970 (31.7)	<0.001
Alcohol use	972,680 (3.2)	950,360 (3.3)	22,320 (1.5)	<0.001
Diabetes	7,507,372 (24.4)	6,773,697 (23.2)	733,675 (49.2)	<0.001
Hypertension	11,918,611 (38.8)	11,124,116 (38.1)	794,495 (53.3)	<0.001
Dyslipidemia	7,374,080 (24.0)	6,751,960 (23.1)	622,120 (41.7)	<0.001
Metabolic syndrome	54,665 (0.18)	42,515 (0.15)	12,150 (0.82)	<0.001
Hepatic Encephalopathy	141,055 (0.46)	135,125 (0.46)	5,930 (0.40)	<0.001
Esophageal Varices	136,490 (0.44)	132,160 (0.45)	4,330 (0.29)	<0.001
Thrombocytopenia	207,180 (0.67)	198,220 (0.68)	8,960 (0.60)	<0.001
Ascites	375,715 (1.2)	362,545 (1.2)	13,170 (0.88)	<0.001
NASH	218,950 (0.71)	189,085 (0.65)	29,865 (2.0)	<0.001
Hemochromatosis	17,620 (0.06)	16,495 (0.06)	1,125 (0.08)	<0.001
Num. of Elixhauser's comorbidities				<0.001
. 0	6,017,751 (19.6)	5,980,596 (20.5)	37,155 (2.5)	
. 1	5,497,450 (17.9)	5,370,295 (18.4)	127,155 (8.5)	
. 2	5,892,861 (19.2)	5,664,446 (19.4)	228,415 (15.3)	
. 3+	13,304,462 (43.3)	12,207,037 (41.8)	1,097,425 (73.6)	
CCI, mean±SE	1.5±0.01	1.5±0.01	2.2±0.01	<0.001
CCI				<0.001
. 0	13,119,086 (42.7)	12,851,466 (44.0)	267,620 (18.0)	
. 1	6,576,351 (21.4)	6,209,246 (21.2)	367,105 (24.6)	
. 2	4,346,256 (14.2)	4,038,196 (13.8)	308,060 (20.7)	
. 3+	6,670,831 (21.7)	6,123,466 (21.0)	547,365 (36.7)	

Data presented as Weighted Frequency (%) unless otherwise stated.

NASH: non-alcoholic steatohepatitis.

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