

## Evidence for liver injury in the setting of obstructive sleep apnea

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### ABSTRACT

**Introduction.** Obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD) are both strongly associated with obesity. Whether OSA is an independent risk factor for liver injury is uncertain. **Objective.** To assess the hypothesis that OSA is associated with liver injury independent of obesity. **Materials and methods.** We reviewed the histories of 73 consecutive patients referred to a hospital-based sleep lab because of suspected OSA. OSA was determined to be present if the apnea-hypopnea index was  $> 10$ . Obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>. Patients were included for analysis if they had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels obtained within 60 days of sleep study. Patients with evidence of viral hepatitis, autoimmune-, metabolic- or established alcoholic-liver disease were excluded. Patients who reported alcohol intake equivalent to a dose  $\geq 20$  g/day were also excluded. 53 of 73 patients met study criteria. Patients were subdivided for analysis into groups meeting or not meeting OSA and obesity criteria, and having or not having elevated aminotransferase levels. **Results.** 35/53 patients (66%) had OSA. 31/53 (58%) patients were obese. 15 (28%) and 12 (23%) patients had elevated AST and ALT, respectively. Mean age, gender distribution, mean BMI and percentage with either diabetes or hyperlipidemia were not significantly different in those with or without OSA. Elevated ALT was found in 11/35 (31%) patients with OSA, compared to 1/18 patients without OSA ( $p = 0.041$ ). Frequency of elevated AST [obese 11/31 (35%); non-obese 4/22 (18%)] or ALT [obese 10/31 (32%); non-obese 2/22 (9%)] was not significantly different in the obese and non-obese cohorts. **Conclusions.** OSA may be a risk factor for liver injury independent of obesity. The prevalence and nature of liver disease in the setting of OSA should be determined with larger, prospective studies. The impact of OSA treatment, if any, on liver injury should be similarly evaluated.

**Key words.** Obstructive sleep apnea. Hypoxia. Nonalcoholic fatty liver disease. Obesity.

### INTRODUCTION

Obstructive sleep apnea (OSA) is a common medical condition characterized by repetitive episodes of upper airway collapse during sleep associated with varying degrees of arterial oxygen desaturation (hypoxia), leading to excessive daytime somnolence and fatigue. Continuous positive airway pressure (CPAP) is effective therapy for OSA, although many

have difficulty tolerating the therapy. Weight reduction, oral devices, and surgical therapy can be successful in selected groups of patients. Potential consequences of OSA include reduced quality of life, hypertension, excessive daytime sleepiness, and increased risk of all cardiovascular disease.<sup>1</sup> OSA has also been associated with increased levels of inflammatory mediators that have been associated with cardiovascular disease, such as C-reactive protein. Obesity is present in most patients with OSA, and studies demonstrate an association with insulin resistance (IR) as well.<sup>2-4</sup>

Nonalcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of liver injury. Steatosis alone –without inflammation or fibrosis– constitutes one end of the spectrum and carries a benign prognosis. For reasons not fully understood, many patients with simple steatosis develop nonalcoholic steatohepatitis (NASH). Besides the fatty-inflamma-

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tory infiltrate implied by the term, NASH often involves varying degrees of necrosis and fibrosis, and roughly 20% of patients with NASH ultimately develop cirrhosis.<sup>5</sup> A small percentage of these progress to decompensated cirrhosis with or without hepatocellular carcinoma, leading to death or liver transplantation.<sup>6</sup> NAFLD is strongly associated with obesity.<sup>7,8</sup>

A logical question arises: are OSA and NAFLD separate end-organ manifestations of the obesity epidemic, or is there an independent relationship between the two? At present the prevalence and spectrum of liver disease in the setting of OSA are poorly defined. Our intent was to perform a preliminary investigation of the potential interaction between OSA and liver injury, using common liver blood tests as a surrogate marker. We tested the hypothesis that OSA may be a risk factor for liver injury, independent of obesity.

## MATERIALS AND METHODS

Consent for this retrospective study was obtained from our Institutional Review Board. We reviewed the histories of 73 consecutive patients referred to our hospital sleep lab because of suspected OSA. Patients had formal polysomnography and measurement of body mass index (BMI). All of the patients underwent overnight polysomnography at a hospital based sleep laboratory accredited by the American Academy of Sleep Medicine. All studies were scored by registered polysomnographic technicians and were reviewed by one of the authors (JP) board certified by the American Board of Sleep Medicine, who was blinded to the results of liver blood tests. Apneas were defined as a complete cessation of airflow or greater than 80% reduction in the airflow signal lasting ten seconds or longer. Hypopneas were defined as a respiratory event with a 30% or greater reduction in the airflow signal associated with a desaturation of 4% or greater. All studies included at least two channels of electroencephalogram, electrooculogram, submental electromyogram (EMG), measurement of airflow via pressure transducer,

chest and abdominal wall motion by respiratory inductive plethysmography, oximetry, a single lead electrocardiography, and EMG of both anterior tibialis muscles.

Most patients were referred to sleep study from primary care providers or specialists at our institution. Patients who had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels obtained within 60 days of sleep study were included. The upper limit normal cutoff values for AST and ALT were  $\leq 29$  IU/L and  $\leq 31$  IU/L, respectively. Aminotransferase values were categorically recorded as normal or elevated, with mean and range determined in each cohort (obese, non-obese; OSA present or absent). Age, gender, and the presence or absence of diabetes and hyperlipidemia were recorded. Patients with reported alcohol intake equivalent to a dose  $\geq 20$  g/day, those in whom alcohol history was deemed unreliable, and those discovered to have preexisting or chronic viral, alcoholic, autoimmune or metabolic liver disease were excluded. 53/73 patients met criteria for study inclusion.

The patients were divided according to the presence or absence of OSA, defined as an apnea-hypopnea index  $> 10$ . Obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>. Statistical analysis was performed using the chi-square method (Yates corrected p-values), Fisher's exact test and t-tests for comparison of means.

## RESULTS

OSA was present in 35/53 patients (66%). 60% of study patients (32/53) were male. The bio-demographic data of patients meeting study criteria are shown in table 1. Mean age, gender and obesity percentage were not significantly different in patients with or without OSA.

Obesity criteria were met by 31/53 patients (58%). Elevated AST ( $> 29$  IU/L) and ALT ( $> 31$  IU/L) were found in 15/53 (28%) and 12/53 (23%) patients, respectively. Mean AST was 27.3 (range 8-80) and mean ALT was 28.3 (range 6-70).

**Table 1.** Bio-demographics of patients with and without OSA.

|                               | OSA (n = 35) | No OSA (n = 18) | P-value |
|-------------------------------|--------------|-----------------|---------|
| Mean age (years)              | 63.6         | 67.7            | 0.308   |
| Male gender                   | 66% (23/35)  | 50% (9/18)      | 0.417   |
| Mean BMI (kg/m <sup>2</sup> ) | 33.3         | 30.6            | 0.310   |
| Diabetes or $\uparrow$ lipids | 71% (25/35)  | 50% (9/18)      | 0.216   |

**Table 2.** Association of OSA with AST and ALT.

|                   | OSA (n = 35) | No OSA (n = 18) | P-value      |
|-------------------|--------------|-----------------|--------------|
| ↑ AST (> 29 IU/L) | 11 (31%)     | 4 (18%)         | 0.539        |
| Mean AST (Range)  | 28.1 (11-80) | 25.7 (8-41)     | 0.480        |
| ↑ ALT (> 31 IU/L) | 11 (31%)     | 1 (6%)          | 0.041        |
| Mean ALT (range)  | 30.9 (6-70)  | 22.1 (9-45)     | <b>0.024</b> |

**Table 3.** Association of obesity with AST and ALT.

|                   | Obese (n = 31) | Not obese (n = 22) | P-value |
|-------------------|----------------|--------------------|---------|
| ↑ AST (> 29 IU/L) | 11 (35%)       | 4 (18%)            | 0.285   |
| Mean AST (Range)  | 28.4 (11-44)   | 26.4 (8-80)        | 0.526   |
| ↑ ALT (> 31 IU/L) | 10 (32%)       | 2 (9%)             | 0.098   |
| Mean ALT (range)  | 31.3 (6-70)    | 23.8 (9-44)        | 0.051   |

We analyzed aminotransferase levels in patients meeting and not meeting OSA criteria. Elevated aminotransferase levels were more common among patients with OSA (Table 2). For patients with elevated ALT, which is more sensitive than AST in predicting liver injury, the association with OSA reached statistical significance ( $p = 0.041$ ). Mean ALT was also significantly higher in patients with OSA. By contrast, neither frequency of elevated aminotransferase levels nor mean aminotransferase levels differed significantly in the obese and non-obese cohorts (Table 3). Thus OSA, but not obesity, was associated with elevated ALT in this population.

## DISCUSSION

The presence of elevated aminotransferase levels in roughly a third of our OSA patients suggests that liver dysfunction is common in this syndrome. The finding that OSA outperformed obesity as a predictor of increased ALT suggests that liver injury may be a *consequence* of apnea, at least in some patients.

Hypoxia may be a final common cause of hepatic insult via several different pathways. First, low-flow states such as cardiogenic shock or acute hepatic artery thrombosis may cause massive hepatocellular necrosis (shock liver).<sup>9,10</sup> Second, right heart failure with passive liver congestion can trigger centrilobular necrosis and congestive fibrosis.<sup>11</sup> And third, hypoxic hepatitis from severe arterial desaturation in the setting of OSA has been described in several reports which, importantly, exclude circulatory failure as a potential factor.<sup>12,13</sup> Liver biopsy in these OSA cases demonstrated centrilobular necrosis, as would

be predicted in hypoxic injury given the normally decreasing portal-to-central  $pO_2$  gradient in the lobule. By contrast, centrilobular necrosis is not a prominent feature of NAFLD. Thus an association between OSA and fatty liver, particularly one independent of obesity, must involve a different mechanism.

Clearly OSA and NAFLD patients may exhibit common phenotypic traits (obesity, insulin resistance). But at present, data are limited and conflicting regarding whether OSA may induce or exacerbate histological liver injury independent of obesity. Tanne *et al.*<sup>14</sup> showed OSA to be associated with steatohepatitis independent of body weight, whereas 2 other series revealed an association with elevated ALT but not pathology as assessed by liver biopsy.<sup>15,16</sup> The impact of OSA therapy on liver histology is similarly unknown, though a study from Japan demonstrated improvement in ALT after treatment of OSA with CPAP,<sup>17</sup> as did a U.S. trial in children with OSA.<sup>18</sup>

Limitations to this study include its retrospective nature without controlled timing of aminotransferase testing, and the use of blood tests as a surrogate marker for histological liver injury. The authors recognize the lack of strong correlation between aminotransferase levels and degree of liver disease, as well as the tendency for patients' aminotransferase levels to fluctuate in response to numerous factors. Our data represent a preliminary finding, and these results are presented as a basis for future prospective analysis involving controlled, regimented screening for liver disease in the setting of OSA, with histological sampling of liver tissue for appropriate patients.

## CONCLUSION

In conclusion, this study adds to the small body of literature regarding an association between OSA and liver disease. Our findings support the hypothesis that OSA is an independent risk factor for liver injury. Implications of our study include the consideration of OSA in patients with elevated aminotransferase levels. Additional investigation with prospective studies involving larger numbers of patients is needed to confirm our hypothesis, and to clarify the prevalence and nature of hepatic dysfunction in OSA. Furthermore, similar inquiry is needed regarding the impact of OSA treatment, if any, on the course of NAFLD and other types of liver disease.

## DISCLOSURES

No relevant financial disclosures or conflicts of interest pertaining to this work.

Clinical Trial Registration Number: N/A.

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