Influence of Obstructive Sleep Apnea on Fatty Liver Disease: Role of Chronic Intermittent Hypoxia

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BACKGROUND: Currently the common pathogenetic mechanisms in nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA) are gaining increased attention. The aim of this study is to find out the influence of chronic intermittent hypoxemia and OSA related parameters to the severity of NAFLD. METHODS: We examined the liver functions tests and ultrasonographic data of liver as well as markers of OSA severity (apnea-hypopnea index [AHI], oxygen desaturation index, minimum oxygen saturation, percentage of time spent with S_{pO_2} < 90%) of 106 subjects. RESULTS: Fatty liver disease was diagnosed in 71 subjects (group 1), and the remaining 35 subjects were taken as controls (group 2). The prevalence of OSA was 71.2% versus 35.7% for group 1 and 2, respectively (P < .001). As NAFLD severity increased from mild to severe form, mean AHI and oxygen desaturation index values also increased significantly. Our multivariate analysis showed that AHI, oxygen desaturation index, lowest desaturation values, and percentage of sleep duration with S_{pO_2} < 90% were independent predictors of NAFLD after adjustment for BMI, weight, and insulin resistance. Furthermore, the most correlated parameter for the severity of NAFLD was found as the duration of hypoxia during sleep. CONCLUSIONS: The prevalence of NAFLD was higher in patients with severe OSA, suggesting a role for nocturnal hypoxemia in the pathogenesis of fatty liver disease. *Key words: fatty liver disease; sleep apnea; chronic intermittent hypoxia.* [Respir Care 2012;57(2):244–249. © 2012 Daedalus Enterprises]

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent primary liver disease representing a spectrum of liver diseases ranging from simple fatty infiltration without inflammation to steatohepatitis or end-stage liver diseases. Insulin resistance and dyslipidemia are thought to be the key promoters of fatty acid deposition in the liver.[1-2] Although central obesity, advanced age, and hyperlipidemia are clinical predictors of NAFLD, none of these factors universally cause NAFLD.[3] More prospective studies are needed to determine the true risk factors for the development and progression of NAFLD to identify patients whom might benefit from treatment trials, with highest risk.

Obstructive sleep apnea (OSA) is a disorder that is characterized by recurrent upper airway collapse during sleep, leading to sleep fragmentation and daytime sleepiness with chronic intermittent hypoxia (CIH). OSA is also a very common condition, affecting up to 2–4% of adults, and with an increasing prevalence, up to 35% in obese individuals.[4,5] Patients with OSA are often overweight or obese, and they frequently exhibit metabolic aberrations. The independent association of OSA with insulin resistance has been researched, and experimental studies in humans and animals have demonstrated that intermittent hypoxia and reduced sleep duration due to sleep fragmentation, as occur in OSA, exert adverse effects on glucose metabolism.[6-8]

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DOI: 10.4187/respcare.01184

Currently the common pathogenetic mechanisms in NAFLD and OSA are gaining increased attention. They are both more common in obese individuals. Nocturnal hypoxemic episodes during sleep apnea can raise systemic oxidative stress and serum lipid peroxidation,[9] which has been implicated in the pathogenesis of the NAFLD, nonalcoholic steatohepatitis (NASH), and its progression to advanced stages of hepatic fibrosis.[10,11] Daltro et al[12] have shown that OSA was associated with insulin resistance but not with the severity of NAFLD in obese patients. On the other hand Mishra et al[13] have shown that, in 101 patients awaiting bariatric surgery, OSA was a risk factor for progression of NAFLD to NASH. So influence of OSA on NAFLD is not clear. The aim of this study is to research if OSA relates to NAFLD with the link of CIH. In order to find out this relationship, we examined the liver function tests and ultrasonographic data of liver as well as markers of OSA severity (apnea-hypopnea index [AHI], oxygen desaturation index [ODI], minimum oxygen saturation, and percentage of time spent with $S_{pO_2} < 90\%$) to see which factors correlate best with the presence and severity of NAFLD.

QUICK LOOK

Current knowledge

Nonalcoholic fatty liver disease (NFLD) is associated with chronic intermittent hypoxemia and obstructive sleep apnea (OSA). The common physical finding in this relationship appears to be to obesity.

What this paper contributes to our knowledge

Patients with OSA and nocturnal hypoxemia may be at risk for developing NAFLD. Nocturnal hypoxemia may represent a key pathophysiologic factor in the development of NAFLD.

Methods

Subjects and Methods

All consecutive patients referred to overnight polysomnography because of symptoms of sleep apnea between December 2008 and May 2009 were included in the study. All of the patients' polysomnography tests were performed in the same unit. A total of 112 patients had polysomnography testing during that period, but 6 patients were excluded as they did not want to have abdomen ultrasonography. This was a prospective case control study. All subjects provided written informed consent prior to study participation. This study was approved by our local ethics committee.

All patients were seen and examined by a gastroenterologist after polysomnography test. The presence or a history of hypertension, diabetes mellitus, or dyslipidemia were also recorded. Extensive clinical and laboratory data, including fasting liver function tests, blood glucose levels, and insulin levels, were available for each patient. Subjects with excess alcohol intake (defined as $>$ 20 g/d for males and 10 gm/d for females), viral hepatitis, and other causes of chronic liver disease were excluded. Fasting insulin sensitivity was estimated by using the homeostasis model assessment (HOMA) of insulin resistance in all non-diabetic patients. The value of HOMA was calculated by the following equation and depicted as HOMA-IR value:

$$\text{Fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}/22.5$$

All the participants' heights and weights were measured by the same person, with the same equipment. Weight was measured by using a calibrated hospital scale, with subjects dressed in normal indoor clothing, without shoes. Height was measured against a wall, using a fixed tape measure with subjects standing barefoot on a hard surface, in centimeters. Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2). Patients were evaluated in 2 groups, according to their BMI: BMI $\leq$ 29.9 kg/m^2 (group 1 nonobese), and BMI $\geq$ 30 kg/m^2 (group 2 obese). Blood pressure was also recorded after at least 5 min of rest in a chair, with feet on the floor, and arm supported at heart level, using a mercury sphygmomanometer.

Ultrasound

Abdominal ultrasound was carried out using a 5 MHz curvilinear probe (G60S 2004, Philips, Holland) by a trained operator who was blinded to all clinical and laboratory characteristics of participants. Both subcostal and intercostal scanning was done. Normal liver parenchyma was seen as solid homogenous echo texture, which was midway between the renal cortex and pancreatic echogenicity. The findings of hepatic steatosis at sonography include increased echogenicity and sound attenuation. The severity of fatty liver was determined by measuring the liver/kidney echogenicity ratio (hepatorenal index).[14,15]

Polysomnographical Evaluation

Overnight polysomnography was recorded with a Grass polysomnogram (model PSG36-2, Grass Technologies, West Warwick, Rhode Island), which recorded the following parameters: electrocardiogram; central, temporal, and occipital electroencephalogram; bilateral electro-oculogram; submental and anterior tibialis electomyogram;

nasal air flow (using a nasal cannula and pressure transducer); naso-oral air flow (using a thermistor); and respiratory effort (using chest and abdominal piezoelectric belts). The electromyelogram, electrooculogram, and electroencephalogram leads were applied according to the international 10–20 electrode placement system. Oxyhemoglobin saturation (S_{pO_2}) was monitored using a pulse oximeter (Biox 3740, Ohmeda, Louisville, Colorado). Sleep staging was scored according to the criteria of the American Academy of Sleep Medicine's *Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, published in 2007. Apneas were defined as decrements in air flow $\geq$ 90% from baseline for $\geq$ 10 seconds. Hypopneas were defined as a $\geq$ 30% decrease in flow lasting at least 10 seconds and associated with a $\geq$ 4% oxyhemoglobin desaturation. The number of apneas and hypopneas per hour of sleep was calculated to obtain the AHI. Respiratory events were derived primarily from the nasal cannula-pressure transducer. The ODI was defined as the total numbers of episodes of oxyhemoglobin desaturation $\geq$ 4% from the immediate baseline, $\geq$ 10 seconds but $<$ 3 min, divided by the total sleep time. The percentage of total sleep duration with oxygen saturation levels below 90% ($S_{pO_2} < 90\%$) was calculated. OSA is grouped as mild, moderate, and severe according to the AHI values of 5–14 events/hour; 15–29 events/hour, and $>$ 30 events/hour, respectively.

Statistical Analysis

Comparisons on continuous variables were made using the Student *t* test or Wilcoxon-Mann-Whitney test. Categorical variables were compared using chi-square or the Fisher exact test. Pearson simple linear regression and correlation analysis were used to evaluate the interrelationship between parameters. Multivariate analyses were conducted on factors that were significant in the univariate analysis to identify features that are independently associated with NAFLD. A stepwise selection method was used with the multivariate analysis. A *P* value of $<$ .05 was considered significant for all analyses, which were performed with SPSS version 13.0 software (SPSS, Chicago, Illinois).

Results

One hundred six (27 female) subjects were included in the study. All patients' data for complete clinical and anthropometric profile findings, ultrasonographical results, and serum samples were available.

Fatty liver disease was diagnosed in 71 subjects according to ultrasound findings (group 1), and the remaining 35 subjects who had normal abdominal ultrasonography were taken as controls (group 2). We found that nearly 67% of patients referred for a clinical sleep study looking for OSA had NAFLD. The mean ages were 51.4 $\pm$ 12.4 years and 47.2 $\pm$ 14.4 years for groups 1 and 2, respectively. There were no significant differences between groups for sex, age, or associated illnesses. Obesity was more common in NAFLD patients (45%) than controls (36.2%). We measured waist circumference as a marker of visceral fat, and mean waist circumference for mild, moderate, and severe NAFLD patients was found to be 105.8, 139.7, and 120.5 cm respectively ($P = .31$). There were no significant differences for liver function levels between groups. We found that insulin resistance was significantly more in the NAFLD group (Table 1).

Table 1. Comparisons of Demographic and Clinical Characteristics of Subjects With NAFLD and Non-NAFLD

	NAFLD Group 1 ($n = 71$)	Non-NAFLD Group 2 ($n = 35$)	*P*
Sex (M/F), no.	53/18	26/9	.97
Age, mean $\pm$ SD, y	51.4 $\pm$ 12.4	47.2 $\pm$ 14.4	.13
Diabetes mellitus (%)	8.4	5.7	.07
Hyperlipidemia (%)	17.1	16.9	.16
Hypertension (%)	30.9	20.0	.08
Sleep apnea (%)	71.2	35.7	$<$ .001
BMI, mean $\pm$ SD, kg/m^2	33.1 $\pm$ 7.4	29.2 $\pm$ 5.2	.02
ALT, median (range), U/L	26.0 (5.0–144.0)	22.0 (10.0–45.0)	.03
AST, median (range), U/L	20.0 (12.0–56.0)	18.0 (11.0–29.0)	.01
ALT/AST ratio	1.20	1.24	.71
GGT, median (range), U/L	34.5 (9.0–194.0)	28.0 (14.0–67.0)	.17
HOMA-IR, median (range), U/L	3.2 (00.7–41.0)	1.6 (0.4–2.9)	$<$ .001
Fasting glucose, median (range), mg/dL	98.5 (82.0–195.0)	88.0 (72.0–129.0)	$<$ .001

NAFLD = non-alcoholic fatty liver disease
BMI = body mass index
ALT = alanine aminotransferase
AST = aspartate aminotransferase
GGT = gamma glutamyltransferase
HOMA-IR = homeostasis model assessment of insulin resistance

Sixty-six percent of patients had evidence of clinically important OSA, defined as an AHI $\geq$ 15 events/h. Although there were no differences in liver function tests for patients with and without OSA, we found a significant correlation ($P < .004$) between OSA and both NAFLD presence and severity. The percentage of NAFLD in mild, moderate, and severe OSA was 59%, 58.3%, and 78.2%, respectively. As NAFLD severity increased from mild to severe form, mean AHI and ODI values also increased significantly. Especially in severe NAFLD, OSA syndrome was found to be more common (Fig. 1).

Specifically, the higher BMI in group 1 could be a confounder. Age might also play a role, although it was not statistically significant. Our multivariate analysis showed that AHI, ODI, lowest desaturation values, and

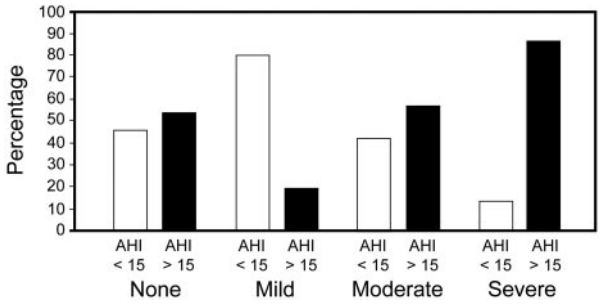

Fig. 1. Association between obstructive sleep apnea and severity of nonalcoholic fatty liver disease. AHI = apnea-hypopnea index (events/h).

percentage of sleep duration with $S_{pO_2} < 90\%$ were independent predictors of NAFLD after adjustment for BMI, weight, age, and insulin resistance. Furthermore, the most correlated parameter for the severity of NAFLD was found to be the duration of hypoxia (Table 2).

There were no significant differences in the results of liver function tests grouped by severity of OSA (Table 3). Furthermore, to evaluate the role of hypoxemia on liver function tests we grouped patients according to their mean oxygen saturation during sleep, but also this was not significant (Table 4).

Discussion

Our results showed that the prevalence of NAFLD was higher in patients with severe OSA, suggesting a role for nocturnal hypoxemia in the pathogenesis of fatty liver. A better understanding of the pathogenesis of NAFLD will lead to novel therapies for the conditions that still remain difficult to treat. In 190 biochemically defined NAFLD patients, sleep-related breathing disorders were found in 46% patients, according to the Modified Berlin Sleep Apnea Questionnaire.[16] Moreover, in patients whose liver biopsies showed more advanced disease, the prevalence of OSA symptoms tended to be higher, and also an increase in serum aminotransferase levels has been demonstrated in patients with OSA.[17] In our study we also found the incidence of OSA as 67% by polysomnography in the NAFLD group.

Pathophysiologic mechanisms such as sympathetic activation, endothelial dysfunction, oxidative stress, systemic inflammation, and insulin resistance are present in patients with OSA, and they may influence the development and progression of systemic diseases. Although the data dealing with the pathophysiology of NAFLD are advancing, nevertheless, insulin resistance plays a fundamental role in the pathogenesis of fatty liver.[11,18] Obesity and insulin resistance are distinguished by increased adipocyte mass and increased hormone-sensitive lipase activity, which in turn leads to up-regulation of lipolysis and increased uptake of free fatty acids by the liver.[19] Insulin resistance decreases the inhibitory effects of insulin on peripheral lipolysis, increasing the availability of free fatty acids (FFAs). Data from recently published cross-sectional and prospective studies have implied that CIH is an additional causal factor in the development of NAFLD, which is independent from obesity and the metabolic syndrome.[20] In our study, we also found that AHI and ODI values were independent predictors of NAFLD after adjustment for BMI, weight, and insulin resistance. Measurement of waist/hip ratio can be important to predict visceral obesity, but unfortunately we measured only waist circumferences and we could not find any relationship between waist circumferences and severity of NAFLD. One of the limitations of our study; was the lack of waist/hip ratio. Specifically, the higher BMI in group 1 could be a confounder. The difference in BMI could be a limitation of this study, but our multivariate analysis showed that after adjustment for BMI, still, AHI lowest desaturation values and percentage of sleep duration with $S_{pO_2} < 90\%$ were independent predictors of NAFLD.

Sleep apnea causes recurrent nocturnal oxygen desaturations with an increase in oxidative stress. The consequences of oxidative stress are lipid peroxidation, cell degeneration and necrosis, apoptosis, pro-inflammatory cytokine expression, liver stellate cell activation, and fibrogenesis. Multiple possible sources of oxidative stress have been identified and include mitochondrial dysfunction, hepatic cytochrome CYP2E1, β oxidation by peroxisomes in mitochondria, and recruited inflammatory cells.[21-22] We found that severity and duration of hypoxia as a result of apnea were independent predictors of NAFLD. Previous studies have reported that approximately one half of NAFLD patients also have symptoms of OSA, and that oxygen desaturation during sleep is a risk factor for developing latent steatohepatitis, especially in patients with substantial hepatic steatosis.[16]

Eighty-five patients who had a sleep study followed by a liver biopsy during obesity surgery were analyzed for their OSA status and liver histology. It was found that obese patients with OSA had statistically significantly elevated levels of alanine aminotransferase and more histological evidence of progressive liver disease than non-OSA obese patients.[23] In our study we could not show elevated levels of liver function tests in the OSA syndrome group; this could be because our patients' mean BMI was significantly lower than theirs (33.1 kg/m^2 vs 55.1 kg/m^2), as they selected their patients from the ones who would have obesity surgery.

An animal study of the effect of CIH on 15 lean mice without obesity found that, in the absence of obesity, CIH leads to a mild liver injury via oxidative stress and excessive glycogen accumulation in hepatocytes, and sensitizes the liver to a second insult.[24] In an another animal study,

Table 2. Polysomnographic Parameters of Subjects According to Severity of NAFLD After Adjusting for Body Mass Index, Weight, and Insulin Resistance*

Polysomnographic Parameter	Non-NAFLD	Mild NAFLD	Moderate NAFLD	Severe NAFLD
Apnea-hypopnea index	16.0 (0.4–113.9)	25.1 (1.7–78.4)	25.9 (0.8–103.4)	36.6 (4.3–89.9)
Oxygen desaturation index	4.5 (3.2–5.8)†‡	10.7 (6.4–15.0)§	21.5 (18.7–24.2)†‖	60.3 (52.2–68.4)‡§‖
Sleep duration with $S_{pO_2} < 90\%$, %	5.9 (0.1–100)†‡¶	11.8 (2.0–87.0)¶	9.5 (0–93.8)†‖	45.0 (1.2–100)‡‖
Lowest desaturation value, %	85.0 (50.0–93.0)†‡¶	78.0 (50.0–93.0)¶	80.0 (50.0–94.0)†	77.0 (50.0–89.0)‡
Mean nocturnal oxygen saturation value, %	94.0 (74.6–96.0)†‡¶	92.6 (85.4–96.0)	92.0 (77.8–96.1)†	90.8 (86.3–97.0)‡

* All values are expressed as median (range).
† The difference between non-nonalcoholic fatty liver disease (NAFLD) and moderate NAFLD groups is statistically significant ($P = .002$).
‡ The difference between non-NAFLD and severe NAFLD groups is statistically significant ($P < .001$).
§ The difference between mild NAFLD and severe NAFLD groups is statistically significant ($P = .003$).
‖ The difference between moderate NAFLD and severe NAFLD groups is statistically significant ($P = .002$).
¶ The difference between non-NAFLD and mild NAFLD groups is statistically significant ($P < .001$).

Table 3. Comparison of Liver Function Tests of Subjects With Different Polysomnographic Results*

Liver Function Test	Non-OSAS (no. = 14)	Mild OSAS (no. = 21)	Moderate OSAS (no. = 24)	Severe OSAS (no. = 46)	*P*
ALT (U/L)	23.5 (11.0–52.0)	25.0 (12.0–144.0)	26.0 (10.0–75.0)	22.0 (5.0–74.0)	.54
AST (U/L)	18.0 (12.0–26.0)	19.0 (11.0–51.0)	21.0 (12.0–56.0)	18.0 (11.0–52.0)	.23
ALT/AST ratio	1.14 (0.79–2.42)	1.43 (0.61–2.82)	1.39 (0.71–1.91)	1.27 (0.28–2.29)	.49
GGT (U/L)	29.0 (9.0–47.0)	36.0 (14.0–194.0)	27.5 (14.0–118.0)	29.0 (13.0–139.0)	.19

* All values are expressed as median (range).
OSAS = obstructive sleep apnea syndrome
ALT = alanine aminotransferase
AST = aspartate aminotransferase
GGT = gamma glutamyltransferase

Table 4. Comparison of Liver Function Tests of Subjects With Different Oxygen Saturations

Liver Function Test	MNOS < 90%	MNOS ≥ 90%	*P*
ALT (U/L)	26.70	26.25	.29
AST (U/L)	21.20	20.70	.24
ALT/AST ratio	1.39	1.23	.48
GGT (U/L)	40.40	39.30	.89

OSAS = obstructive sleep apnea syndrome
MNOS = mean nocturnal oxygen saturation
ALT = alanine aminotransferase
AST = aspartate aminotransferase
GGT = gamma glutamyltransferase

hepatocellular-specific gene deficient mice were exposed to a 10% O_2 (hypoxic) or 21% O_2 (control) atmosphere for 7 days, and the findings of this study demonstrated that hypoxia alone aggravated and accelerated the progression of NASH by up-regulating the expression of lipogenic genes, by down-regulating genes involved in lipid metabolism, and by decreasing insulin sensitivity.[25] Our results similarly suggest that in the setting of hepatic steatosis, repeated nocturnal hypoxemic episodes may act as the "oxidative hit," and may be one of the underlying factors promoting development of histological NAFLD.

A limitation of our study was that the diagnosis of NAFLD was based on liver ultrasonography. Although liver biopsy represents the best diagnostic tool for fatty liver, it cannot be widely performed on apparently healthy-looking subjects, for ethical reasons. On the other hand, liver ultrasonographic scanning has a good correlation with histological findings of fatty infiltration, and has been proposed worldwide as a method of evaluation for different degrees of fatty liver.[26,27] In this study, we followed the criteria described by Needleman et al,[14] which showed an accuracy of 88% in the diagnosis and staging of fatty liver from a direct comparison between the pathological and ultrasonographic findings.

Conclusions

In conclusion, we postulate that repetitive oxyhemoglobin desaturation or severe hypoxemia because of frequent hypopneic and apneic episodes in sleep apnea patients may promote inflammation and oxidative stress. These remarkable associations raise the possibility that OSA may be a novel risk factor for NAFLD. Further prospective and

interventional studies are needed to find out whether the treatment of OSA may delay the development or reduce the severity of NAFLD.

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