Sleep Apnea and Fatty Liver Are Coupled Via Energy Metabolism

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Background:
Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by intermittent hypoxia. Non-alcoholic fatty liver disease is the most common cause of chronic liver disease worldwide. We aimed to evaluate the relationship between OSA and fatty liver.

Material/Methods:
We enrolled 176 subjects to this study who underwent polysomnography (PSG) for suspected OSA. The control group included 42 simple snoring subjects. PSG, biochemical tests, and ultrasonographic examination were performed all subjects.

Results:
The simple snoring and mild, moderate, and severe OSA groups included 18/42 (42.86%), 33/52 (63.5%), 27/34 (79.4%), and 28/48 (79.2%) subjects with hepatosteatosis, respectively. There were significant differences in hepatosteatosis and hepatosteatosis grade between the simple snoring and the moderate and severe OSA groups. Logistic regression analysis showed that BMI and average desaturation were independently and significantly related to hepatic steatosis.

Conclusions:
Our study shows that BMI and the average desaturation contribute to non-alcoholic fatty liver in subjects with OSA. In this regard, sleep apnea may trigger metabolic mitochondrial energy associated processes thereby altering lipid metabolism and obesity as well.

MeSH Keywords:
Body Mass Index • Fatty Liver • Sleep Apnea, Obstructive

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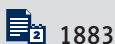
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Background

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by intermittent hypoxia (IH), which leads to hypoxemia, hypercapnia, sleep fragmentation, increased respiratory effort, and increased sympathetic activity. OSA commonly affects middle-aged adults, affecting 4% of men and 2% of women [1,2]. However, the prevalence of sleep-disordered breathing in men and women who do not have daytime somnolence is approximately 24% and 10%, respectively. Moreover, in obese and elderly populations, this value increases to 60% [3].

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, affecting 30% of the general adult population and 60–70% of diabetic and obese patients [4]. NAFLD is a significant public health problem; in a 5-year population-based follow-up, the presence of NAFLD increased overall healthcare costs by 26%, after controlling for comorbidities [5].

Obstructive sleep apnea syndrome has been associated with the features of metabolic syndrome, including obesity [6], hypertension [7], dyslipidemia [8], and insulin resistance [9], some of which are thought to contribute to the pathogenesis of NAFLD [10]. Therefore, this study evaluated the relationship between OSA and fatty liver.

Material and Methods

Subjects

This study was approved by the local ethics committee in accordance with the Helsinki Declaration. Written informed consent was received from the OSA syndrome subjects and control subjects before enrollment in the study. This study enrolled 176 subjects who underwent polysomnography (PSG) for suspected OSA between January 2013 and April 2015 at our sleep center. Exclusion criteria were: severe disease of the circulatory, respiratory, central nervous, or digestive systems; alcohol intake >20 g/d for males and >10 g/d for females; regular use of hepatotoxic drugs; evidence of hepatitis; use of hyperlipidemia drugs; and subjects with diabetes mellitus. Blood tests and ultrasound imaging of the subjects were performed the morning of the PSG. The OSA subjects had an apnea-hypopnea index (AHI) ≥5, while the subjects with an AHI <5 were considered contols. The OSA subjects were subdivided into mild, moderate, and severe OSA groups based on the American Academy of Sleep Medicine criteria, with an AHI of 5–14, 15–29, and ≥30 events/h, respectively.

Demographic data and laboratory tests

We collected demographic data, including a history of hypertension, diabetes mellitus, and medications. The physician who collected these data was blinded to the blood and PSG test results. The height and weight of all subjects were measured by the same person and with the same equipment using a calibrated hospital scale. Oher baseline characteristics recorded in all patients included age, sex, and body mass index (BMI), which was calculated by dividing body weight by height squared (kg/m^2).

Fasting blood samples were drawn into heparinized tubes, and centrifuged at 3000 rpm for 10 min to separate the plasma. The samples were analyzed within 2 h. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum cholesterol and triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), platelet count, and hemoglobin level were measured using standard techniques.

PSG

Overnight PSG was performed using a 16-channel Embla device (Medcare, Reykjavik, Iceland) under continuous monitoring by a sleep technician. The system consists of 4 electroencephalogram channels (with electrodes placed at C4-A1, C3-A2, O2-A1, and O1-A2), 2 electrooculogram channels, and a submental electromyogram (EMG); it monitors nasal airflow using a nasal pressure cannula, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position, electrocardiogram readings, and tracheal sound. Sleep-disordered breathing events were scored manually by the same examiner according to the 2012 American Academy of Sleep Medicine criteria. Apnea was defined as complete cessation of airflow lasting more than 10 s. Hypopnea was defined as a reduction in airflow >30% lasting more than 10 s accompanied by ≥4% desaturation or arousal. The average number of episodes of apnea and hypopnea per hour of sleep was measured as the AHI. Sleep stages were scored using standard criteria with 30-s epochs, and were reviewed and verified by a certified sleep physician. The pulmonologist who evaluated the PSG was blind to the ultrasonography results. The duration of desaturation, lowest saturation, mean saturation, average desaturation, and other polysomnography parameters were recorded.

Ultrasound imaging

Using B-mode sonography, the presence or absence and severity of fatty infiltration were graded on a scale from 0 to 3, indicating absent, mild, moderate, and severe hepatosteatosis, respectively, as reported by Mihmanli et al. [10]. These correspond to increasing degrees of hepatic echogenicity with poorer visualization of the intrahepatic vessels and diaphragm. Grade 0

Table 1. Demographic, clinical characteristics and polysomnographic parameters in subjects with OSA groups and control (simple snoring) group.

	Groups				p value
	Simple Snoring	Mild OSA	Moderate OSA	Severe OSA	
Subjects (n)	42	52	34	48	
Sex (f/m)	11/31	14/38	9/25	12/36	0.997
Age	45.09±10.08	42.87±9.63	47.59±10.79	46.96±10.04	0.112
AHI (event/h)	2.9±3.4	9.5±3.8	20.2±5.3	55.9±23	<0.001
BMI (kg/m^2)	28.35±4.71	30.11±6.17	34.14±7.7	32.7±6.23	<0.001
Hepatosteatosis (n/%)	18/42 (42.86%)	33/52 (63.5%)	27/34 (79.4%)	28/48 (79.2%)	0.001
Hepatosteatosis grade	.74±0.96	1.19±1.12	1.65±1.12	1.54±1.03	0.001
Duration of desaturation (min)	9.36±24.71	34.11±59.1	56.86±52.82	47.54±37.12	<0.001
Lowest desaturation (%)	85.88±7.01	82.67±4.91	77.21±8.96	69.06±12.46	<0.001
Avarage saturation (%)	91.98±2.26	91.12±2.14	89.06±4.44	85.41±7.3	<0.001
Avarage desaturation (%)	5.72±7.33	5.1±0.59	5.84±1.05	8.27±3.78	0.001
AST (UI/L)	24.12±9.60	22.29±9.07	24.94±7.47	27.65±10.89	0.045
ALT (UI/L)	26.14±12.63	27.16±11.71	30.71±16.47	37.73±23.04	0.004
Cholesterol (mg/dL)	192.12±44.96	195.54±32.68	183.0±36.53	193.34±38.07	0.512
LDL (mg/dL)	114.67±38.89	120.84±31.21	111.18±27.43	117.40±30.73	0.585
HDL (mg/dL)	38.40±7.99	40.2±10.85	40.73±10.34	37.43±7.22	0.318
Triglycerides (mg/dL)	197.60±141.92	177.06±94.44	166.22±102.67	198.63±98.03	0.488
Hb (g/dL)	15.25±1.34	14.95±1.8	15.05±1.37	15.56±1.67	0.258

(control) subjects had normal liver echogenicity. Grade 1 subjects had a minimal diffuse increase in hepatic echogenicity, with normal visualization of the diaphragm and walls of the intrahepatic vessels. Grade 2 subjects had a moderate diffuse increase in hepatic echogenicity, with slightly impaired visualization of the hepatic veins and diaphragm. Grade 3 subjects had a marked increase in echogenicity with poor penetration of the posterior portion of the right lobe of the liver, and poor or no visualization of the hepatic veins and diaphragm. The radiologist who evaluated the ultrasound imaging was blind to the PSG results.

Statistical analyses

Statistical analyses were performed using SPSS 21. Continuous data are expressed as the means ± standard deviation (SD). Statistical comparisons were performed using one-way analysis of variance. We compared AHI, hepatosteatosis grade, age, lowest saturation, BMI, duration under 90% saturation, average saturation, AST and ALT levels, lipid profile, hemoglobin, and platelet count between the OSA subjects and controls.

Logistic regression analysis of the factors that affected hepatic steatosis independently was performed. Results were considered statistically significant when the *p*-value was ≤0.05.

Results

The study enrolled 176 patients, including 130 males. The mean age was not significantly different in the non-OSA and mild, moderate, and severe OSA groups. The sex distribution was not significantly different between the control and OSA groups, but the percentage of males was higher than that of females in all groups. Table 1 summarizes the demographic parameters, clinical characteristics, and PSG parameters. The simple snoring and mild, moderate, and severe OSA groups included 18/42 (42.86%), 33/52 (63.5%), 27/34 (79.4%), and 28/48 (79.2%) subjects with hepatosteatosis, respectively (*p*=0.001).

The BMI, AHI, hepatosteatosis grade, duration of desaturation, lowest desaturation, mean saturation, average desaturation,

Table 2. Bonferroni test results for studied parameters.

Multiple comparisons					
Dependent variable	(I) Groups	(J) Groups	Mean difference (I-J)	Std. error	Sig.
Hepatosteatoz	Simple snoring	Moderate OSA	−.36555	.10528	.004
		Severe OSA	−.36310	.09642	.001
Hepatosteatosis grade	Simple snoring	Moderate OSA	−.90896	.24493	.002
		Severe OSA	−.80357	.22432	.003
Duration of desaturation	Simple snoring	Mild OSA	−24.75175	9.60799	.065
		Moderate OSA	−47.50567	10.62465	.000
		Severe OSA	−38.18220	9.78849	.001
Lowest desaturation	Simple snoring	Moderate OSA	8.67217	2.03756	.000
		Severe OSA	16.81555	1.86807	.000
	Mild OSA	Severe OSA	13.60417	1.76654	.000
	Moderate OSA	Mild OSA	−5.46078	1.94489	.033
		Severe OSA	8.14338	1.96905	.000
Avarage saturation	Simple snoring	Severe OSA	6.56311	.97729	.000
	Mild OSA	Severe OSA	5.70711	.92417	.000
	Moderate OSA	Simple snoring	−2.91679	1.06595	.041
		Severe OSA	3.64632	1.03012	.003
Avarage desaturation	Simple snoring	Severe OSA	−2.54228	.87949	.026
	Mild OSA	Severe OSA	−3.16667	.83987	.001
	Moderate OSA	Severe OSA	−2.42255	.92703	.059
ALT	Simple snoring	Severe OSA	−11.58631	3.51969	.007
	Mild OSA	Severe OSA	−10.56917	3.36617	.012

and AST and ALT levels differed significantly among the groups. There were no differences in the other parameters. BMI differed significantly between the simple snoring and the moderate and severe OSA groups (*p*=0.002 for simple snoring *vs.* moderate OSA groups, *p*=0.002 for simple snoring *vs.* severe OSA groups). There were no differences in BMI between the moderate OSA and the simple snoring and mild and severe OSA groups.

Parameters that differed between the groups were identified using one-way analysis of variance and Bonferroni correction. The significant results are given in Table 2. There were significant differences in hepatosteatosis and hepatosteatosis grade between the simple snoring and the moderate and severe OSA groups. In addition, AHI, BMI, hepatosteatosis grade, lowest desaturation, mean desaturation, AST, ALT, cholesterol, HDL, and triglyceride levels differed significantly when the subjects were separated into hepatosteatosis and non-hepatosteatosis groups (*p*-values 0.004, <0.001, <0.001, 0.007, <0.001, 0.005, <0.001, 0.045, 0.043, and 0.029, respectively)

Using logistic regression, BMI and average desaturation were independently and significantly related to hepatic steatosis (*p*=0.014, r=1.1126, and *p*=0.008 and r=2.327, respectively) (Table 3). Receiver operating characteristic curve analysis was performed to examine the average desaturation and hepatosteatosis. The cut-off value was 4.85% for average desaturation on hepatosteatosis (sensitivity was 80% and specificity was 57%) (Figure 1).

Discussion

Our data indicate that BMI and the average desaturation contribute to non-alcoholic fatty liver in subjects with OSA. The BMI and average desaturation (%) increased progressively from simple snoring to severe OSA; hepatosteatosis and hepatosteatosis grade also increased significantly. The average desaturation was a risk factor for hepatic steatosis after adjusting for BMI.

Table 3. Logistic regresyon analyse results basing on hepatosteatosis.

|	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
							Lower	Upper
Sex	−.765	.649	1.392	1	.238	.465	.130	1.659
Age	−.012	.024	.264	1	.607	.988	.942	1.035
AHI	−.024	.017	2.044	1	.153	.976	.944	1.009
BMI	.119	.048	6.016	1	.014	1.126	1.024	1.238
Duration of Desaturation	.004	.005	.434	1	.510	1.004	.993	1.014
LowestDesaturation	.020	.045	.196	1	.658	1.020	.934	1.114
Mean Saturation	.034	.089	.146	1	.703	1.034	.869	1.231
Avarage Desaturation	.845	.321	6.941	1	.008	2.327	1.241	4.363
Cholesterol	.018	.048	.148	1	.701	1.019	.927	1.119
LDL	−.006	.049	.014	1	.907	.994	.904	1.094
HDL	−.054	.050	1.191	1	.275	.947	.859	1.044
Triglycerides	−.004	.010	.150	1	.699	.996	.977	1.015
Hb	.064	.187	.117	1	.732	1.066	.739	1.539
Constant	−14.691	8.003	3.370	1	.066	.000		
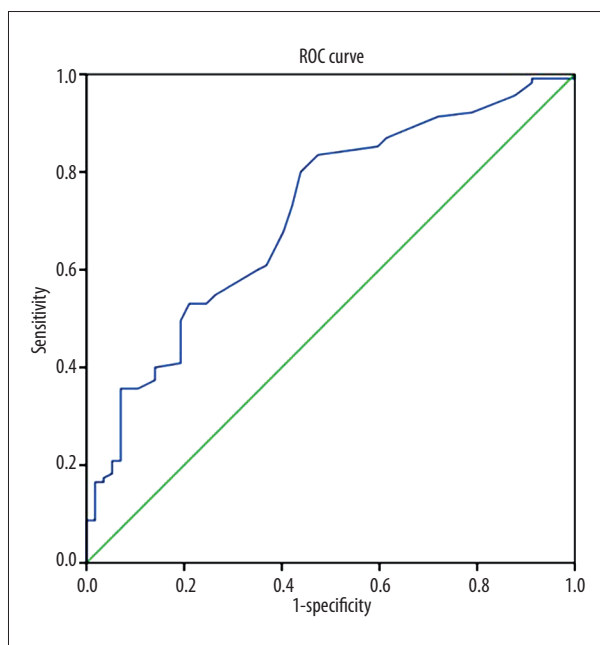
Figure 1. Area under the curve=0.713. Cut off value is 4.85% for avarage desaturation on hepatosteatosis. (Sensitivity is 80% and specificity is 57%).

Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of chronic intermittent hypoxia and sleep fragmentation, which increase sympathetic activity and promote oxidative stress, proinflammatory cytokine production, platelet aggregation, endothelial dysfunction, and metabolic dysregulation [11]. Collectively, these mechanisms provide the pathophysiological basis for increased risk of fatty liver observed in these patients.

Recently, OSAS has been associated with non-alcoholic fatty liver disease (NAFLD) [12]. NAFLD is the most common chronic liver disease worldwide and about 30% of the general adult population and 60–70% of diabetic and obese patients have NAFLD [13]. The liver damage of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH).

Chronic intermittent hypoxia (CIH) is a key feature in the pathophysiology of OSAS. The mechanism is probably similar to that of ischemia-reperfusion injury. In OSAS patients, some oxidative stress markers are augmented and can increase inflammation, endothelial dysfunction, and the development of atherosclerosis [14].

Savransky et al. showed that CIH induces hyperglycemia and hepatic lipid peroxidation and enhances the activity of nuclear factor kappa B (NF-κB), a master regulator of the inflammatory response. Liver histology is characterized by swelling and a significant increase in the accumulation of glycogen in hepatocytes. Therefore, CIH may independently lead to mild liver injury in the absence of factors that induce obesity [15].

Hypoxia modulates target gene expression through a number of transcription factors, including hypoxia-inducible factors (HIFs). HIFs are heterodimers consisting of α and β subunits. HIF-α subunits are produced constitutively in normoxic cells and are immediately degraded via hydroxylation by 3

prolyl-hydroxylases. In OSAS patients, CIH can increase active HIF levels. In an animal model, CIH led to hypercholesterolemia and hepatic lipid peroxidation, in the absence of obesity [12].

Recent experimental evidence has connected OSAS to the pathogenesis and progression of NAFLD, another obesity-related disorder, which is associated with increased cardio-metabolic and liver-related risk [16]. In cellular and animal models, CIH promoted hepatic triglyceride accumulation, necroinflammation, and fibrosis via the activation of several cellular pathways, including hypoxia-inducible factors, NF-κB, and the unfolded protein response [17]. Furthermore, epidemiological studies have documented an association of OSAS with increased prevalence and severity of NAFLD, and a few trials have documented the benefits of OSAS treatment on transaminase elevation and radiological steatosis [18–20].

Turkay et al. examined liver functions tests, liver ultrasonography, and markers of OSA severity (AHI, oxygen desaturation index, minimum oxygen saturation, and percentage of duration of desaturation) and concluded that as the severity of NAFLD increased from mild to severe, the mean AHI and oxygen desaturation index also increased significantly [21]. Their study differed from ours in that they investigated the presence of OSA in subjects with or without fatty liver.

Few studies have focused on hepatosteatosis in subjects with OSA. We found that the BMI, AHI, hepatosteatosis grade, duration of desaturation, lowest desaturation, mean saturation, average desaturation, and AST and ALT levels differed significantly among the 4 groups. In addition, AHI, BMI, hepatosteatosis grade, lowest desaturation, mean desaturation, AST, ALT, cholesterol, HDL, and triglyceride levels differed significantly in the subjects with hepatosteatosis. However, only BMI and average desaturation had independent effects on hepatosteatosis in subjects with OSA. This study cannot explain why the lowest saturation, mean saturation, and duration of desaturation had no effects on hepatosteatosis. Further studies should examine this topic.

Conclusions

Average desaturation and BMI were the parameters with the greatest independent effects on hepatosteatosis in the subjects with OSA. Hepatosteatosis in individuals with OSA should be monitored carefully with ultrasonography. OSA patients should be encouraged to use a continuous positive airway pressure (CPAP) device and lose weight to prevent development of fatty liver.

Conflict of interest

None.

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