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ORIGINAL RESEARCH

Risk Factors of Nonalcoholic Fatty Liver Disease and Liver Fibrosis in Non-Obese Patients with Obstructive Sleep Apnea

Ningfang Lian[1,*], Jiawei Wu[1,*], Biying Wang[1], Su Lin[2], Jiefeng Huang[1], Jia Chen[1], Qichang Lin[1]

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Fujian Medical University; Fujian Provincial Sleep-Disordered Breathing Clinic Center; National Regional Medical Center, Binhai Campus of The First Affiliated Hospital, Fujian Medical University; Institute of Respiratory Disease, Fujian Medical University, Fuzhou, People's Republic of China; [2]Liver Research Center, The First Affiliated Hospital of Fujian Medical University, Fuzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qichang Lin, Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Fujian Medical University, No. 20, Chazhong Road, Taijiang District, Fuzhou, Fujian Province, 350005, People's Republic of China, Tel +86-591-87981698, Fax +86-591-83318716, Email linqc_fy@126.com

Purpose: Liver injury in non-obese obstructive sleep apnea (OSA) patients has received much attention in recent years. This study aimed to investigate risk factors of nonalcoholic fatty liver disease (NAFLD) and liver fibrosis in non-obese patients with OSA.

Methods: A retrospective study was conducted in the Sleep Center of the First Affiliated Hospital of Fujian Medical University. All consecutive non-obese patients with suspected sleep apnea admitted to the center were enrolled. The clinical characteristics of patients with simple snoring and with different severity OSA were compared. Multivariate logistic regression models were used to analyze the risk factors of NAFLD and liver fibrosis.

Results: A total of 410 patients were enrolled. The levels of triglyceride, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased with the aggravation of OSA (All $p<0.05$). Among non-obese patients with OSA, 17 (5%) were diagnosed with liver fibrosis and 228 (65%) with NAFLD; Apnea-hyponea index (AHI) was an independent predictor for NAFLD and liver fibrosis [OR (95% CI): 1.02 (1.00–1.03), 1.04 (1.00–1.07), both $p<0.05$]; hypertriglyceridemia was an independent predictor for NAFLD [OR (95% CI): 1.13 (1.12–1.99), $p<0.05$].

Conclusion: NAFLD and liver fibrosis were common in non-obese OSA patients and the severity of OSA was an independent risk factor for them.

Keywords: obstructive sleep apnea, non-alcoholic fatty liver disease, liver fibrosis

Introduction

Obstructive sleep apnea (OSA) is a chronic respiratory disease characterized by periodic hypoxia and reoxygenation during sleep.[1] The prevalence of OSA has raised to approximately 25% of adults in USA.[2] OSA usually occurs in obese individuals, but increasing evidence indicates that OSA is also common in non-obese population.[3] Among individuals aged 30 to 49 years with a body mass index (BMI) less than 25, the prevalence of OSA among men is 7.0%.[4]

OSA resulted in multiple organs injury, including cardiovascular injury and metabolic disorders.[5] OSA and metabolic syndrome shared considerable overlap with risk factors, including obesity, sedentary behavior, and genetics.[6] Nocturnal oxygen saturation parameters were independent risk factors for Type 2 Diabetes among OSA Patients.[7] In recent years, OSA-related liver injury has received much attention. Savransky et al reported that OSA was associated with nonalcoholic steatohepatitis in obese subjects.[8] Zhang et al found apnea-hyponea index (AHI) was an independent risk factor for elevated alanine aminotransferase (ALT) levels in severely obese patients.[9] Huang et al reported that intermittent hypoxia was an independent predictor for nonalcoholic fatty liver disease (NAFLD) in severe OSA patients.[10] Wojciech et al found increased liver stiffness in patients with metabolic comorbidities and severe OSA.[11] Most of the previous clinical studies focused on obese people, as obesity was an

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important risk factor for both OSA and liver injury. The mechanism of liver injury in OSA patients was due to intermittent hypoxia related systemic inflammatory, oxidative stress, mild tissue ischemia and increased output of the sympathetic nervous system.[12] The pathophysiological injury associated with intermittent hypoxia occurred not only in obese people but also in non-obese people. So, liver injury in non-obese OSA patients deserved more attention.

NAFLD is a common chronic liver disease featured by the accumulation of lipid in the liver. The disease spectrum includes simple hepatic steatosis, steatohepatitis, fibrosis and cirrhosis. Previous studies found that the degree of liver fibrosis determined the outcomes in NAFLD patients.[13] Fibrosis-4 Index (FIB-4) has been widely used in recent years as a noninvasive method for detecting liver fibrosis with acceptable sensitivity and specificity.[14]

This study aimed to discuss the risk factors of NAFLD and liver fibrosis in non-obese OSA patients.

Materials and Methods

The retrospective study was conducted in Sleep Respiratory Disease Research Center, First Affiliated Hospital of Fujian Medical University. The informed consents were obtained from the study participants prior to study commencement. All consecutive patients with suspected sleep apnea admitted to the center were enrolled in the study between January 2, 2016 and December 23, 2019. Including criteria were as follows: (1) All subjects enrolled aged 18–80 years. (2) BMI <28kg/m^2, met the non-obese standard of Chinese population.[15] (3) The subjects completed overnight polysomnography. (4) The abdominal ultrasonography was performed during hospitalization. (5) With completed clinical data. Subjects with infectious disease within 1-month, alcoholic liver disease, liver malignancy, various viral hepatitis or other known chronic liver disease were excluded. Sedatives and naps were prohibited prior to sleep monitoring to minimize the interferences with the results. This study complied with the Declaration of Helsinki. The study design was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University.

All data were collected from electronic medical records. Age, sex, height, weight, neck circumference, waist circumference and Epworth Sleepiness Scale (ESS) were measured at admission. Sleep monitoring was performed using polysomnography respiratory monitoring system (Condi Australia). AHI, mean oxygen saturation (MSaO2), lowest oxygen saturation (LSaO2), the percentage of sleep time with SpO2<90% (T90%) and oxygen desaturation index (ODI) were obtained from the polysomnography monitoring report. Apnea was defined as at least 90% drop in oronasal air flow for at least 10 s. Hypopnea was defined as at least 30% drop in oronasal air flow for ≥10 s associated with ≥4% oxygen desaturation or at least 50% drop in oronasal air flow for ≥10 s associated with ≥3% oxygen desaturation. The diagnosis and severity of OSA were based on 2012 American Academy of Sleep Medicine (AASM) criteria as follows:[16] Without OSA, AHI < 5 events/h; mild-to-moderate OSA, AHI 5.0–29.9 events/h; severe OSA, AHI 30–49.9 events/h; very severe OSA, AHI ≥ 50.0 events/h. Blood routine test, liver function, blood glucose, blood cholesterol, and triglycerides were performed on the next day after Polysomnography in fasting conditions.

Fatty liver disease in the study was diagnosed via the results of abdominal ultrasonography. After excluding the subjects with excessive alcohol consumption, NAFLD was diagnosed. Fibrosis-4 Index (FIB-4) was calculated as following: Age (ys) ×AST (IU/L)/(platelet count (×10^9/L) ×ALT (IU/L) $^{1/2}$). The values of Fib-4 upper than 2.67 were defined as with liver fibrosis.[17] All the subjects with elevated levels of ALT or AST were defined as liver injury. The levels of ALT >40 U/L in males or >31 U/L in females was defined elevated ALT.[18]

Statistical Analysis

After the normality test, continuous variables were described using mean± standard deviation or median (interquartile range) value. Categorical variables were described as percentages. The analysis of variance was used to compare multiple groups of continuous variables. The chi-square test was used to compare categorical variable. Furthermore, binary logistic regression models were built to identify independent risks of NAFLD and liver fibrosis. All statistical analyses were performed using SPSS 22.0. The significance was set at a P value less than 0.05.

Results

A total of 410 subjects were included in this study. The mean age of was 53.0± 14.4 years, and 324 (79%) were male. The median value of BMI was 25.3 (23.7–26.6) kg/m^2. A total of 59 (14%) patients were simple snoring and 351 (86%) patients met the diagnostic criteria of OSA.

The Comparison of the Baseline Characteristics Among Four Groups

The comparison of the baseline characteristics among four groups are shown in Table 1. There were significant differences in age, BMI, neck circumference, waistlines, and sleep related parameters (AHI, ESS score, T90%, LSaO2, MSaO2 and ODI) among patients with simple snoring, mild-moderate, severe and very severe OSA groups (all P<0.05). The levels of triglyceride increased with the aggravation of OSA, while the levels of high-density lipoprotein cholesterol decreased with the aggravation of OSA (both P<0.05), shown in Table 2.

Table 1 The Basic Characteristics and Sleep Parameters of Patients in Four Groups

	Control N=59	Mild-to-Moderate N=190	Severe N=97	Very Severely N=64	P value
Male (%)	40 (68%)	151 (79%)	81 (84%)	52 (81%)	0.096
Age (years)	51.0±15.1	54.3±14.7	55.0±13.22	47.8±12.83	0.006
Hypertension (%)	29 (49.2%)	101 (52.9%)	45 (47.9%)	26 (40.7%)	0.373
Diabetes (%)	6 (9.4%)	8 (13.6%)	38 (19.9%)	14 (14.6%)	0.201
Hyper lipidaemia (%)	4 (6.8%)	23 (12.0%)	16 (16.8%)	10 (15.6%)	0.282
Smoking (%)	12 (20.3%)	60 (31.4%)	28 (28.8%)	20 (31.3%)	0.201
Lipid-lowering therapy (%)	4 (6.8%)	8 (4.2%)	9 (9.3%)	3 (4.7%)	0.355
Neck circumference (cm)	37.0 (34.8–38.5)	38.0 (36.0–40.0)	38.8 (37.0–40.0)	40.0 (37.0–41.0)	<0.001
Waistlines (cm)	90.2 (82.3–95.0)	93.8 (89.0–97.0)	95.0 (90.0–99.5)	96.0 (92.3–102.0)	<0.001
ESS	4 (2–8)	6 (3–9)	8 (4–10)	8 (6–12)	0.009
AHI	3.4 (1.8–3.8)	15.9 (9.7–21.7)	38.3 (33.8–42.6)	62.7 (53.6–71.0)	<0.001
BMI (kg/m^2)	24.1 (22.6–26.1)	25.5 (23.7–26.5)	25.7 (24.2–26.6)	26.2 (24.8–27.0)	0.001
Ts90 (%)	0.1 (0.0–1.1)	2.2 (0.7–8.2)	18.5 (8.1–36.5)	58.7 (28.9–144.1)	<0.001
LSaO2 (%)	88 (84–90)	82 (77–86)	77 (66–81)	66 (65–75)	<0.001
MSaO2 (%)	96 (95–96)	95 (94–96)	93 (92–94)	91 (89–93)	<0.001
ODI	1.9 (1.1–4.0)	9.5 (5.6–14.4)	28.9 (23.0–36.0)	55 (45–65)	<0.001

Notes: Data were presented as n (%), median (IQR) or mean ± standard deviation.
Abbreviations: BMI, body mass index; AHI, apnea-hyponea index; ESS, Epworth Sleepiness Scale; MSaO2, mean oxygen saturation; LSaO2, lowest oxygen saturation; T90%, the percentage of sleep time with SpO2<90%; ODI, oxygen desaturation index.

Table 2 Metabolic Markers and Liver Function Among Four Groups

	Control N=59	Mild-to-Moderate N=190	Severe N=97	Very Severely N=64	P value
Glucose (mmol/l)	4.8 (4.5–5.4)	5.0 (4.5–5.7)	4.9 (4.6–5.6)	4.9 (4.6–5.7)	0.647
SBP (mmHg)	131±15	132±17	132±16	133±12	0.953
DBP (mmHg)	79±10	80±12	80±11	84±10	0.054
HDL (mmol/l)	1.04 (0.89–1.23)	1.03 (0.90–1.23)	1.01 (0.91–1.27)	0.95 (0.84–1.06)	0.006
Triglyceride (mmol/l)	1.3 (0.9–1.8)	1.4 (1.1–2.0)	1.6 (1.0–2.4)	2.1 (1.4–2.7)	<0.001
Cholesterol (mmol/l)	4.3±0.8	4.7±1.0	4.6±1.0	4.6±0.9	0.111
LDL (mmol/l)	2.7±0.7	3.0±0.9	2.9±0.9	2.9±0.9	0.072
Total bilirubin (μmmol/l)	11.4 (7.1–14.8)	11.6 (8.6–15.0)	10.9 (8.5–13.8)	10.9 (8.1–13.7)	0.490
ALT (u/l)	20 (13–30)	24 (17–38)	24 (18–33)	30 (22–42)	<0.001
AST (u/l)	21±7	23±9	23±11	28±18	0.006
ALP (u/l)	72±26	76±35	69±22	67±24	0.091
GGT (u/l)	24 (17–35)	29 (18–55)	27 (19–53)	37 (23–60)	0.002
FiB-4	1.04 (0.8–1.58)	1.01 (0.74–1.41)	1.11 (0.72–1.52)	0.82 (0.62–1.17)	0.019
NAFLD (%)	33 (55.9%)	121 (63.4%)	52 (53.6%)	55 (85.9%)	<0.001
Liver injury (%)	9 (15.3%)	49 (25.8%)	22 (22.7%)	21 (32.8%)	0.050

Notes: Data were presented as n (%), median (IQR) or mean ± standard deviation.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline Phosphatase; GGT, gamma glutamyltransferase; Fib-4, Fibrosis-4 Index; NAFLD, nonalcoholic fatty liver disease.

NAFLD and Liver Fibrosis in Non-Obese OSA

Among non-obese patients with OSA, 17 (5%) were diagnosed with liver fibrosis and 228 (65%) with NAFLD; While in simple snoring group, 0 (0%) liver fibrosis and 33 (56%) NAFLD were diagnosed. Meanwhile, the significant differences of ALT, AST and GGT among all groups were found (all P< 0.05). The lowest values were found in simple snoring group and the highest values were found in severe OSA group. There were no differences in total bilirubin or ALP among all groups. The ratio of liver injury and NAFLD were significantly different among all groups, and the incidence of liver injury and NAFLD was the highest in severe OSA group, shown in Table 2.

The Risk Factor of NAFLD and Fibrosis in Non-Obese OSA

Table 3 shows the correlations between NAFLD, liver fibrosis and the other variables in non-obese OSA patients. BMI, triglyceride, glucose and ODI were significantly correlated with NAFLD (all P<0.05). Age, hypertension history, triglyceride and cholesterol were significantly correlated with liver fibrosis (all P<0.05).

As shown in Table 4, Logistic regression suggested that AHI, BMI and triglyceride were independent predictors for NAFLD in non-obese OSA patients (P<0.05). After adjusting for various confounding factors, AHI was an independent predictor for liver fibrosis in non-obese OSA patients (P<0.05).

Table 3 Spearman's Rank Correlation Coefficients Between NAFLD, Liver Fibrosis and Clinical Characteristics in OSA Patients

	NAFLD		Liver Fibrosis	
	r	p values	r	p values
Male sex	−0.054	0.318	−0.077	0.153
Age (years)	−0.039	0.472	0.227	<0.001
Hypertension	0.075	0.161	0.125	0.019
Diabetes	0.005	0.922	0.010	0.859
Hyperlipemia	0.090	0.093	0.025	0.642
BMI (kg/m^2)	0.318	<0.001	−0.052	0.337
Triglyceride (mmol/l)	0.259	<0.001	−0.166	0.002
Cholesterol (mmol/l)	0.04	0.453	−0.155	0.004
Glucose (mmol/l)	0.124	0.002	0.036	0.508
AHI	0.09	0.092	0.012	0.829
ODI	0.112	0.036	0.016	0.767
LSaO2	−0.029	0.592	−0.088	0.100

Abbreviations: BMI, body mass index; AHI, apnea-hyponea index; ODI, oxygen desaturation index; LSaO2, lowest oxygen saturation; NAFLD, nonalcoholic fatty liver disease.

Table 4 Logistic Regression Analysis of NAFLD and Liver Fibrosis in OSA Patients

	NAFLD		Liver Fibrosis	
	OR (95% CI)	p values	OR (95% CI)	p values
Age	–		1.11 (1.05–1.17)	<0.001
Sex	–		0.14 (0.02–1.23)	0.075
BMI	1.13 (1.01–1.27)	0.032	1.03 (0.81–1.30)	0.818
Triglyceride	1.13 (1.12–1.99)	0.006	0.33 (0.11–0.99)	0.050
Cholesterol	1.07 (0.84–1.37)	0.571	0.71 (0.39–1.39)	0.352
Glucose	1.02 (0.89–1.12)	0.721	0.80 (0.50–1.27)	0.340
AHI	1.02 (1.00–1.03)	0.046	1.04 (1.00–1.07)	0.045

Abbreviations: BMI, body mass index; AHI, apnea-hyponea index; NAFLD, nonalcoholic fatty liver disease.

Discussion

This study showed that the incidence of NAFLD and liver fibrosis was high in non-obese OSA patients. AHI is an independent risk factor for NAFLD and liver fibrosis in non-obese OSA patients.

The correlation between OSA and liver injury has attracted more and more attention. Some studies suggested that OSA-related intermittent hypoxia was an independent risk factor for liver enzyme elevation in addition to confounding factors such as obesity.[19,20] Although NAFLD is commonly associated with obesity, non-obese individuals has gradually attracted the attention of researchers.[21,22] It was reported that around 40% of the global NAFLD population was classified as non-obese. In our study, 65% non-obese OSA patients had NAFLD, the incidence was higher than that of the control group (56%). Especially in very severe non-obese OSA patients, the incidence of NAFLD reached 86%.

In previous study, liver enzymes did not increase with the aggravating of OSA in non-obese OSA patients.[23] This is different from the results of our study. The levels of ALT, AST and GGT elevated in OSA patients in our study, especially in very severe OSA patients. The differences may be related to the small sample size of previous study, only 106 cases. Furthermore, in this study, the very severe subgroup was separated from the severe OSA patients. The increased liver enzyme and incidence of liver injury in very severe group supported that severe intermittent hypoxia was an important cause of liver injury.

For non-obese OSA patients, AHI and hypertriglyceridemia were independent risk factors for NAFLD. Previous studies found that insulin resistance was more commonly in non-obese NAFLD patients than in healthy subjects.[22] Insulin resistance and dysfunctional lipid metabolism were common complications of OSA.[24,25] Furthermore, a twin study showed the OSA and hypertriglyceridemia shared common genetic background; Excluding the confounding effects of obesity, genetically increased triglyceride levels increased the risk of OSA.[26,27] So, we speculated that genetic background and intermittent hypoxia-associated lipid metabolism disorders and insulin resistance may be responsible for NAFLD in non-obese OSA individuals. This finding suggested that obesity should not be the screening criterion for NAFLD in OSA patient. Even lean patients with severe OSA should be screened for NAFLD.

In the study, the diagnosis of liver fibrosis was based on Fib-4, a non-invasive indicator. A 2.67 was used as the cut-off value of Fib-4.[28] Age is one of the variables used to calculate this index. In this study, the younger average ages in very severe OSA patients may lead to the lower Fib-4 value. The diagnostic value of Fib4 still lagged behind that of invasive tests such as liver biopsy. As a result, a more reliable method to diagnose liver fibrosis should be explored in future studies.

This study had some limitation: (1) The nature of this retrospective study might compromise the conclusion. (2) Fatty liver, liver injury and liver fibrosis were diagnosed by non-invasive methods. It may affect the reliability of research conclusions.

In conclusion, NAFLD and liver fibrosis was common in non-obese OSA patients. AHI was an independent risk factor for NAFLD and liver fibrosis in non-obese OSA patient. Intense monitoring and evaluation of liver function in non-obese patients with severe OSA should be considered.

Data Sharing Statement

Data is available on request from the correspondence author.

Author Contributions

Ningfang Lian designed the study and revised the manuscript, Jiawei Wu analyzed the data and prepared the manuscript, Jiefeng Huang and Jia Chen collected the data and performed manuscript drafting, Biying Wang searched the literature, analyzed the data and revised the manuscript, Su Lin analyzed the data and revised the manuscript, Qichang Lin designed the study, reviewed the results and made critical comments on the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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