

Elevated Serum Liver Enzymes in Patients with Obstructive Sleep Apnea-hypopnea Syndrome

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Abstract

Background: Obstructive sleep apnea-hypopnea syndrome (OSAS) is associated with elevated liver enzymes and fatty liver. The purpose of this study was to measure serum liver enzyme levels in patients evaluated by polysomnography (PSG) and the factors associated with liver injury in OSAS patients.

Methods: All patients referred to PSG for evaluation of sleep apnea symptoms between June 2011 and November 2014 were included in this study. Demographic data and PSG parameters were recorded. Serum alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase levels were systematically measured. OSAS patients were divided into mild, moderate, and severe groups according to the apnea-hypopnea index (AHI) values of 5–14 events/h, 15–29 events/h, and ≥ 30 events/h.

Results: A total of 540 patients were enrolled in this study; among these patients, 386 were male. Elevated liver enzymes were present in 42.3% of OSAS patients (32.4% in mild/moderate group; 51.0% in severe group) and 28.1% patients without OSAS. Patients with OSAS had higher body mass index (BMI) ($P < 0.01$). In the bivariate correlation, the liver enzymes level was negatively correlated with age and the lowest arterial oxygen saturation (SaO₂), and was positively correlated with BMI, oxygen desaturation index, percent of total time with oxygen saturation level $< 90\%$ (TS90%), AHI, total cholesterol (TC), and triglyceride (TG). In logistic regression analysis, Age, BMI, TS90%, TC, and TG were included in the regression equation.

Conclusions: Our data suggest that OSAS is a risk factor for elevated liver enzymes. The severity of OSAS is correlated with liver enzyme levels; we hypothesize that hypoxia is one of main causes of liver damage in patients with OSAS.

Key words: Hypoxia; Liver Enzyme; Obstructive Sleep Apnea

INTRODUCTION

Obstructive sleep apnea-hypopnea syndrome (OSAS) is a common medical condition characterized by repetitive episodes of upper airway collapse during sleep. These episodes are associated with varying degrees of arterial oxygen desaturation and brain arousals leading to excessive daytime sleepiness and fatigue. According to epidemiological studies, the prevalence of OSAS is 4% in adults and up to 45% in obese individuals.^[1,2] These studies have shown that OSAS is not only associated with metabolic syndrome but also is an independent risk factor for cardiovascular and cerebrovascular diseases.

Recent studies have also reported that OSAS is strongly associated with elevated liver enzymes and fatty liver.^[3-6] However, whether OSAS is an independent risk factor

for liver injury is uncertain. Some studies have reported that OSAS is associated with elevated serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels.^[4,7-13] Most of these studies enrolled only morbidly obese patients, and some of them used ambulatory polygraphic monitoring or nocturnal oximetric recording.^[4,8] The discrepancy among these studies may be due to the small sample sizes or different inclusion criteria.

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The purpose of this study was to measure the level of serum liver enzymes including ALT, AST, and gamma-glutamyl transferase (GGT) in subjects with various weights and determine the relationship between OSAS and elevated liver enzymes. Our study analyzed data from a larger sample population. All patients in this study were evaluated with polysomnography (PSG).

METHODS

Subjects

A total of 575 patients who underwent PSG for suspected OSAS from June 2011 to November 2014 in Sleep Center at the Second Affiliated Hospital of Soochow University were enrolled in this study. Patients who had undergone PSG or received therapy for OSAS were not enrolled in this study. Exclusion criteria were as follows: Severe diseases in circulation, respiratory, central nervous, or digestive systems; alcohol intake >20 g/d for males and >10 g/d for females; regular use of hepatotoxic drugs; or evidences of hepatitis. From our initial enrollment, 17 patients with no liver enzymes tests, 6 patients with hepatitis B, 9 patients with chronic obstructive pulmonary disease, 2 patients with renal failure, and one patient with myocarditis were ruled out this study. After excluding these patients, 540 patients remained in our study. All patients provided their informed consent, and the approval for this study was obtained from the Research Ethics Committee of the Second Affiliated Hospital of Soochow University.

Polysomnography

All subjects underwent overnight PSG lasting more than 7 h. PSG was performed with an E-Series System (Compumedics Propriety Limited, Australia). During PSG, various body functions were monitored by electroencephalogram, submental electromyogram, electrooculogram, nasal and oral airflow utilizing both thermistor and nasal-pressure technologies, respiratory inductance plethysmography, pulse oximetry, electrocardiography, and bilateral lower extremity electroencephalogram. Body posture was also monitored. All data were analyzed 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*.^[14] Apnea was defined as the complete cessation of airflow lasting ≥ 10 s. Hypopnea was defined as a 30% or greater reduction in airflow or respiratory effort lasting ≥ 10 s accompanied by a 4% or greater desaturation. Hypopnea was also defined as a 50% or greater reduction in airflow or respiratory effort lasting ≥ 10 s accompanied by a 3% or greater desaturation or micro-arousal. Obstructive sleep apnea was defined as the absence of airflow with continued chest wall and abdominal movement for at least two breaths. The apnea-hypopnea index (AHI) was defined as the number of apneic and hypopneic episodes per hour of monitoring. The oxygen desaturation index (ODI) was defined as the total number of episodes of oxyhemoglobin desaturation $\geq 4\%$ from the immediate baseline lasting ≥ 10 s but < 3 min divided by total sleep time. The lowest arterial

oxygen saturation (SaO_2) (L-SaO_2) and the percentage of total time with oxygen saturation level $< 90\%$ (TS90%) at night were calculated. All studies were scored by a registered polysomnographic technician who was blinded to the results of the liver enzyme tests.

Demographic data and laboratory tests

We collected the demographic data including past medical history of hypertension, diabetes mellitus, dyslipidemia, and medications. The doctor who collected these data was blinded to the liver enzyme 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. Subjects were dressed in normal indoor clothing and without shoes during measurements.

Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2). Obesity was defined as a BMI ≥ 28 kg/m^2 , and overweight was defined as a BMI ≥ 24 kg/m^2 .^[15]

Blood pressure was measured at the end of PSG monitoring between 6 and 7 a.m. when patient was awake on the bed. A mercury sphygmomanometer was used. Hypertension was defined as systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg.

Fasting blood was drawn from the median cubital vein and centrifuged at 3000 r/min for 10 min. The serum was analyzed with an Au5400 automatic biochemical analyzer (Olympus Corporation, Japan) for liver enzymes, glucose, and lipids. Dyslipidemia was diagnosed if the patients were received antihyperlipidemic drug treatment or had a triglyceride (TG) level of > 1.7 mmol/L and/or total cholesterol (TC) level of > 5.72 mmol/L. Patients were considered to have diabetes mellitus if they had a fasting blood glucose level of ≥ 7.1 mmol/L or ≥ 11.1 mmol/L at any time. The upper limit normal values for ALT, AST, and GGT were 43 U/L, 38 U/L, and 50 U/L, respectively. Aminotransferase values were categorically recorded as normal or elevated. Patients with elevated liver enzymes were defined as those with at least one elevated enzyme value.

Grouping

Based on the *American Academy of Sleep Medicine criteria*, OSAS was categorized as mild, moderate, or severe according to AHI values of 5–14 events/h, 15–29 events/h, and ≥ 30 events/h. Mild and moderate OSAS patients were grouped together.

Statistical analysis

All data were analyzed with Statistical Product and Service Solutions (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA). Participants were categorized into three groups: Non-, mild/moderate-, and severe-OSAS. Clinical characteristics were presented according to these three groups. Continual variables were expressed as mean \pm standard deviation (SD). Comparisons among the three groups were performed using an analysis of variance test and comparisons between two groups were computed

by Student–Newman–Keuls test. Distribution of categorical variables was expressed as percentage. Comparisons in rates among three groups were performed using the Chi-square test and comparisons between each two groups were performed using the partition of Chi-square test. Liver enzymes were nonnormal distribution, so it was expressed as median (range). Liver enzymes were compared among and between each of the three groups using a rank test. Also, correlations between PSG parameters, age, BMI, blood lipids, and liver enzymes levels were assessed using bivariate correlation analysis. The following risk factors: Age, Epworth Sleepiness Scale (ESS) score, BMI, L-SaO₂, TS90%, ODI, AHI, TC, and TG were analyzed using binary logistic regression for the presence of elevated serum liver enzymes (liver enzymes were considered as a multcategory variable). Differences were considered as statistically significant if the *P* value was <0.05.

RESULTS

Patient characteristics and polysomnographic parameters

A total of 540 patients were included in the study, 386 of them were male. The mean age was not significantly different in non-OSAS group, mild/moderate-OSAS group, and severe-OSAS group. Gender distribution was not significantly different between the non-OSAS group and mild/moderate-OSAS groups, but the percentage of male patients in the severe-OSAS group was higher than that in other groups.

Elevated liver enzymes were present in 42.3% of patients with OSAS. Elevated GGT was present in 40.3% of OSAS patients, which was significantly higher than in patients without OSAS (*P* < 0.001). Elevated AST was present in 8.3%

of the patients with OSAS and was not significantly different from the patients without non-OSAS (8.4%, *P* = 0.971). Elevated AST was present in 12.0% of the patients with severe OSAS and was significantly higher than that in the patients with mild/moderate OSAS (4.1%, *P* = 0.007).

The levels of TC and TG in patients with elevated serum liver enzymes were 4.8 ± 1.2 mmol/L and 2.3 ± 1.6 mmol/L, which were higher than those in patients without elevated serum liver enzymes (*P* < 0.001).

The mean ESS in OSAS patients was 8.7 ± 5.1, which was significantly higher than that in patients without OSAS (6.1 ± 4.8, *P* < 0.001). AHI, ODI, and TS90% in patients with OSAS were significantly higher than in patients without OSAS (*P* < 0.001). L-SaO₂ was lower in OSAS patients than that in non-OSAS patients (*P* < 0.001) [Table 1].

Level of liver enzymes

The level of ALT and GGT in patients with OSAS was significantly higher than those in patients without OSAS (*P* < 0.001). AHI values were positively correlated with ALT and GGT levels. The AST levels were not significantly different in non-OSAS, mild/moderate OSAS, and severe OSAS patients [Table 2].

Influence of liver enzymes

In the bivariate correlation, we analyzed the relationship between ALT, AST, GGT levels and age, BMI, ESS, ODI, TS90%, L-SaO₂, AHI, TC, and TG. The ALT, AST, and GGT levels were negatively correlated with age and L-SaO₂ and positively correlated with TC, TG, BMI, ODI, TS90%, and AHI. The ALT and AST level was positively correlated with ESS [Table 3].

Table 1: Demographic, clinical characteristics and polysomnographic parameters in patients according to the presence of OSAS and its severity

Parameters	Non-OSAS	Mild/moderate OSAS	Severe OSAS	<i>P</i>
Subjects, <i>n</i>	178	170	192	
Male gender, <i>n</i> (%)	107 (60.1)	115 (67.6)	164 (85.4)*†	<0.001
Age (years), mean ± SD	58.4 ± 14.4	58.6 ± 13.6	55.9 ± 15.0	0.140
BMI (kg/m ²), mean ± SD	23.2 ± 3.4	25.4 ± 3.5‡	28.1 ± 5.4‡§	<0.001
SBP (mmHg), mean ± SD	129.1 ± 20.2	135.6 ± 19.8‡	138.7 ± 18.7‡	<0.001
DBP (mmHg), mean ± SD	84.7 ± 10.9	88.1 ± 10.2‡	92.2 ± 11.3‡§	<0.001
Hypertension, <i>n</i> (%)	97 (54.5)	109 (64.1)	153 (79.7)*†	<0.001
Diabetes mellitus, <i>n</i> (%)	10 (5.6)	22 (12.9)	46 (24.0)*†	<0.001
Dyslipidemia, <i>n</i> (%)	64 (36.0)	78 (45.9)	103 (53.7)*	0.003
Elevated ALT, <i>n</i> (%)	18 (10.1)	17 (10.0)	47 (24.5)*†	<0.001
Elevated AST, <i>n</i> (%)	15 (8.4)	7 (4.1)	23 (12.0)†	0.026
Elevated GGT, <i>n</i> (%)	44 (24.7)	52 (30.6)	94 (49.0)*†	<0.001
Elevated liver enzymes, <i>n</i> (%)	50 (28.1)	55 (32.4)	98 (51.0)*†	<0.001
ESS, mean ± SD	6.1 ± 4.8	7.1 ± 4.7	10.1 ± 5.8‡§	<0.001
AHI (events/h), mean ± SD	1.3 ± 0.5	15.3 ± 7.4‡	57.0 ± 19.0‡§	<0.001
L-SaO ₂ (%), mean ± SD	89.0 ± 13.8	84.9 ± 5.5‡	74.3 ± 12.0‡§	<0.001
TS90% (%), mean ± SD	1.6 ± 0.9	3.7 ± 1.4	22.5 ± 3.0‡§	<0.001
ODI (episodes/h), mean ± SD	1.8 ± 1.1	12.9 ± 8.0‡	52.4 ± 33.0‡§	<0.001

*Compared with non-OSAS, *P* < 0.05; †Compared with mild/moderate OSAS, *P* < 0.05; ‡Compared with non-OSAS, *P* < 0.05; §Compared with mild/moderate OSAS, *P* < 0.05. OSAS: Obstructive sleep apnea-hypopnea syndrome; BMI: Body mass index; SBP: Systolic blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ESS: Epworth Sleepiness Scale; AHI: Apnea-hypopnea index; L-SaO₂: The lowest SaO₂; TS90%: Percentage of total time with oxygen saturation level <90%; ODI: Oxygen desaturation index.

Table 2: The level of liver enzymes (mmol/L) in patients according to the presence of OSAS and severity

Liver enzymes	Non-OSAS	Mild/moderate OSAS	Severe OSAS	P
ALT	18.0 (3.0–250.0)	19.0 (5.0–399.0)	26.0 (7.0–179.0)*†	<0.001
AST	21.0 (9.0–115.0)	19.0 (7.0–126.0)	20.0 (9.0–113.0)	0.101
GGT	21.0 (6.0–594.0)	23.0 (5.0–198.0)	33.0 (7.0–339.0)*†	<0.001

Data were expressed as vaules (normal range). *Compared with non-OSAS, $P<0.05$; †Compared with Mild/Moderate OSAS, $P<0.05$. OSAS: Obstructive sleep apnea-hypopnea syndrome; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

In the logistic regression analysis, age, BMI, TS90%, TC, and TG were included in the regression equation. The equation was $Y = -5.073 - 0.019 \times \text{age} + 0.098 \times \text{BMI} + 0.023 \times \text{TS90\%} + 0.191 \times \text{TC} + 0.320 \times \text{TG}$.

DISCUSSION

Our data indicated that OSAS was associated with hypertension, diabetes mellitus, obesity, and dyslipidemia. The percentages of patients with hypertension and diabetes mellitus were higher in the severe OSAS group than that in the other groups. Hypertension was present in 72.4%, dyslipidemia in 50%, and diabetes mellitus in 18.8% of OSAS patients. From these findings, we inferred that blood pressure was more easily affected by OSAS. These results were different from those obtained in previous studies.^[4,7,13]

Jouët *et al.* found that in 62 morbidly obese patients undergoing bariatric surgery, elevated liver enzymes including ALT, AST, and GGT were present in 25%, 42.9%, and 52.8% of non-, moderate-, and severe-OSAS patients, respectively.^[4] Another study performed on OSAS patients found elevated liver enzymes in 8.6%, 18%, and 32% of non-, moderate-, and severe-OSAS patients, respectively.^[16] We attribute the difference between these results and those in our study to the small sample sizes and different selection criteria used in the prior studies. Compared to previous studies, the number of subject is relatively larger in this study. In addition, our study did not exclude nonobese patients, which made our sample more representative of the general population.

In our study, elevated liver enzymes were present in 42.3% of the OSAS patients, which was 14% higher than that in patients without OSAS. Our data showed that the severity of OSAS was positively correlated with the prevalence rate of elevated liver enzymes (51% in the severe-OSAS group, 32.4% in the mild/moderate OSAS group). A meta-analysis demonstrated that 13.3% of the patients with OSAS had elevated ALT levels and 4.4% of patients with OSAS had elevated AST levels.^[17] Byrne *et al.* found that elevated ALT levels were present in 31% of the patients with OSAS.^[3] Our study found that 16.7% of the OSAS patients had elevated ALT levels, which was similar to the results in the meta-analysis. Our results may have differed from those in Byrne's study because we defined OSAS as AHI >5/h, whereas OSAS was defined as AHI >10/h in Byrne's study. We also found that elevated GGT was present more often in OSAS patients than in non-OSAS patients, which suggests that GGT is affected by OSAS. Both ALT and GGT levels were higher in patients with severe OSAS than in those

Table 3: Correlation analysis of liver enzymes with polysomnographic parameters, BMI and age

Parameters	ALT		AST		GGT	
	r	P	r	P	r	P
Age	-0.266	<0.001	-0.156	<0.001	-0.185	<0.001
BMI	0.277	<0.001	0.234	<0.001	0.210	<0.001
ESS	0.132	0.003	0.128	0.004	0.079	0.077
ODI	0.157	<0.001	0.117	0.007	0.137	0.002
TS90%	0.195	<0.001	0.153	<0.001	0.147	0.001
L-SaO ₂	-0.179	<0.001	-0.127	0.003	-0.101	0.02
AHI	0.206	<0.001	0.138	0.001	0.125	0.004
TC	0.119	0.006	0.144	0.001	0.198	<0.001
TG	0.203	<0.001	0.198	<0.001	0.354	<0.001

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; BMI: Body mass index; ESS: Epworth Sleepiness Scale; L-SaO₂: The lowest SaO₂; TS90%: Percentage of total time with oxygen saturation level <90%; ODI: Oxygen desaturation index; AHI: Apnea-hypopnea index; TC: Total cholesterol; TG: Triglyceride.

without OSAS, especially GGT levels which were 12 mmol/L higher. Our results suggest that OSAS has a greater impact on the GGT level than it does on the other enzymes.

The meta-analysis found that the association between OSAS and elevated ALT levels is related to sex-independent of BMI and diabetes mellitus.^[17] Mishra *et al.* found that the frequent nocturnal hypoxic episodes in morbidly obese patients with OSAS may be a risk factor for developing steatohepatitis and hepatic fibrosis and that nadir oxygen saturation is independently associated with nonalcoholic steatohepatitis in the subset of nonalcoholic fatty liver disease subjects with OSAS.^[18] However, Daltro *et al.* found that the elevated ALT and AST levels are independent of AHI, the lowest pulse oxygen saturation, and TS90%.^[9] In our result, we found that younger patients had higher liver enzymes levels. This may be because younger patients' alcohol intake is higher than that of older patients in our study but not high enough to meet exclusion criteria. In addition to obesity and high levels of TC and TG, intermittent hypoxic episodes and hypersomnia may elevate the liver enzymes level. Finally, BMI, age, TS90%, TC, and TG were included in the regression equation. Therefore, we concluded that obesity, age, blood lipids, and hypoxia are major risk factors for elevated liver enzymes. Our data also showed that the duration of hypoxia had a greater impact on liver enzymes than the severity of hypoxia.

We speculated the mechanisms for liver injury from hypoxia are based on metabolic changes triggered by the hypoxia.

Liver hypoxia, reoxygenation, and catecholamine-mediated systemic metabolic changes cause metabolic changes in the liver, such as mitochondrial anaerobic respiration. Liver biopsies in nonalcoholic fatty liver disease patients showing mitochondrial changes support this hypothesis.^[19] Similarly, intermittent hypoxia promotes oxidative stress in and damage to the liver.^[20] A previous study has shown that hypoxia acts as a major stimulus of angiogenesis and fibrogenesis, particularly by the activation of hypoxia-inducible factor-1 α and vascular endothelial growth factor signaling pathways^[21] or by inducing migration of activated hepatic stellate cells.^[22]

This study has a few limitations. The research was the retrospective study. We did not obtain liver enzyme levels after OSAS treatment and liver histology for the patients.

In conclusion, OSAS is a risk factor for elevated liver enzymes. The duration of hypoxia had a greater impact on liver enzymes than the degree of hypoxia. We hypothesize that hypoxia is one of the main causes of liver damage in patients with OSAS. Because monitoring liver function through enzyme levels involves only routine venipuncture, we recommend routine screening in patients with OSAS.

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Conflicts of interest

There are no conflicts of interest.

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