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# Liver functions in patients with obstructive sleep apnea syndrome

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## ABSTRACT

**Objectives:** Objective. Previous studies showed that obstructive sleep apnea syndrome (OSAS) was associated with liver diseases such as elevated liver enzyme levels and hepatic steatosis. The aim of this study was to assess the relationship between serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and OSAS and its severity.

**Methods:** A total of 617 patients who underwent PSG (polysomnography) between January 2016 and May 2017 were evaluated in this study. AST, ALT, total cholesterol, triglyceride levels and body mass index were analyzed. The data were analyzed using the Student's t-test, ANOVA, Chi-square test, and Pearson's correlation coefficient.

**Results:** Five hundreds and thirty patients with OSAS and 60 healthy controls were included in the study. Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level. There was a statistically significant difference in ALT and AST levels between the OSAS and control groups ($p < 0.001$ and $p < 0.001$, respectively). In the OSAS group, there was a statistically significant positive relationship between serum ALT and AST levels and apnea-hypopnea index (AHI), apnea index, oxygen desaturation index. Both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients ($p < 0.001$ and $p < 0.001$, respectively). ALT level was statistically significantly higher in patients without hypertension than in patients with hypertension ($p < 0.001$). In OSAS patients without hypertension, there was a statistically significant relationship between serum ALT and AST levels and AHI (r =0.223, $p < 0.001$ and r =0.142, $p = 0.007$; respectively).

**Conclusion:** OSAS is a risk factor for elevated liver enzyme levels. Hypoxia plays an important role on liver enzymes in OSAS patients.

**Keywords:** Liver enzymes, obstructive sleep apnea syndrome, hypertension

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Obstructive sleep apnea syndrome (OSAS) is a clinical condition that occurs when the upper airway collapses during sleep and repeatedly stops breathing for brief moments. Breathing is fully and partially blocked [1]. The prevalence of OSAS is estimated to be 3-7% among males and 2-5% among females [2]. OSAS is accompanied by a variety of metabolic abnormalities such as insulin resistance, hypertension, obesity, and liver diseases [3]. The sympathetic nervous system activation and hypoxia

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due to apnea/hypopnea and the oxidative stress due to reoxygenation are the main causes of cardiovascular and metabolic events for OSAS [4]. Hepatic steatosis can manifest itself with asymptomatic elevation of liver enzymes, although liver biopsy is required for the diagnosis of liver diseases. Although the pathogenesis of hepatic steatosis is not clear, obesity and insulin resistance have been found to be associated with hyperlipidemia and hypertension [5].

A previous study found that high body mass index (BMI) and presence of OSAS were independently associated with an elevation in serum aminotransferase levels [6]. A study conducted in mice demonstrated the effect of chronic intermittent hypoxia-induced oxidative stress on the liver [7]. In studies, it was found that OSAS was associated with some liver diseases such as elevated liver enzyme levels and hepatic steatosis. However, it is debatable whether OSAS is an independent risk factor for liver damage [8]. Serum AST and ALT levels are the most commonly used markers for screening fatty liver disease. Some studies found that serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated in patients with OSAS. The aim of this study was to evaluate serum ALT and AST levels in OSAS patients and to determine the relationship between OSAS severity and liver enzymes.

## METHODS

A total of 617 patients who underwent polysomnography (PSG) between January 2016 and May 2017 were evaluated in this study. Patients who had chronic pulmonary disease, renal disease, liver disease and who drank more than 20 g of alcohol per day and who received hepatotoxic drugs were excluded. Seven patients were excluded because they had COPD and liver disease. Twenty patients were excluded because their liver enzyme levels could not be reached. Finally, 590 patients were included in the study. Additional diseases (Diabetes mellitus, hypertension), age, gender, and BMI were recorded from patient files. AST, ALT, glucose, total cholesterol, and triglyceride levels were evaluated by analyzing routine blood samples. The upper limit was taken as 38 for AST and 41 for ALT.

Overnight polysomnographic recordings were taken from the patients using a video camera. Sleep and physiological variables were monitored with a Grass PSG device. 10-channel electroencephalography, submental electromyography (EMG), right and left eye electrooculography, electrocardiography, oronasal airflow (thermal sensor and nasal pressure transducer), body position, thoracic and abdominal motion sensor (inductance plethysmography), measurement of arterial blood oxygen saturation using finger pulse oximetry, and left and right leg motion sensors (EMG) were used. Apnea was defined as a ≥ 90% decrease in airflow signal for ≥ 10 sec. At least 90% of the event's duration must meet the amplitude reduction criteria for apnea. Obstructive apnea was defined as the absence of breathing for 10 seconds or more, despite an effort to breathe. Central apnea was defined as the absence of airflow and respiratory effort lasting for at least 10 seconds. Mixed apnea was defined as a lack of respiratory effort during the initial apneic period followed by gradually increasing effort against an occluded upper airway. Hypopnea was defined as an airflow decrease of ≥ 30% compared with the baseline for at least 10 s plus oxygen desaturation ≥ 3. At least 90% of the event's duration must meet the amplitude reduction criteria for hypopnea. OSAS was categorized into severity levels of mild (apnea-hypopnea index [AHI]: 5-14.9 events/h), moderate (AHI: 15-29.9 events/h), and severe (AHI: ≥ 30 events/h). The patients were divided into mild-moderate OSAS group (Group 1) and severe OSAS group (Group 2). The patients with AHI < 5 were considered as a control group.

### Statistical Analysis

The SPSS 20.0 statistical software package was used for the statistical analysis of data. The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. For normally distributed continuous variables, the Independent t-test was used for comparing the means of two groups, and the one-way ANOVA was used for comparing the means of multiple groups. If the ANOVA result was significant, the Dunnett's and Tukey's multiple comparison tests were used to determine which group caused the difference. While the Dunnett's test was used in paired

**Table 1.** Demographic, clinical, and polysomnographic parameters of obstructive sleep apnea syndrome and control groups

| | OSAS | Control | *p* value |
|---|---|---|---|
| **Age (years)** | 49 ± 12 | 48 ± 10 | > 0.05 |
| **Male (gender)** | 64% | 51.7% | > 0.05 |
| **BMI (kg/m2)** | 31.63 ± 5.5 | 30.76 ± 5.3 | > 0.05 |
| **AHI (events/h)** | 32.6 ± 25.8 | 2.4 ± 1.4 | < 0.0001 |
| **AI (events/h)** | 20.1 ± 25 | 3.5 ± 1.5 | < 0.0001 |
| **ODI** | 27.6 ± 24.1 | 4.6 ±3.1 | < 0.0001 |
| **TS90%** | 16.9 ± 24.5 | 4.5 ± 3.1 | < 0.0001 |
| **Minimum saturation (%)** | 80.5 ± 9.4 | 89 ± 3.7 | < 0.0001 |
| **SO2 (%)** | 92.5 ± 3.9 | 94.7 ± 2.1 | < 0.0001 |
| **Glicose (mg/dl)** | 113 ± 35.2 | 102 ± 22.4 | < 0.001 |
| **Total cholesterol (mg/dl)** | 217.4 ± 45.1 | 205.9 ± 40.1 | > 0.05 |
| **Triglyceride (mg/dl)** | 162.6 ± 85.7 | 141.3 ± 76.4 | > 0.05 |
| **LDL (mg/dl)** | 140 ± 38.3 | 132.3 ± 35.2 | > 0.05 |
| **HDL (mg/dl)** | 45.4 ± 11 | 45.2 ± 12.2 | > 0.05 |
| **AST level** | 25.1 ± 11.9 | 20.4 ± 5.8 | < 0.0001 |
| **ALT level** | 30 ± 20.2 | 21.1 ± 10.3 | < 0.0001 |

AI = apnea index, AHI = apnea-hypopnea index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HDL = high density lipopretein, LDL = low density lipoprotein, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome, $SO_2$= oxygene saturation, TS90% = percent of total time with oxygen saturation level < 90%

comparisons according to the control group, the Tukey's test was used in the comparison of other groups with each other. The relationship between two continuous variables was assessed by the Pearson's test. The Chi-square test was used for the statistical evaluation of categorical variables. While categorical variables were expressed as frequency and percentage, continuous variables were expressed as mean±standard deviation. The risk factors (age, sex, BMI) were analyzed by using lineer regression analysis. A value of $p < 0.05$ was considered statistically significant.

## RESULTS

Five hundreds and thirty patients with OSAS and 60 healthy controls were included in the study. The mean age of the OSAS group was 49 ± 12 years, and the mean age of the control group was 48 ± 10 years. Demographic data are given in Table 1.

Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level. Of the patients in Group 1, 15.8% had an elevated ALT level and 6.3% had an elevated AST level. Of the patients in Group 2, 20.7% had an elevated ALT level and 10.3% had an elevated AST level ($p < 0.05$).

ALT and AST levels were statistically significantly higher in the OSAS group compared to the control group ($p < 0.001$ and $p < 0.001$, respectively). There was a statistically significant difference in AST and ALT levels in Groups 1 and 2 ($p = 0.028$ and $p = 0.006$, respectively) (Table 2).

**Table 2**. The level of liver enzymes according to obstructive sleep apnea syndrome severity

| | Mild-moderate OSAS (Group 1 = 317) | Severe OSAS (Group 2 = 213) | *p* value |
|---|---|---|---|
| AST | 24.1 ± 11.7 | 26.5 ± 12.2 | 0.028 |
| ALT | 28 ± 19.3 | 33 ± 21.1 | 0.006 |

ALT = alanine aminotransferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase

**Table 3**. Correlation of liver enzymes with polysomnographic parameters, age, and body mass index

| | AST | | ALT | |
|---|---|---|---|---|
| | **r** | ***p* value** | **r** | ***p* value** |
| **Age** | -0.136 | 0.002 | -0.240 | <0.0001 |
| **BMI** | 0.116 | 0.008 | 0.125 | 0.004 |
| **AHI** | 0.114 | 0.009 | 0.165 | <0.0001 |
| **AI** | 0.098 | 0.023 | 0.156 | <0.0001 |
| **ODI** | 0.117 | 0.007 | 0.172 | <0.0001 |

AI = apnea index, AHI = apnea-hypopnea index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, ODI = oxygen desaturation index

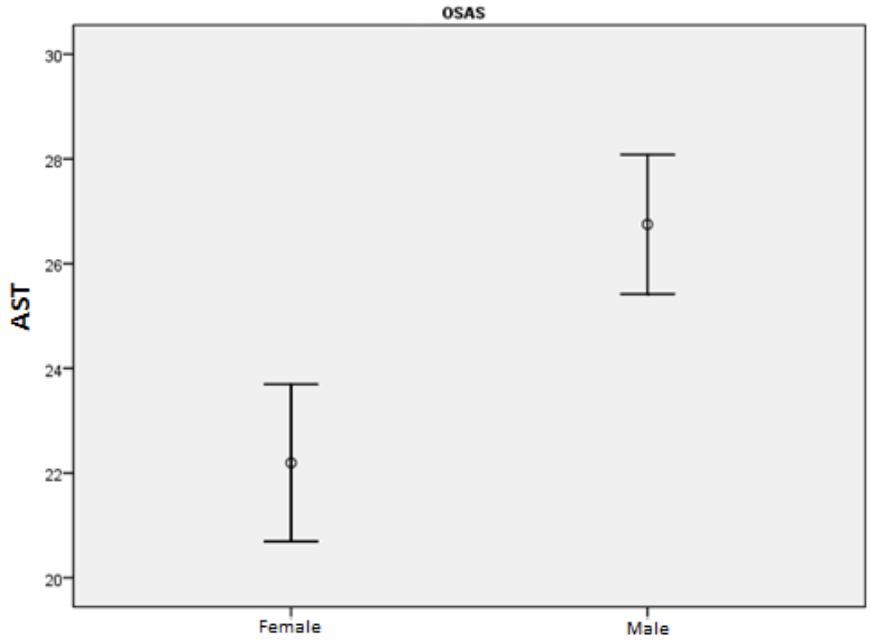


**Figure 1**. The difference of AST levels between male and female (AST = aspartate aminotransferase).

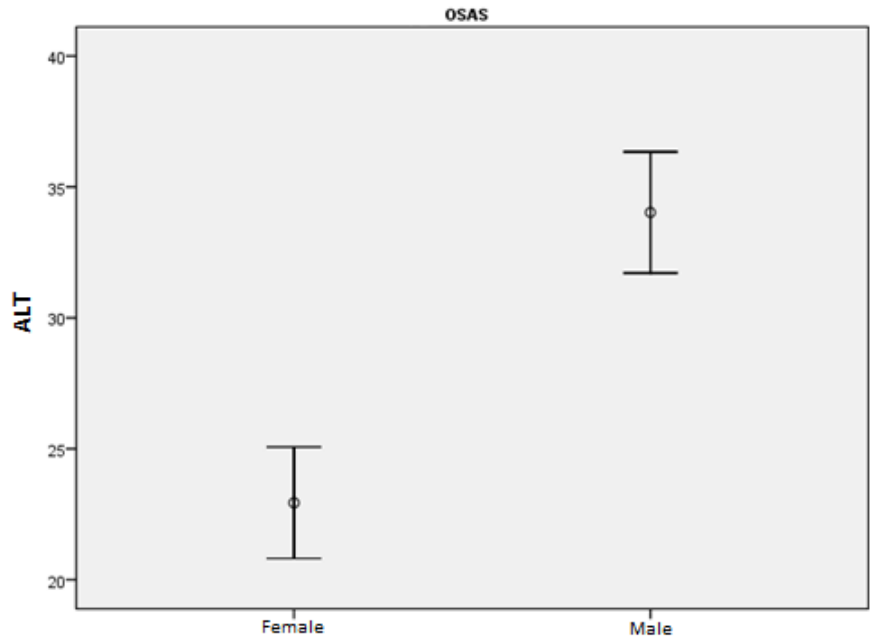


**Figure 2.** The difference of ALT levels between male and female (ALT = alanine aminotransferase).

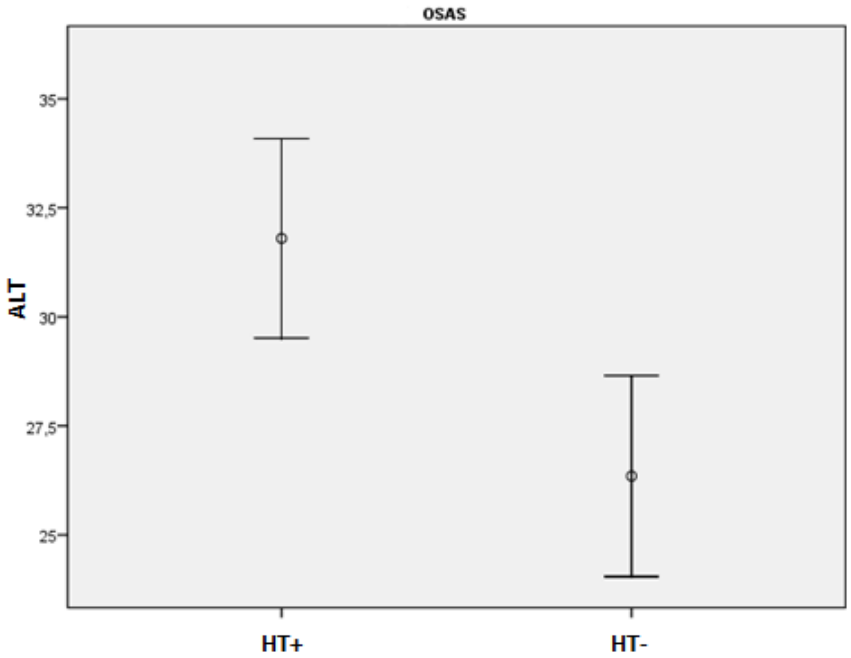


**Figure 3.The** difference of ALT levels in OSAS patients with hypertension and without hypertension (ALT = alanine aminotransferase, HT = hypertension, OSAS = obstructive sleep apnea syndrome).

In the OSAS group, there was a statistically significant difference in AST and ALT levels between genders. Both AST and ALT levels were statistically significantly higher in male patients than in female patients ($p < 0.001$ and $p < 0.001$, respectively) (Figures 1 and 2).

In the OSAS group, there was a statistically significant positive relationship between serum ALT and AST levels and AHI, apnea index, oxygen desaturation index. In the OSAS group, serum ALT and AST levels showed a statistically significant negative relationship with age and a statistically significant positive relationship with BMI (Table 3).

In the OSAS group, there was a statistically significant difference between those with ALT ≤ 41 and those with ALT > 41 in terms of age, BMI, and AHI ($p < 0.05$). In the OSAS group, there was a statistically significant difference in AST and ALT levels between non-obese and obese patients (according to body mass index). Both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients ($p < 0.001$and $p < 0.001$, respectively).

Hypertension was detected in 32.4% of OSAS patients. In the OSAS group, there was a statistically significant difference in ALT level between patients with and without hypertension. ALT level was statistically significantly higher in patients without hypertension than in patients with hypertension ($p < 0.001$) (Figure 3). In the control group, there was no statistically difference in AST and ALT levels and AHI value between patients with and without hypertension. In OSAS patients without hypertension, there was a statistically significant relationship between serum ALT and AST levels and AHI (r = 0.223, $p < 0.001$ and r = 0.142, $p$ =0.007, resspectively).

In 143 patients having normal cholesterol and triglyceride levels in the OSAS group, serum ALT level had a statistically significant but weak positive correlation with AHI, apnea index, oxygen desaturation index and a statistically significant but weak negative correlation with age (r = 0.242, $p$ =0.004; r = 0.180, $p$ =0.032; r = 0.241, $p$ = 0.004 and r = -0.234, $p$ = 0.005; respectively). When 143 patients having normal cholesterol and triglyceride levels in the OSAS group were examined, serum AST level had a statistically significant but weak negative correlation with only age (r = -0.243, $p$ = 0.003).

An adjusted linear regression analysis was conducted for AST and ALT variables as dependent variables. Age, sex and BMI adjusted regression equations were given. OSAS was an independent risk factor for abnormal liver enzymes.

For OSAS and control group AST = 8.097 +

3.615×control - 0.090×age + 4.824×sex + 0.353×BMI; ALT = 7.807×control – 0.291×age + 10.767×sex + 0.710×BMI.

For OSAS (mild-moderate and severe group) AST = 15.405 – 0.099×age + 4.90×sex + 0.363×BMI; ALT = 15.953 – 0.318×age + 11.019×sex + 0.721×BMI.

## DISCUSSION

In our study, there was a statistically significant difference in ALT and AST levels between the OSAS and control groups. In the OSAS group, both AST and ALT levels were statistically significantly higher in male patients than in female patients. Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level.

In a study conducted by Jouet *et al*. [9] in obese patients, serum ALT, AST, and GGT levels were found to be increased (25%, 42.9%, and 52.8%; respectively). In another study examining OSAS and serum AST, ALT, and GGT levels, elevated liver enzyme levels were present in 42.3% of OSAS patients. A meta-analysis showed that 4.4% of OSAS patients had an elevated ALT level and 13.3% of OSAS patients had an elevated AST level [10]. There was a relationship between elevated liver enzyme level and OSAS severity (respectively, 51% for severe group and 32.4% for mild-moderate group) [11]. In our study, elevated ALT and AST levels were statistically significantly higher in severe OSAS group (Group 2) (20.7% and 10.3%, respectively) than in mild-moderate OSAS group (15.8% and 6.3%, respectively). In a study involving 163 patients, elevated liver enzyme levels were present in 20% of OSAS patients. This was identified as a strong predictor of elevated liver enzymes in OSAS patients with AHI > 50 [6].

In a study in which OSAS patients were classified according to severity, ALT level was statistically significantly higher in severe OSAS group than in mild-moderate OSAS group [11]. In our study, AST and ALT levels were statistically significantly higher in severe OSAS group than in mild-moderate OSAS group.

Chin *et al*. [12] found that abnormal liver enzyme levels were present in 35% of obese patients with OSAS. Of the obese patients with OSAS in our study, 21.3% had an elevated ALT level and 10.6% had an elevated AST level. In our study, both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients.

In our study, no relationship was found between serum AST and ALT levels and minimum oxygen saturation level. Unlike our study, a study involving 109 patients demonstrated that there was a significant relationship between serum AST and ALT levels and minimum oxygen saturation level and percent of total time with oxygen saturation level <90% (TS90%). Moreover, there was a significant correlation between serum ALT level and age [13]. In our study, there was a significant relationship between serum AST and ALT levels and age.

Daltro *et al*. [14] found that serum AST and ALT levels were elevated independently of AHI, minimum oxygen saturation, and TS90%). In our study BMI, age and sex were included in the regression equation. Our study showed that OSAS is a risk factor for abnormal liver enzymes compared to control group independent of BMI, sex and age but we did not find an association related to severity. Mishra *et al*. [15] showed that nocturnal intermittent hypoxia was a risk factor for the development of hepatic steatosis and liver fibrosis in morbidly obese patients with OSAS.

In a study conducted in OSAS patients, it was found that total cholesterol and triglyceride levels were statistically significantly higher in group with elevated ALT and AST levels than in group with normal ALT and AST levels. In this study, cholesterol and triglyceride levels were not categorized as normal or elevated [11]. In our study, there were significant correlations between ALT and AHI, apnea index, oxygen desaturation index in 143 patients with normal cholesterol and triglyceride levels in the OSAS group. In another study conducted in OSAS patients, serum AST and ALT levels were measured before continuous positive airway pressure (CPAP) therapy and after one-night of CPAP therapy and then were compared to each other. However, no significant difference was detected. That study had some limitations such as the fact that it included a very small number of patients and the control group did not exist [16].

Liver hypoxia, reoxygenation, and catecholamine-mediated metabolic changes cause metabolic changes in the liver, for example, mitochondrial anaerobic breath. Liver biopsies in nonalcoholic fatty liver

patients indicating mitochondrial changes showed this speculation. A past report has demonstrated that hypoxia goes about as a noteworthy of angiogenesis and fibrogenesis, especially by the actuation of hypoxia-inducible factor-1α and vascular endothelial growth factor flagging pathways or by initiating movement of activated hepatic stellate cells [17, 18]. In the light of these data, OSAS is a risk factor for elevated liver enzyme levels. Liver damage occurs after hypoxia. AST, ALT are nonspesific to define liver disease but it can be guide for detecting liver diseases.

### The Limitations of the Study

This study has a few limitations. The research was retrospective, liver histology was not evaluated and also liver enzyme levels were not evaluated after CPAP therapy.

## CONCLUSION

Evaluating liver enzymes in our routine tests plays an important role in clinical practice. The fact that how liver enzyme levels are affected by CPAP therapy should be examined with large-scale studies.

*Conflict of interest*

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