



Association of Aminotransferase Levels with Severity of Obstructive Sleep Apnea

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Authors' contributions

This work was carried out in collaboration between all authors. Author PA designed the study, wrote the protocol and coordinated the research. Author FS collected the data and helped in drafting the manuscript. Author MM analyzed the data and author MF wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is associated with several metabolic disorders. The hypoxia due to OSA can alter liver function and increases the risk of nonalcoholic fatty liver disease and hepatic necrosis. Serum aminotransferase levels are predictive factors for liver injury. In this study we aimed to evaluate association between serum aminotransferase levels and severity of OSA.

Materials and Methods: Sixty six patients who their OSA disorder was confirmed with PSG entered the study. All patients had Body Mass Index (BMI) above 30. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in a group of 33 patients with severe OSA (AHI \geq 30) were compared to 33 patients with mild OSA (5<AHI<15). We also searched for correlation between factors of hypoxemia such as apnea hypopnea index (AHI), Oxygen

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Desaturation Index (ODI) and percentage of time spent with SPO₂<90% (%T<90) with serum aminotransferase levels.

Results: Mean levels of AST were (21.33±8.62) and (21.15±9.39) in severe and mild group respectively. Mean levels of ALT were also measured as (24.24±14.07) and (19.82±9.74) in severe and mild group respectively. The levels of AST and ALT were not significantly different in these two groups (P-value=0.935), (P-value = 0.142). Mean ODI in severe and mild group was (56.33±26.97) (14.00±10.46) (P-value <0.001) and T<90% was (33) 100% and (14) 42.4% (P-value <0.001) respectively which were significantly higher in severe group.

Conclusion: The results from this study showed no significant correlation between serum aminotransferase levels and severity of OSA.

Keywords: Sleep-disordered breathing; obstructive sleep apnea; non-alcoholic fatty liver disease; serum aminotransferases.

1. INTRODUCTION

Obstructive sleep apnea (OSA) is a condition with recurrent episodes of apnea due to the obstruction of the upper airway and decreased oxyhemoglobin saturation. It usually results in sleep disturbances and arousals during sleep [1,2]. Its prevalence varies between 7-14% in males and 2-7% in females [3,4]. According to the American Academy of Sleep Medicine (AASM), Apnea-hypopnea Index (AHI) equal to or greater than five in the presence of associated symptoms is considered as OSA. OSA severity is defined as mild, moderate and severe for $5 \leq \text{AHI} < 15$, $15 \leq \text{AHI} < 30$ and $\text{AHI} \geq 30$ respectively [5]. Excessive daytime sleepiness and snoring are the major symptoms of disease. This condition is more common in obese subjects but is not exclusive to them [6]. OSA is associated with several metabolic disorders such as dyslipidemia [7], insulin resistance, hypertension [8], elevated serum levels of aminotransferases, nonalcoholic fatty liver disease [2,9], and hepatic necrosis [10]. Serum aminotransferases including Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) are biomarkers that are measured to assess liver function. They are present in plasma in low concentration (less than 40 IU/L). Elevation of serum aminotransferases shows some degree of liver damage, which is commonly seen is fatty liver disease [11]. There are several studies showing the association between OSA and serum aminotransferase levels which is indicating fatty liver disease [10]. OSA can lead to insulin resistance, alteration of lipid metabolism and eventually result in development of nonalcoholic fatty liver disease [12]. Singh et al. [9] reported prevalence of 46-63% of OSA in patients with high levels of aminotransferases in whom imaging studies and biopsy were indicative of fatty liver disease.

Additionally, treatment with CPAP decreases the serum level of aminotransferases after 1 to 6 months of nasal CPAP treatment [13].

We hypothesized that OSA severity is associated with altered liver function and elevated serum aminotransferases. In order to test this hypothesis, we measured and compared all the important factors involved in metabolic diseases (including BMI, blood pressure, level of fasting blood sugar and level of blood lipids) as well as OSA severity markers (AHI, oxygen desaturation index, percentage of time spent with SPO₂<90%) in two groups of patients with mild and severe OSA to determine the association of AHI and serum aminotransferase levels. We also searched for correlation of hypoxemia factors such as Oxygen Desaturation Index (ODI) and percentage of time spent with SPO₂<90% (%T<90) with serum aminotransferase levels.

2. MATERIALS AND METHODS

This study was approved by ethics committee of National Research Institute of Tuberculosis and Lung Disease (sbu.rec. 346/ 21.5.2011). Study subjects were selected among patients presenting to Masih Daneshvari Hospital's sleep laboratory by consecutive sampling. Patients with a positive history of viral or autoimmune hepatitis, known hepatic disease, alcohol consumption, chronic heart disease, hypothyroidism, acromegaly, history of taking hepatotoxic drugs, pulmonary obstructive diseases and central sleep apnea were excluded from the study. BMI of all subjects was over 30. A written informed consent was obtained from all patients. A questionnaire was filled out for all subjects including information related to OSA and history of previous diseases.

Patients underwent full-night polysomnography. The minimum duration of sleep had to be 3

hours. The AASM criteria were used in this study for definition of hypopnea and apnea [5]. The number of apneas and hypopneas per hour of sleep were calculated and defined as Apnea-Hypopnea Index (AHI). Patients with moderate OSA ($15 \leq \text{AHI} < 30$) were excluded from the study. $\text{AHI} \geq 30$ was considered as severe OSA while $\text{AHI} \geq 5$ and less than 15 was considered as mild OSA. Oxygen Desaturation Index (ODI) was defined as number of events of hypoxemia by more than 3% desaturation from baseline oxygen level per hour of sleep.

Finally 66 eligible patients who were diagnosed with mild and severe OSA participated in the study. The patients divided into two groups consisting patients with severe OSA as case group and subjects with mild OSA as control group. A venous blood sample was obtained in order to determine the serum level of aminotransferases. AST and ALT >40 IU/L were considered abnormal.

Data were analyzed using SPSS version 14.0 software. Pearson's correlation coefficient was used for expressing the correlation between serum level of aminotransferases and Oxyhemoglobin Desaturation Index (ODI). P-value <0.01 was considered statistically significant for the correlations. After ensuring the normal distribution of variables with non-parametric Kolmogorov-Smirnov test, t-student test was used for comparison of quantitative variables. Chi square test and Fisher's exact test were used for comparison of qualitative

variables. P-value <0.05 was considered statistically significant in these tests.

3. RESULTS

A total of 66 eligible subjects were studied out of which 33 were placed in the group with mild OSA and the remaining 33 in the the group with severe OSA. Male to female ratio in this study was 25/41. Demographic characteristics of subjects are demonstrated in Table 1. As observed in Table 1, the mean serum level of AST and ALT were higher in the severe OSA group but the differences were not statistically significant.

ALT >40 IU/L was observed in 2 subjects in the severe OSA group and the levels of AST and ALT were not significantly different in these two groups (P-value= 0.935 and 0.142, respectively). The mean ODI was significantly higher in the severe OSA group (P-value <0.001). Pearson's correlation coefficient was used to determine the presence and power of correlations. The results of Pearson's correlation coefficient are summarized in Table 2. As seen in Table 2, the correlation coefficients were positive between serum levels of AST, ALT, and ODI. However, based on the obtained coefficients, the power of this correlation was weak.

The relationship of percent of time below 90% saturation ($\%T < 90$) with AST and ALT serum levels is demonstrated in Table 3.

Table 1. Demographic characteristics, laboratory and polysomnographic data of patients

	Mild OSA	Severe OSA	Total	P- value
Age	58.67±12.57	57.91±11.8	58.32±12.11	0.811
Sex				
Male	12(36.4%)	13(39.4%)	25(37.9%)	0.8
Female	21(63.6%)	20(60.5%)	41(37.9%)	
Time spent with $\text{SPo}_2 < 90\%$	14(42.4%)	33(100%)	47(71.2%)	<0.0001
DM	6(18.2%)	8(24.6%)	14(21.2%)	0.544
HTN	14(42.4%)	14(42.4%)	28(42.4%)	>0.999
Hyperlipidemia	1(3%)	2(6.1%)	3(4.5%)	>0.999
CVA	1(3%)	1(3%)	2(3%)	>0.999
AST mean (IU/L)	21.15±8.44	21.33±8.62	21.24±8.44	0.935
ALT mean (IU/L)	19.82±9.71	24.24±14.07	22.03±12.21	0.142
ODI	14±10.46	56.33±26.97	35.17±53.33	<0.001
ALP mean (IU/L)	505.88±53.96	199.94±53.35	202.91±53.32	0.654

SpO2: Peripheral saturation of oxygen, DM: Diabetes mellitus, HTN: Hypertension, CVA: Cerebrovascular accident, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ODI: Oxygen desaturation index, ALP: Alkaline phosphatase

Table 2. The correlation of AST and ALT with ODI

	ODI	P- value
AST	0.042	0.738
ALT	0.166	0.182

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ODI: Oxyhemoglobin desaturation index

Table 3. The correlation of percentage of time time spent with low SPO2 with AST and ALT

	T<90	T>=90	Total	P- value
AST	21.94±9.06	19.53±8.64	21.24±8.94	0.325
ALT	23.13±13.31	19.32±8.65	22.03±12.21	0.254

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

4. DISCUSSION

We assessed the association between serum aminotransferase levels with OSA severity by comparing serum levels of AST and ALT in patients with mild OSA and patients with severe OSA and did not find any significant relationship. Our finding is in agreement with Moosavi et al.'s study which compared serum aminotransferase levels between patients with OSA and healthy subjects [14]. Norman et al. [2] also found no correlation between serum aminotransferase levels and AHI, while they found significant association between markers of hypoxia with serum aminotransferase levels. There are also animal studies demonstrate that the hepatic damage caused by OSA is more strongly associated with the severity of hypoxemia rather than the number of airflow limitation episodes alone [15,16]. It seems that severe reductions in SPO2 that are technically defined as ODI>3% are more effective in increasing the serum level of liver enzymes which confirms the theory that a severe hypoxia is more capable of causing oxidative changes compared to a moderate but long-term hypoxia [17].

We found a weak correlation between ODI and serum levels of AST and ALT, similar to previous studies [18,19]. It seems that the liver damage due to OSA is more strongly affected by the severity of hypoxemia rather than AHI, while the predictive effect of % T<90 was not observed in our study as mentioned by Norman et al. [2]. Another study assessed a group of patients with nonalcoholic fatty liver disease (NAFLD) and authors proved that AHI, ODI and % T<90 are independent predictors of NAFLD [20].

The current study had several limitations. Although history taking and physical examinations were performed with utmost precision, it seems that more accurate

examinations are required for detecting metabolic syndromes like hemochromatosis or Wilson's disease. Thus, the possibility of presence of underlying hepatic diseases cannot be ruled out. Histopathologic findings obtained through liver biopsy were not available in our study and we had to use the serum level of aminotransferases in order to detect liver damage; whereas, some studies that have demonstrated the relationship of OSA and fatty liver disease have used liver biopsy [10,13].

Although there are numerous studies have shown that OSA is associated with increase in liver enzymes [13,21,22], our finding did not show the same results.

5. CONCLUSION

The results of present study showed that in patients with OSA, serum level of aminotransferases may more strongly correlate with oxygen saturation rather than severity of apnea-hypopnea indexes. We assumed that if severity of OSA was an important predictive marker for level of aminotransferases, increased enzyme levels should have been observed significantly in severe OSA group despite the small sample size. In order to further confirm this theory, future studies should evaluate OSA patients who have elevated levels of aminotransferases.

DECLARATION

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CONFLICTS OF INTEREST

Authors of this study declare that they have no conflicts of interest in the research.

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