Original Research
Medical Journal of the Islamic Republic of Iran. Vol. 24, No.4, February 2011. pp. 232-237

Effects of obstructive sleep apnea syndrome on serum aminotransferase levels and insulin resistance

Seyed Hamid Moosavy[1], Hossein Froutan[2], Nader Faiazi[3], Parisa Adimi[4], Yasir Andrabi[5], Mohsen Nasiri Toosi[6], Mohamad Kalani[7]

Gastrointestinal Department, Imam Khomeini Hospital of Tehran University of Medical Sciences, Tehran, Iran.

Received: 9 May 2010 Revised: 24 August 2010 Accepted: 5 September 2010

Abstract

Bckground: Patients with obstructive sleep apnea (OSA) are at risk of developing the fatty liver as a result of being overweight. Several studies suggest that OSA per se could be a risk factor for liver injury; and ischemic hepatitis with OSA. The OSA is an independent risk factor for Insulin resistance. Therefore, we investigated liver enzymes and insulin resistance in patients with OSA, and compared with controls.

Methods: Eighty-one consecutive patients with clinical suspicion of OSA were referred to the Sleep Unit of Masih Daneshvary hospital. On the basis of Polysomnography results patients were divided into two groups: The OSA and non-OSA cases, and also patients without OSA were used as internal controls. The Serum levels of liver enzymes were measured in all patients and abdominal ultrasound examination performed for screening the fatty liver and its grading. Insulin resistance was calculated via homeostasis model assessment (HOMA).

Results: The OSA was present in 41 and absent in 40 patients. Age, sex and body mass indices were not significantly different in two groups. The mean of alanine aminotransferase (ALT) was 31.24±14.05 IU/L in OSA and 29.97±8.9 IU/L in non-OSA ($p= 0.349$) and aspartate aminotransferase (AST) was 29.07±9.6 IU/L in OSA and 26.85±6.7 IU/L in non-OSA ($p= 0.389$). The mean of HOMA was 2.05±18.2 in OSA and 1.5±0.54 in non-OSA ($p< 0.001$).

Conclusion: This study shows that OSA, independent of overweight conditions, is not a risk factor for abnormal liver enzymes. However, the OSA per se seems to be associated with increase in insulin resistance and severity of fatty liver.

Keywords: Obstructive sleep apnea, serum aminotransferase, insulin resistance.

Introduction

The obstructive sleep apnea (OSA) is a common condition with prevalence estimates of 2% to 4% in the general population [1]. The majority of patients are obese and therefore at risk for fatty liver [2].

However, several studies suggest that OSA per se could be a risk factor for liver injury independent of overweight and several cases of ischemic hepatitis during severe OSA have been reported [3-4]. Moreover epidemiological studies have shown that the OSA is an independent risk factor for impairment of glucose homeostasis [5-12].

Obesity has been linked to hepatic steatosis

1. **Corresponding author**: Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv. Tehran, Iran. Tel: +9821 66581650, E mail: seyedhamidmoosavy@gmail.com
2. Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Email: froutan@yahoo.com
3. Sleep Unit of Hospital Masih Daneshvary, Shahid Behishti University, Darabad, Tehran, Iran. Email: faiazi@yahoo.com
4. Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Email: adimi@yahoo.com
5. Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Email: yasirandrabi@gmail.com
6. Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Email:nasiritoosi@yahoo.com
7. Department of Gastroenterology, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran. Email:kalani@yahoo.com
**This work was supported by GI department; Imam Khomeini Hospital of Tehran University of Medical Sciences Tehran, Iran.*

(fatty liver), which occurs in about 90% of patients with unexplained chronic elevations in serum aminotransferase levels [13] Hepatic steatosis is common in many industrialized countries [14] with almost a quarter of adults having excessive fat accumulation in the liver [15,16]. It is also a significant risk factor for serious liver disease, [17] which may contribute to obesity-related morbidity and mortality. At least 20% of patients with hepatic steatosis develop cirrhosis, half of whom die of liver-related causes within a decade of diagnosis, making liver disease the second leading cause of death in these patients.17 Hepatic steatosis is also associated with hyperinsulinemic insulin resistance in humans [18,19] and in various animal models [20-22] raising the possibility that enhancing insulin sensitivity may reduce hepatic fat deposition. Since obstructive sleep apnea leads to insulin resistance and visceral fat accumulation and increases serum leptin levels, it may also affect hepatic function [14]. Indeed, hepatocytes from fatty livers have increased sensitivity to anoxia [23] and frequent hypoxic episodes in patients with OSA syndrome could hinder hepatic function.

We believed that OSA-induced insulin resistance and direct liver hypoxia could possibly be involved in the pathogenesis of liver disease associated with OSA. In view of the fact that few data concerning the prevalence and characterization of liver injury in patients with OSA independent of the body weight is present, this study was designed to access liver injury, and insulin resistance in patients with OSA, taking into account their overweight conditions.

Method

Between April 2008 and January 2009, 81 consecutive patients with clinical suspicion of OSA were referred to the Sleep Unit of Masih Daneshvary hospital. Exclusion criteria were as follows: decompensated cardiac or respiratory insufficiency, treatment for OSA, alcohol intake higher than 20 g/d, regular use of hepatotoxic drugs, known liver disease, and history of liver transplantation. All patients gave their informed consent, and the study was approved by the local ethics committee.

The following data were recorded at the time of polysomnography: age, sex, body mass index (BMI), history of diabetes, and hypertriglyceridemia. The Overweight condition was defined as a BMI higher than 25 kg/m^2.

Polysomnography: Measurements included sleep stage (electroencephalogram, electrooculogram, and submental electromyogram), nasal airflow (nasal cannulae) and oral airflow (thermistor), rib cage and abdominal wall motion (respiratory inductance plethysmography), and arterial oxygen saturation (SaO_2). All polysomnographic data were analyzed visually. Apnea was defined as cessation of airflow for more than 10 seconds. The number of apnea and hypopnea episodes per hour of sleep, or apnea hypopnea index (AHI) was calculated. The OSA was present when the AHI was 10/hr or above, and absent when it was less than 10/hr [14,15]. Patients were divided into two groups on the basis of Polysomnography results: OSA and non-OSA cases. The patients without OSA were used as internal controls.

After a 10-hour overnight fast, in the morning immediately after sleep, venous blood samples were drawn to determine levels of ALT, AST, triglycerides, glucose, and insulin. All measurements were performed on fresh serum. Plasma aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were routinely assayed on a Synchron CX4-CE analyzer (Beckman-Coulter Instruments, Palo Alto, CA) at 30°C. Patients with elevated liver enzymes were defined as having serum ALT, AST higher than the upper limit of normal (40 IU/L). Serum insulin level was determined via radioimmunoassay. Insulin resistance was calculated via homeostasis model assessment (HOMA) as follows:

$$\text{HOMA} = \frac{\text{Fasting glucose } (\mu\text{mol/L}) \times \text{Insulin } (\text{mU/L})}{22.5}$$

Table 1.Characteristics of Patients in OSA and non-OSA groups.

	OSA (n=41)	Non- OSA (n=40)	P_ value
Age (years)	50.1±11.6	50.4±11.7	0.899
Gender (Male/Female)	18/23	18/22	0.921
BMI	41.3±4.4	41.04±3.8	0.743
AST	29.07±9.6	26.85±6.7	0.389
ALT	31.24±14.05	29.97±8.9	0.349
Fasting Blood Sugar	103.8±18.2	101.9±16.6	0.636
HOMA	2.05±18.2	1.5±0.54	<0.001*
Cholesterol	260.8±38.9	248±33.5	0.116
Triglyceride	244.4±45.6	234. 5±44.8	0.326

* Significant

Abdominal ultrasonic examination was performed for fatty liver and its grading. The probe was positioned in the right intercostal space in each patient so that stable parenchymal echo images of the liver could be obtained.

Statistical analysis: Qualitative variables were expressed as a percentage and compared using the Chi- square and Fisher's exact tests. Continuous variables were expressed as the mean ± standard deviation (SD) and compared using the Student t-test. The relationships between continuous variables were analyzed by Pearson's correlation. Differences considered significant if the P-value was less than 0.05.

Results

Eighty-one patients were involved in this study. The OSA was present in 41 and absent in 40 patients. Mean age of patients with OSA was 50.1±11.6 years as compared to 50.4±11.7 years in non-OSA patients, and showed no statistical significance (p>0.05). The ratio of male to female in OSA group was 18:23 as compared to 18:22 in non-OSA group, and this difference also was not statistically significant (p=0.921).

Our results show that mean BMI in patients with OSA was 41.3±4.4 kg/m2 when compared to 41.04±3.8 kg/m2 in non-OSA patients. This difference was not statistically significant (p=0.743, t-test). Table 1 shows characteristics of patients with or without OSA. The mean value of lab indices for AST,ALT, FBS, HOMA, triglyceride and cholesterol in the two groups were compared using student t-test and results are shown in table 1. Seven patients (17.1%) had serum AST higher than the upper limit of normal (40 IU/L) in OSA groups and 2 patients (5%) in non-OSA (p=0.084). Ten patients (24.4%) had serum ALT higher than the upper limit of normal (40 IU/L) in OSA group in comparison to 4 patients (10%) in non- OSA (p=0.087).

The results of our study showed that the

Table 2. The correlation of AHI and O_2 saturation with AST, ALT, FBS and HOMA.

Variables	Pearson correlation coefficient	P Value
AHI & AST	0.073	0.650
AHI & ALT	- 0.064	0.690
AHI & FBS	- 0.107	0.504
AHI & HOMA	0.460	0.002*
O2 saturation & AST	0.054	0.738
O2 saturation & ALT	- 0.128	0.426
O2 saturation & FBS	- 0.282	0.074
O2 saturation & HOMA	- 0.357	0.022*

*correlation is significant

Table 3. Frequency of Steatosis grades in OSA and non-OSA patients as determined by abdominal ultrasound.

Sonographic results Group	Normal	Mild Steatosis	Moderated Steatosis	Severe Steatosis	Total Steatosis
OSA	26 (63.4%)	4 (9.8%)	8 (19.5%)	3 (7.3%)	15 (36.6%)
Non- OSA	31 (77.5%)	7 (17.5%)	2 (5%)	0 (0%)	9 (22.5%)

mean for oxygen saturation in OSA group was 87.3±7 and for AHI was 28.8±11.6. On the basis of these results 46.3% (19 patients) with OSA condition had O_2 saturation below normal limit while allpatients had abnormal values of AHI. The correlation between AHI and AST, ALT, FBS and HOMA, and O_2 saturation and ALT, FBS and HOMA are shown in Table 2.

Our finding showed that steatosis was present in 15 patients (36.6%) in OSA groups and 9 patients (22.5%) in non-OSA (p=0.165). Table 3 compares the frequency of steatosis grades in OSA and non-OSA groups as determined by sonography of liver.

Discussion

Results from our study show that the patients under study in the 2 groups were not significantly different so far as demographics were concerned, including age and gender, furthermore there was no significant difference in BMI of OSA and non-OSA groups, thus having no confounding effect in this study.

Our results show that mean AST and ALT levels had no statistically significant difference between OSA and non-OSA groups. In a study done by Florence et al., AST was not significantly different in OSA and non-OSA groups, however, ALT showed a significant difference in the two groups [24]. The serum ALT and AST values have long been used as surrogate markers of liver injury [25-26]. It is, however, well known that the ALT and AST values do not correlate well with the severity of liver disease noted on liver biopsy in subjects with chronic liver disease [26]. Also there was no significant correlation between AHI with AST and ALT. From these findings it does not seem that OSA can induce damage to hepatocites independently, which is in contradiction to the findings of Savransky [27] Tanné [28] Jouët [29] and Singh [30].

Results of our study show that no statistically significant difference in FBS, triglycerides and cholesterol was present in OSA and non-OSA groups. However, a strong and statistically significant relation existed between insulin resistance and OSA. The HOMA showed a strong correlation with severity of OSA and also with oxygen saturation, such that with increase in oxygen saturation, insulin resistance was decreased, and in view of the fact that BMI of OSA and non-OSA groups had no statistically significant difference, it can be speculated that this correlation was independent of other variables under consideration. This result was also in concordance with the results obtained by Florence, [24] further reaffirming this relation. The mechanism whereby OSA results in insulin resistance and fatty infiltration of the liver has yet to be elucidated. The OSA is associated with increased nocturnal sympathetic activity and high serum glucagon and corticosteroids levels and urinary chatecholamines, which increase insulin resistance [31]. Indeed, an altered hypothalamus-pituitary-adrenal axis has been reported in patients with OSA [11]. Also, it seems OSA can cause insulin resistance by stress oxidative mechanism.

However, more studies are needed to reach a definitive result and elucidate the probable mechanism.

Previous studies demonstrated that ultrasonography has relatively high sensitivity (82-94%) and specificity(66-95%) in detecting fatty liver. On the basis of new abdominal ultrasound scoring system for fatty liver suggested by Hamaguchi et al., our patients were either

normal or had mild, moderate or severe steatosis [32]. A statistically significant relation was present between severity of steatosis and OSA, such that moderate and severe steatosis were seen more frequently in OSA group as compared to controls. However, presence or absence of steatosis in the 2 groups lacked statistical significance. Absence of this difference can be partly contributed to the small sample size; therefore further studies on larger groups can prove helpful in this regard.

Conclusion

In conclusion, based on the findings of this study, further studies on larger groups are required to confirm that an association exists between liver enzymes, insulin resistance and OSA, independent of overweight states. Furthermore, to determine whether OSA contributes to the pathogenesis of non-alcoholic fatty liver disease (NAFLD), patients should be screened for OSA and referred for formal polysomnographic testing where appropriate.

Conflicts of Interest: The authors declare that they have no conflicts of interests.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleepdisordered breathing among middle-aged adults. N Engl J Med 1993;328: 1230-1235.

2. Strollo PJ, Rogers RM. Obstructive sleep apnea. N Engl J Med 1996;334: 99-104.

3. Henrion J, Colin L, Schapira M, Heller FR. Hypoxic hepatitis caused by severe hypoxemia from obstructive sleep apnea. J Clin Gastroenterol 1997; 24:245-249.

4. Mathurin P, Durand F, Ganne N et al. Ischemic hepatitis due to obstructive sleep apnea. Gastroenterology 1995; 109:1682-1684.

5. Stoohs R, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. Am J Respir Crit Care Med 1996;154: 170-174.

6. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002; 165:670-676.

7. Wilcox I, McNamara S, Collins F, Grunstein R, Sullivan C. "Syndrome Z": the interaction of sleep apnea, vascular risk factors and heart disease. Thorax 1998; 53:S25–S28.

8. Brooks B, Cistulli P, Borkman M, Ross G, McGhee S, Grunstein R. Obstructive sleep apnea in obese non insulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness.J Clin Endocrinol Metab 1994;79:1681-1685.

9. Vgontzas AN, Papanicolaou DA, Bixler EO et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1331-1333.

10. Punjabi NM, Ahmed MM, Polotsky VY, Beamer BA, O'Donnell CP. Sleep-disordered breathing, glucose intolerance, and insulin resistance. Respir Physiol Neurobiol 2003;136:167-178.

11. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165:677-682.

12. Poupon RE, Schellenberg F, Nalpas B, Weill J. Assessment of the transferring index in screening heavy drinkers from a general practice. Alcohol Clin Exp Res 1989;13:549-553.

13. Daniel S, Ben-Menachem T, Vasudevan G, et al. Prospective evaluation of unexplained chronic liver transamine abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol. 1999; 94:3010-3014.

14. James O, Day C. Non-alcoholic steatohepatitis: another disease of affluence. Lancet 1999;353:1634-1636.

15. el-Hassan AY, Ibrahim EM, al-Mulhim FA, Nabhan AA, Chammas MY. Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence on patient management. Br J Radiol 1992; 65:774–778.

16. Bellentani S, Tiribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. Hepatology 1994; 20:1442-1449.

17. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116: 1413-1419.

18. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 1999;107:450–455.

19. Marceau P, Biron S, Hould FS, et al. Liver pathology and the metabolic syndrome X in severe obesity. J Clin Endocrinol Metab 1999; 84:1513–1517.

20. Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM. Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis.

Proc Natl Acad Sci USA1997;94: 2557–2662.

21. Kushi A, Sasai H, Koizumi H, et al. Obesity and mild hyperinsulinemia found in neuropeptide Y-Y1 receptor-deficient mice. Proc Natl Acad Sci USA 1998; 95:15659–15664.

22. Shimomura I, Hammer RE, Richardson JA, et al. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes Dev 1998;12:3182–3194.

23. Caraceni P, Ryu HSM, Subbotin V, et al. Rat hepatocytes isolated from alcohol-induced fatty liver have an increased sensitivity to anoxic injury. Hepatology 1997; 25:943-949.

24. Florence T, Frederic G, Olivier C, et al. Chronic liver injury during obstructive sleep Apnea. Hepatology 2005; 41(6): 1290-1296.

25. Karmen A, Wroblewski F, LaDue JS. Transaminase activity in human blood. J Clin Invest 1955;34:126-133.

26. Kallei L, Hahn A, Roder VZ. Correlation between histological findings and serum transaminase values in chronic diseases of the liver. Acta Med Scand 1964; 175:49-56.

27. Savransky V, Bevans S, Nanayakkara A, et al. Chronic intermittent hypoxia causes hepatitis in a mouse model of diet-induced fatty liver. Am J Physiol Gastrointest Liver Physiol 2007; 293(4): 871-7.

28. Tanné F, Gagnadoux F, Chazouillères O, et al. Chronic liver injury during obstructive sleep apnea. Hepatology 2005;41(6):1290-6.

29. Jouët P, Sabaté JM, Maillard D et al. Relationship between obstructive sleep apnea and liver abnormalities in morbidly obese patients: a prospective study. Obes Surg 2007;17(4):478-85.

30. Singh H, Pollock R, Uhanova J, Kryger M, Hawkins K, Minuk GY. Symptoms of obstructive sleep apnea in patients with nonalcoholic fatty liver disease. Dig Dis Sci 2005 Dec;50(12):2338-43.

31. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897-1904.

32. Hamaguchi M, Kojima T, Itoh Y et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007;102:2708-2715.