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Can the Apnea-Hypopnea Index Be a Marker of Liver Fibrosis in Patients with Obstructive Sleep Apnea?

Obstrüktif Uyku Apnesi Olan Hastalarda Apne-Hipopne İndeksi Karaciğer Fibrozisi Belirteci Olur mu?

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Abstract

Objective: The aim of this study; to examine the relationship between hepatosteatosis, non-alcoholic steatohepatitis (NASH) and hepatic fibrosis and the severity of obstructive sleep apnea syndrome (OSAS).

Materials and Methods: Our study included 120 patients who underwent polysomnography in the otorhinolaryngology outpatient clinic between January 2021 and January 2022, and who had previously undergone liver biopsy under ultrasonography (USG) guidance. Patients with simple snoring with apnea-hypopnea index (AHI) <5 were taken as the control group. Patients with alcohol use, viral hepatitis and other chronic liver diseases were excluded. All patients were evaluated by USG and liver biopsy. The relationship between hepatosteatosis, NASH and fibrosis with AHI, oxygen desaturation index (ODI) and minimum pO_2 (min-pO_2) were examined.

Results: The presence of steatohepatitis, NASH, and fibrosis was higher in the OSAS group than in the control group ($p<0.05$). The presence of NASH and fibrosis was higher in the severe OSAS group than in all other groups ($p<0.05$). There was a strong positive linear relationship between AHI with hepatosteatosis and NASH, and a very strong positive linear relationship with fibrosis ($p<0.001$). When the distinction between fibrosis negative and fibrozis positive patients for these variables were compared, the performance of AHI [0.959 (0.907-0.987)] was compared with that of ODI [0.843 (0.766-0.903)] and min-pO_2 performance [0.804 (0.722-0.871)], AHI was found to be significantly higher ($p<0.05$).

Conclusion: The performance of the AHI was higher than the ODI and min-pO_2 in distinction between fibrosis (-) and fibrozis (+) patients and NASH (-) and NASH (+) patients.

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

Öz

Amaç: Bu çalışmanın amacı; hepatosteatoz, non-alkolik steatohepatit (NASH) ve hepatik fibröz ile obstrüktif uyku apne sendromunun (OUAS) derecesi arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Çalışmamıza Ocak 2021-Ocak 2022 tarihleri arasında kulak burun boğaz polikliniğinde polisomnografi yapılan ve daha önceden ultrasonografi (USG) eşliğinde karaciğer biyopsisi yapılmış olan 120 hasta dahil edildi. Apne-hipopne indeksi (AHİ) <5 olan basit horlama hastaları kontrol grubu olarak alındı. Alkol kullanımı, viral hepatit ve diğer kronik karaciğer hastalığı olan hastalar çalışma dışı bırakıldı. Tüm hastalar USG ve karaciğer biyopsisi ile değerlendirildi. Hepatosteatoz, NASH ve fibroz ile AHİ, oksijen desatürasyon indeksi (ODİ) ve minimum pO_2 (min-pO_2) arasındaki ilişki incelendi.

Bulgular: Steatohepatit, NASH ve fibrozis varlığı OUAS grubunda kontrol grubuna göre daha yüksekti ($p<0,05$). Şiddetli OUAS grubunda NASH ve fibrozis varlığı diğer tüm gruplara göre daha yüksekti ($p<0,05$). AHİ ile hepatosteatoz ve NASH arasında güçlü bir pozitif doğrusal ilişki ve fibrozis ile çok güçlü bir pozitif doğrusal ilişki vardı ($p<0,001$). Bu değişkenler açısından fibrozis negatif ve fibrozis pozitif hastalar arasındaki ayrım karşılaştırıldığında, AHİ [0,959 (0,907-0,987)] performansı, ODİ [0,843 (0,766-0,903)] ve min-pO_2 performansı [0,804 (0,722-0,871)] değerlendirildi, AHİ anlamlı olarak yüksek bulundu ($p<0,05$).

Sonuç: Fibrozis (-) ve fibrozis (+) hastaları ile NASH (-) ve NASH (+) hastaları arasındaki ayrımda AHİ performansı ODİ ve min-pO_2'den daha yüksekti.

Anahtar Kelimeler: Apne-hipopne indeksi, fibrozis, obstrüktif uyku apnesi, alkolsüz yağlı karaciğer hastalığı

Introduction

Obstructive sleep apnea syndrome (OSAS) is a life-threatening disease in which recurrent upper airway obstructions occur during sleep. Its prevalence, which is 2-7% in the general population, increases up to 47-70% in the obese population.[1] Recurrent hypoxic episodes in OSAS cause sympathetic nervous system activation and oxidative stress in the entire body. The resulting free oxygen radicals cause irregularity in adipocytes, inflammation in hepatocytes, and abnormal fatty

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acids accumulation in the liver. Some studies are showing that chronic intermittent hypoxia in OSAS is associated with non-alcoholic fatty liver disease (NAFLD).[2]

NAFLD is a broad spectrum disease that progresses from simple fatty liver disease to end-stage liver failure. The prevalence of NAFLD is 20-30% and increases up to 57-74% in patients with obesity. Although histologic findings are similar to those of alcoholic hepatitis, the main determinant is that the patients do not use alcohol. In adipose tissue, the imbalance that occurs as a result of increased synthesis of de nova fatty acids and increased release of non-esterified fatty acids, impaired hepatic triglyceride excretion with excessive dietary fat intake, and decreased beta-oxidation cause fat in hepatocytes.[3] NAFLD is divided into two categories. The first is non-progressive NAFL without inflammation and fibrosis, and the second is non-alcoholic steatohepatitis (NASH), a progressive form with lobular inflammation and perisinusoidal fibrosis.[4] NASH progression may be the cause of cirrhosis and hepatocellular carcinoma in some patients. The 5-year survival of patients with cirrhotic NASH is estimated as 67% and 10-year survival as 59%. In some studies, the mechanism leading to progression from hepatic steatosis to NASH is thought to be hepatocyte damage caused by an imbalance between prooxidant and antioxidant mediators resulting from chronic oxidative stress.[5]

In the diagnosis of NAFLD, the gold standard diagnostic method in differentiating between simple adiposity and NASH is liver biopsy. Although imaging methods are sufficient to detect the presence of fat, they are insufficient for the presence of inflammation and fibrosis. Arısoy et al.[6] evaluated hepatosteatosis with ultrasonographic imaging in patients with OSAS and found more hepatosteatosis in the OSAS group compared with simple snoring. In addition, as the degree of OSAS increased, the degree of hepatosteatosis also increased. Body mass index (BMI) and mean-pO_2 were found to be responsible for hepatosteatosis. As far as we know, there are limited studies investigating NAFLD and fibrosis histologically in patients with OSAS and explaining with which polysomnography (PSG) parameter they are associated.

This study aimed to examine the relationship between the severity of hypoxia and hepatosteatosis, NASH, and fibrosis in patients with OSAS using ultrasonography (USG), liver biopsy and histopathologic diagnostic methods.

Materials and Methods

Our study was conducted in patients aged 18-77 years who applied to the otorhinolaryngology outpatient clinic of our hospital between January 2021 and January 2022 with complaints of snoring and sleep apnea. These patients were retrospectively screened and those who had liver biopsy under the guidance of USG in the gastroenterology clinic of our hospital were included in the study. Liver biopsy and USG results of a total of 187 patients were obtained from the hospital information system. A total of 120 patients who met the study criteria were included in the study. Informed consent was obtained from all patients.

PSG results were evaluated according to the American Academy of Sleep Medicine criteria and patients were grouped according to AHI (5-15 mild, 15-30 moderate and ≥30 severe OSAS, AHI <5 patients with simple snoring were taken as the control group).[6] This study was approved by the Local Ethics Committee (Adana City Training and Research Hospital Clinical Research Ethics Committee; decision number: 1592, date: 14.10.2021).

Patients who used hepatotoxic and hyperlipidemia drugs, had hepatitis, used alcohol (defined as more than 20 g per day for men and more than 10 g per day for women), had cardiovascular-respiratory-digestive system disease, those without laboratory, ultrasound and PSG results, those who could not undergo biopsy were excluded from the study.[3,7]

The biochemical blood results of the patients were obtained from the hospital information system [total serum cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)] BMI (kg/m^2) of all patients was calculated by the same person.

PSG

PSG recordings of all patients were evaluated sleep and physiological variables were monitored using the Comet-PLUS Grass® PSG device. Sleep disturbance events were calculated manually by the same investigator (2012 American Academy of Sleep Medicine criteria).[6] The oxygen desaturation index (ODI), mean-pO_2 and min-pO_2 parameters were recorded.

Ultrasound Image

USG information was scanned retrospectively from patient files and hospital information system and evaluated as follows. Upper abdominal USG were performed using a liver ultrasound (Toshiba Aplio XG4, multifrequency probe 2.5-7 mhz, Japan) device by a blinded gastroenterologist and liver biopsies were taken in accordance with clinical standards. The degree of hepatosteatosis was evaluated according to the rating system of Mihmanli et al.[8] If liver echogenicity is normal, it is stage 0, if there is a slight increase in liver echogenicity, it is stage 1, if there is a moderate increase in liver echogenicity, it is stage 2. In stage 3, the diaphragm and hepatic veins are not visible and there is a marked increase in hepatic echogenicity. We grouped grade 0 as no hepatosteatosis and grade 1-2-3 as hepatosteatosis.

Liver Histology

The pathology results of the patients were reviewed retrospectively from the hospital information system and evaluated as follows. Histopathologic scoring was performed according to the scoring system developed by Kleiner et al.[9] This histopathologic scoring system includes 14 histologic features, four of which are semi-quantitative (steatosis, lobular inflammation, hepatocyte cell ballooning and fibrosis) and the remaining nine are evaluated as "present" or "absent", qualitatively. Steatosis, inflammation in the lobule, and ballooning of hepatocyte cells form the NAFLD activity score (NAS score). The total score is between 0-8. If the NAS score is ≥5, it was evaluated as "definite NASH", NAS scores of 3 and 4 were "probable NASH", and if the NAS score was <3 it was

considered as "not compatible with NASH". Fibrosis was also evaluated as stated in the publication of Kleiner et al.[9] because the NAS score did not include fibrosis.[8] Fibrosis scoring was between 0-4; score 0 was defined as "no signs of fibrosis" and score 4 as "cirrhosis". We scored our patients using the method of Kleiner et al.[9]; fibrosis scores of 0 as no fibrosis, and fibrosis scores of 1-2-3-4 as fibrosis.

Statistical Analysis

Evaluation of continuous variables Shapiro-Wilk test, Student's t-test for two-group comparisons, and One-Way analysis of variance (ANOVA) for more than two-group comparisons were used. The Mann-Whitney U test and Kruskal-Wallis test were used for the variables that did not fit the normal distribution. AHI, ODI, and min-pO_2 cut-offs for NASH, fibrosis, and degree of fibrosis were assessed using receiver operating characteristic (ROC) analysis. Chi-square test was used in the analysis of categorical data. IBM SPSS and MedCalc 19.6 package programs were used in the analysis.

Results

A total of 120 patients, including 23 controls and 97 patients with OSAS, participated in the study. There were 18 patients with mild OSAS, 22 with moderate OSAS, and 57 with severe OSAS. There was no statistically significant difference between the control and OSAS groups in terms of age, sex, and BMI ($p>0.05$). There was no statistically significant difference between the control and OSAS groups in terms of total serum cholesterol, triglyceride, LDL and HDL levels ($p>0.05$). There was a significant difference in AHI, ODI, mean-pO_2, and min-pO_2 values between the OSAS and control groups and between the mild-moderate-severe OSAS groups ($p<0.05$) (Table 1).

The presence of NASH and fibrosis was higher in the severe OSAS group than in all other groups ($p<0.05$) (Table 2).

There was a strong positive linear relationship between AHI with hepatosteatosis, NASH and a very strong positive linear relationship with fibrosis ($p<0.001$). There was a weak positive correlation between ODI with NASH, a moderate positive correlation with hepatosteatosis, and a strong positive correlation with fibrosis ($p<0.001$). There was a moderately negative linear relationship between min-pO_2 with hepatosteatosis, NASH and a strong negative linear relationship between fibrosis ($p<0.001$) (Table 3).

AHI, ODI, and min-SpO_2 medians differed according to the all NASH groups ($p<0.001$) (Table 4).

In the hepatosteatosis and fibrosis positive group, the medians of AHI and ODI were higher, and the medians of min-pO_2 was lower than hepatosteatosis and fibrosis negative group ($p<0.001$) AHI, ODI and min-pO_2 medians differ according to fibrosis groups. As the degree of fibrosis increases, AHI and ODI increase and min-pO_2 decreases ($p<0.001$).

There was no significant difference between AHI, ODI and min-pO_2 in terms of discrimination performance of hepatosteatosis positive and negative patients ($p>0.05$).

Comparing the distinction performances between NASH positive and NASH negative, the performance of AHI [0.795 (0.712-0.863)] compared with the performance of ODI [0.678 (0.578-0.753)] and min-pO_2 [0.756 (0.669-0.830)] was found significantly higher ($p<0.001$). Comparing the distinction performances between fibrosis positive and fibrosis negative, the performance of AHI [0.959 (0.907-0.987)] was compared with that of ODI [0.843 (0.766-0.903)] and min-pO_2 performance [0.804 (0.722-0.871)] was found significantly higher ($p<0.05$) (Table 5).

Discussion

In our study, we found that NAFLD was higher in patients with OSAS than in the control group. We determined that the presence of NASH and fibrosis increased with the degree of disease in OSAS. AHI was more associated with hepatosteatosis, NASH, and fibrosis than ODI and min-pO_2. We have not found a study in the literature evaluating PSG parameters and liver histopathology in patients with OSAS and comparing which PSG parameter is associated with NASH and fibrosis. We think that this aspect of our study will contribute to the literature.

OSAS is a chronic disease that progresses with intermittent hypoxia during sleep and causes inflammation in adipose tissue. The most common PSG parameter used in the evaluation of patients with OSAS is AHI. It is also used to assess the severity of OSAS and grouping the patients. We evaluated the damage in the liver according to three parameters such as AHI, ODI, and min-pO_2. Petta et al.[10] used the Epworth and STOP-Bang scales and Pulixi et al.[11] used the Berlin and Epworth scale, to evaluate liver damage in patients with OSAS, but they did not evaluate it with PSG. In our study, we used PSG, which is the gold standard objective method, to evaluate liver damage in sleep patients. We also divided OSAS into might, moderate, and severe groups and also evaluated ODI and min-SpO_2.

NAFLD is a broad-spectrum disease ranging from simple adiposity to end-stage liver failure. The cause of inflammation here is increased systemic cytokine concentration and endothelial dysfunction.[12] Intermittent hypoxia seen in OSAS has also been shown in studies to cause death in pancreatic B cells and hepatocytes with sympathetic nerve activation.[13,14] Reactive oxygen radicals formed as a result of hypoxia cause hepatocyte damage by causing lipid peroxidation. It has been reported in some studies that hepatosteatosis, lobular inflammation, and fibrosis increase as the severity of OSAS increases.[10]

Hepatosteatosis is a disease that is affected by genetic and environmental factors and is seen at a high rate in the normal population. USG, which can be easily performed in outpatient conditions, is used in the evaluation. There are many classifications used in evaluation of liver injury.[4] We used the Mihmanli classification, which is frequently used in other studies.[8,9] Hepatosteatosis is evaluated between grades 0-3 and grade 3 indicates severe steatosis. In our study, we evaluated the presence of hepatosteatosis instead of its grade. We found hepatosteatosis at a rate of 56.5% in the control group, whereas it was 100% in the OSAS group. Arısoy et al.[6] evaluated both the presence of hepatosteatosis and the grade in their study. As the severity of OSAS increased, the grade of hepatosteatosis also increased. Mean-pO_2 was found to be associated with

Table 1. Age gender, BMI and blood parameters of the groups									
	Control			OSAS			Mild OSAS		
	Mean ± SD	Median [IQR]	Min-max	Mean ± SD	Median [IQR]	Min-max	Mean ± SD	Median [IQR]	Min-max
Age	49.13±13.95	48 [37-61]	25-71	47.94±10.55	50 [41-54]	18-77	41.56±12.28	44 [32-50.25]	18-67
Gender									
Female	14 (60.9%)			59 (60.8%)			10 (55.6%)		
Male	9 (39.1%)			38 (39.2%)			8 (44.4%)		
BMI	32.52±4.42	32 [28-37]	26-40	32.47±5.04	32 [29.2-35]	22-51	30.06±3.85	30.8 [27.35-33]	22-37
Total cholesterol	169.57±40.79	165 [135-196]	90-278	169.13±43.4	165 [130-196]	90-278	171.89±40.73	165 [133.75-197.25]	124-278
Triglyceride	165.96±59.21	164 [126-172]	88-339	206.94±128.32	174 [132-219]	69-821	221.28±181.87	154 [129.25-235]	69-805
LDL-cholesterol	155.22±45.48	145 [122-185]	70-280	154.08±45.1	145 [122-183.5]	70-280	162.72±55.03	143.5 [121-200]	99-280
HDL-cholesterol	40.43±10.95	40 [31-48]	21-65	40.86±10.75	40 [33-48]	21-65	41.5±10.43	45 [30.5-47.75]	21-55
AHI	2.41±1.23	2 [1-4]	1-4.5	42.76±27.46	42 [17-59.5]	7-108.4	8.99±2.45	8.05 [7-9.68]	7-14
ODI	1.42±0.69	1.2 [0.8-2]	0.6-3	27.38±26.03	15.6 [7.4-44.5]	0.4-109.4	11.51±19.96	7.4 [4.1-8.03]	4.1-91
Mean-pO_2	93.3±0.97	93 [92-94]	92-95	90.48±10.48	92.6 [90.95-94]	22-99	93.66±3.31	94 [92.95-95]	82-99
Min-pO_2	86.26±7.8	85 [79-88]	78-100	76.49±11.28	80 [72-85]	50-93.7	85.89±2	87 [84.5-87]	82-88

Table 1. Continued								
	Modarete OSAS			Severe OSAS				
	Mean ± SD	Median [IQR]	Min-max	Mean ± SD	Median [IQR]	Min-max	p^1	p^2
Age	45.82±11.49	49 [35.75-53.25]	25-63	50.77±8.52	51 [44.5-56]	37-77	0.649*	0.013*
Gender								
Female	14 (63.6%)			35 (61.4%)			0.059*	0.088*
Male	8 (36.4%)			22 (38.6%)				
BMI	31.91±4.27	31 [29.3-35]	25-40	33.44±5.41	32 [30-36.5]	24-51	0.820	0.138
Total cholesterol	169.32±41.74	165 [133.75-197.25]	90-278	168.19±45.49	165 [130-196]	90-278	0.846	0.975
Triglyceride	185.5±60.85	189 [153.5-213]	100-400	210.68±128.6	159 [129-241.5]	83-821	0.188	0.500
LDL-cholesterol	148.36±49.39	148.5 [116.25-196]	70-213	153.56±40.2	142 [125.5-178]	70-280	0.992	0.998
HDL-cholesterol	41.73±10.37	40 [33-49]	31-65	40.32±11.13	40 [31-48]	21-65	0.820	0.963
AHI	21.35±5.04	20 [17-25]	15-29.9	61.68±19.25	57 [46.55-75.25]	34.1-108.4	<0.001	<0.001
ODI	11.67±8.51	11.6 [3.78-17]	0.4-27.4	38.45±26.66	37 [15-51.7]	0.7-109.4	<0.001	<0.001
Mean-pO_2	91.13±3.37	92 [90-93.1]	79.6-96.3	86.2±20.84	92 [90-93.1]	22-95	0.042	<0.001
Min-pO_2	82.79±5.83	84 [77.5-86]	73-93.7	71.09±11.43	75 [61.5-80]	50-85	0.001	<0.001

p^1: Mann-Whitney U test *Student's t-test **Chi-square test, p^2: Kruskal-Wallis test *One-Way ANOVA **Chi-square test, OSAS: Obstructive sleep apnea syndrome, BMI: Body mass index, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SD: Standard deviation, IQR: Interquartile range, Min-max: Minimum-maximum, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index

Table 2. Hepatosteatosis, NASH, fibrosis and findings of the groups												
	Control		OSAS		Mild OSAS		Modarete OSAS		Severe OSAS		p^1	p^2
	n	%	n	%	n	%	n	%	n	%		
	Hepatosteatosis											
Negative	10	43.5*	0	0.0	0	0.0	0	0.0	0	0.0	<0.001	<0.001
Positive	13	56.5	97	100.0*	18	100.0	22	100.0	57	100.0		
	NAS score											
≤2 non-NASH	10	43.5	33	34.0	14	77.8	15	68.2	4	7.0	0.038	<0.001
3,4 possible NASH	12	52.2	35	36.1	4	22.2	6	27.3	25	43.9		
5≤ NASH	1	4.3	29	29.9*	0	0.0	1	4.5	28	49.1		
	Fibrozis											
Negative	20	87.0	26	26.8	13	72.2	8	36.4	0	0.0	<0.001	<0.001
Positive	3	13.0	71	73.2*	5	27.8	14	63.6	57	100.0		

OSAS: Obstructive sleep apnea syndrome, NASH: Non-alcohoic steatohepatitis, NAS score: Non-alcoholic fatty liver disease activity score
Chi-square test (p^1: Control & OSAS, p^2: Control & all OSAS groups
*Represents a significantly higher ratio (p<0.05)

Table 3. Spearman Rho correlation values of AHI, ODI and min-pO_2 with hepatosteatosis, NASH and fibrosis				
		Hepatosteatosis	**NASH**	**Fibrosis**
AHI	r	0.683	0.660	0.882
	p	<0.001	<0.001	<0.001
ODI	r	0.556	0.352	0.639
	p	<0.001	<0.001	<0.001
Min-pO_2	r	-0.463	-0.492	-0.677
	p	<0.001	<0.001	<0.001

p: Spearman Rho correlation, NASH: Non-alcoholic steatohepatitis, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, r: correlation coefficient

Table 4. Relationship of AHI, ODI and min-pO_2 to NASH										
	Non-NASH			Possible NASH			NASH			
	Mean ± SD	Median [IQR]	Min-max	Mean ± SD	Median [IQR]	Min-max	Mean ± SD	Median [IQR]	Min-max	p
AHI	14.73±11.46	11.7 [7-23.7]	1-40	30.69±22.59	36 [4-53]	1-68.1	70.89±23.87	74.5 [58-90.78]	3-108.4	<0.001
ODI	11.29±15.72	7 [2.3-15.6]	0.4-91	19.79±19.33	14.4 [1.4-37]	0.4-63	42.41±33.42	45.2 [10.58-64.25]	0.7-109.4	<0.001
Min-pO_2	83.76±4.65	86 [80-87]	73-93.7	78.23±13.24	81 [75-85]	50-100	70.83±10.83	73.5 [61.5-79.25]	50-84	<0.001

NASH: Non-alcoholic steatohepatitis, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SD: Standard deviation, IQR: Interquartile range, Min-max: Minimum-maximum
p: Kruskal-Wallis test

hepatosteatosis, and its sensitivity and specificity were 80% and 57%, respectively. We evaluated min-pO_2, ODI and AHI in assessment of hepatosteatosis. In our comparative study, we found the sensitivity of AHI as 87% and the specificity as 80%. We think that the sensitivity and specificity of AHI are more valuable than mean-pO_2 in the evaluation of hepatosteatosis.

In some animal studies; it has been stated that chronic hypoxia contributes to the development of NASH by causing an increase in the expression of genes that induce hepatic lipogenesis (SREBP-1c, ACC1, ACC2) and a decrease in the expression of genes that cause B-oxidation (CPT1).[15] In addition, increased oxidative stress and its induced inflammation have been held responsible for the development of NASH with the increase of CYP2E1.[16] While evaluating hepatosteatosis with USG, which can be easily performed in outpatient conditions, biopsy and histopathological diagnosis are required for the diagnosis of NASH. In the Aron-Wisnewsky et al.[17] study, ODI was associated with lobular inflammation, while Benotti et al.[18] study min-pO_2 was associated with lobular inflammation. We did not evaluate lobular inflammation in our study. However, we evaluated the presence of NASH using the NAS score. In our comparative study, we found the performance of AHI to be higher than ODI and min-pO_2 in determining the presence of NASH. We think that AHI is more effective than ODI and min-SpO_2 in investigating the presence of NASH.

Table 5. ROC curve analysis of AHI, ODI and min-SpO_2 with NASH, fibrosis and hepatosteatosis						
		AUC (95% CI)	**Criterion**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**p**
NASH	AHI	0.795 (0.712-0.863)	>40	64.94 (53.2-75.5)	100.00 (91.8-100.0)	<0.001
	ODI	0.678 (0.578-0.753)	>28.2	44.16 (32.8-55.9)	93.02 (80.9-98.5)	0.005
	Min-SpO_2	0.756 (0.669-0.830)	≤83	79.22 (68.5-87.6)	62.79 (46.7-77.0)	<0.001
p	<0.001					
Fibrosis	AHI	0.959 (0.907-0.987)	>20	83.54 (73.5-90.9)	97.56 (87.1-99.9)	<0.001
	ODI	0.843 (0.766-0.903)	>9.4	75.95 (65.0-84.9)	87.80 (73.8-95.9)	<0.001
	Min-SpO_2	0.804 (0.722-0.871)	≤80	64.56 (53.0-75.0)	82.93 (67.9-92.8)	<0.001
p	<0.05					
Hepatosteatosis	AHI	0.907 (0.840-0.952)	>4	87.27 (79.6-92.9)	80.00 (44.4-97.5)	<0.001
	ODI	0.875 (0.803-0.929)	>7.6	64.55 (54.9-73.4)	100.00 (69.2-100.0)	<0.001
	Min-SpO_2	0.758 (0.671-0.831)	≤82	62.73 (53.0-71.8)	80.00 (44.4-97.5)	<0.001
p	p>0.05					

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, NASH: Non-alcoholic steatohepatitis, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index
p: ROC Curve Analysis

Chronic intermittent hypoxia increases the synthesis of lysyl oxidase (LOX) by activating hypoxia-inducible factor 1, a major transcription factor activated by hypoxia. In a study, it was found that hepatic fibrosis and the level of the fibrogenic enzyme LOX were associated with the severity of OSAS in patients with severe obesity.[19] It has been observed that this enzyme causes fibrosis by increasing collagen cross-linking in liver cells. Some studies have used the aspartate aminotransferase-to-platelet ratio score to evaluate fibrosis.[20] In our study, we evaluated the patients according to the degree of fibrosis, using the Kleiner classification. Studies have shown that fibrosis is the most important variable in demonstrating liver degeneration.[18] Polysomnography parameters are stronger markers for detecting fibrosis than NASH and hepatosteatosis. In our study, we evaluated the performances of AHI, ODI, and min-pO_2 by performing ROC curve analysis while evaluating fibrosis, and we found the fibrosis evaluation performance of AHI to be higher (0.959%). Aron-Wisnewsky et al.[17] found that fibrosis was associated with ODI. They also evaluated liver pathology as hepatosteatosis,[1] NASH and fibrosis,[17] like us, and used only ODI from PSG scores. ODI was determined as the only independent variable in determining the degree of liver fibrosis. The strongest aspect of this study is to evaluate the association of both AHI and ODI with fibrosis and also to compare with each other.

Study Limitations

Although we think that the parameters used in the diagnosis and grading of the disease are sufficient. It is a fact that the evaluations after the treatment will make positive contributions to the literature. Studies evaluating the histopathological response of OSAS patients to different treatments are needed. *In vitro* studies are needed to investigate hypoxia-induced inflammation.

Conclusion

Non-alcoholic steatosis is a broad-spectrum disease that can progress from simple steatosis to end-stage liver failure and is frequently seen in patients with OSAS. As the severity of OSAS increases, fibrosis increases due to increasing hypoxia and oxidative stress. AHI is more effective than ODI and min-pO_2 in determining hepatocyte damage.

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Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (Adana City Training and Research Hospital Clinical Research Ethics Committee; decision number: 1592, date: 14.10.2021).
Informed Consent: Informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: A.K., E.G., Concept: A.K., S.O.E., Design: A.K., E.G., Data Collection or Processing: A.K., S.O.E., Analysis or Interpretation: A.K., E.G., Literature Search: A.K., S.O.E., Writing: A.K.
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