Govaresh/ Vol. 27, No.2, Summer 2022; 92-98.

Original Article

The Association Between Sleep Disturbance and Liver Stiffness in Patients with Non-alcoholic Fatty Liver Disease

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ABSTRACT

Background:
Non-alcoholic fatty liver disease (NAFLD) is a common disorder leading to severe medical conditions such as liver failure or malignancy. Given the potential relation between sleep disturbance and NAFLD, we aimed to investigate the association between the deterioration of sleep and liver stiffness with NAFLD.

Materials and Methods:
In this cross-sectional study, 134 patients who were proven to have NAFLD were included. Liver stiffness was determined by transient elastography, and sleep patterns were evaluated using Pittsburg Sleep Quality Index (PSQI).

Results:
The results showed that sleep disorder was more prevalent in women ($P = 0.007$), and they had higher liver stiffness than men ($P = 0.001$). Habitual Sleep Efficiency: The adequate sleep time was worsened in patients with more severe liver stiffness ($P = 0.037$). Also, Subjective Sleep Quality that is the self-estimation of patients about sleep quality, was reversely related to liver stiffness ($P = 0.003$). Categorized liver stiffness groups had a negative association between sleep quality and liver stiffness ($P = 0.001$), but there was no significant association between liver stiffness and sleep latency, sleep duration, and daytime dysfunction or using sleeping pills.

Conclusion:
The present study indicates that bad sleep habits and poor sleep quality correlate with increased liver stiffness in patients with NAFLD, suggesting that patients' lifestyle modification can improve the quality of their lives and prevent more severe disorders caused by sleep dysfunction.

Keywords: Sleep disruption, Liver stiffness, NFLAD, Pittsburgh Sleep Quality Index

please cite this paper as:
Parsi A, Hajiani E, Fakhri A, Haghighizadeh MH, Taghizadeh M. The Association Between Sleep Disturbance and Liver Stiffness in Patients with Non-alcoholic Fatty Liver Disease. *Govaresh* 2022;26:92-98.

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Received: 29 May 2021
Revised: 08 Nov. 2021
Accepted: 09 Nov. 2021

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic fat accumulation without secondary causes such as alcohol abuse or other proven liver disorders(1). This term refers to a broad spectrum of liver diseases, from simple steatosis to more severe cirrhosis or hepatocellular carcinoma(2). NAFLD is the most common cause of chronic liver disease worldwide, and the incidence rate is growing rapidly(3) Moghaddasifar and colleagues, in a systematic review, estimated the

total prevalence of fatty liver disease in the Iranian population was about 34%(4).

NAFLD's risk factors are diabetes mellitus, dyslipidemia, and metabolic syndrome. Many lifestyle habits such as low physical activity, poor diet, and sleep disorders might contribute to NAFLD development(5). On the other hand, sleep disturbance may lead to obesity, type 2 diabetes mellitus, metabolic disorders(6-8) and the risk of progression to NAFLD(9,10). However, it is unclear if NAFLD is the cause or consequence of sleep disturbance.

Sleep disturbance has been reported to change eating behaviors and timing of food intake to cause obesity(10), and also gut microbiota alteration is blamed for metabolic changes related to sleep patterns(11). Moreover, obstructive sleep apnea syndrome (OSAS) is associated with NAFLD in several studies suggesting that hypoxia may cause liver steatosis(12). Recently, Kim and colleagues reported a significant relationship between poor sleep quality and NAFLD. (13) Marin-Alejandre and co-workers suggested that short sleep duration and poor quality were associated with liver stiffness(14), however, there were controversial results(9,15). So far, little is known about the relation between liver stiffness and sleep patterns; in this regard, in the current study, we aimed to evaluate this potential association.

MATERIALS AND METHODS

Study population

134 patients were randomly selected among adult patients referred to the gastrointestinal clinic. The patients were diagnosed with fatty liver disease by having elevated alanine aminotransferase (ALT) and liver ultrasonography with pieces of evidence of liver steatosis performed by the same qualified radiologist. Patients with viral hepatitis, a history of alcohol intake, and other known liver diseases like drug-induced hepatitis or autoimmune hepatitis were excluded from the study.

Transient elastography is a safe and accurate method for assessing hepatic fibrosis in chronic liver disease, which is recently preferred to aggressive methods such as liver biopsy(15). In this study, we performed transient elastography for all the patients with NAFLD under fasting conditions. All measurements were categorized into four groups based on Castera transient elastography breakpoints(16). Patients with liver stiffness below 7.1 kPa were included in the F1 group, 7.1 to 9.5 kPa in the F2 group, 9.5 to 12 kPa in the F3 group, and more than 12 kPa in the F4 group. Written consent was obtained from all participants.

Questionnaire survey

To assess sleep quality, we used the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a validated questionnaire used to evaluate seven items: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime function(17). The sum of PSQI scores was determined for all the participants, and sum scores more than 5 were defined as poor sleep quality, and a higher PSQI score indicated more inferior sleep quality. A validated Persian version was used in this study with specificity and sensitivity of 89% and 86%, respectively(16).

Statistical analysis

Descriptive analyses were used to determine the patients' characteristics and describe their sleep behaviors. Independent sample *t* test, Mann-Whitney U test, Chi-square test, one-way analysis of variance (ANOVA), Kruskal-Wallis test, and Fisher's exact test were used to determine differences between groups for continuous and categorical variables, respectively. SPSS software (version 23.0) was used for data analysis. Throughout the analysis, statistical significance was defined as a $P < 0.05$ (two-sided).

RESULTS

Characteristics of the Participants

Of the 134 study participants, 84 (62.7%) were men, and 50 (37.3%) were women. In table 1, differences in liver stiffness and sleep characteristics are compared between the sex groups. Liver stiffness was higher in women (8.7 kPa) than men (6.4 kPa). The prevalence of sleep disturbance is shown according to every sleep subgroup in table 1. Sleep characteristics of patients with NAFLD are shown in table 1. The overall PSQI score of women was more significant than men, which may reveal higher sleep disturbance in women with NAFLD [mean ±SD: women=7.2 ±2.8, and men=5.8±2.6, $p = 0.007$], but there was no difference in other sleep characteristics between sex-

es. Overall, most of the participants (56.7 %) reported poor sleep quality, but no one reported terrible sleep status. Only 14% of the patients ever used sleeping medications, of whom women took more pills than men. Most participants reported no daily dysfunction due to sleepiness (66%) and mainly explained their subjective sleep quality fairly well (64%).

Association between Sleep Characteristics and Liver Stiffness

In table 2, sleep characteristics are compared to every liver stiffness group. The liver stiffness of the participants ranged from 3 to 15.1 (kPa) (mean ± SD = 7 ± 2.4), and about half of the patients (50.7 %) had mild liver fibrosis (lower than 7.5 kPa). 10.5% of the patients had mild fibrosis, 55% had moderate, and 34% had severe fibrosis. Liver stiffness in women was significantly higher than in men ($P = 0.001$).

According to different sleep categories, comparing elastography levels revealed that higher liver stiffness values were significantly associated with a poorer overall sleep quality (total PSQI score) and lower habitual sleep efficiency and Subjective Sleep Quality score. However, there were no significant associations between liver stiffness and other sleep characteristics in the PSQI questionnaire (table 1).

Most patients (62%) did not report daytime dysfunction, and only 3% experienced severe daytime dysfunction. Also, most participants (86%) did not use any sleeping pills.

The total PSQI scores according to different liver fibrosis categories are shown in figure 1 by box plot, demonstrating higher scores in more severe liver status groups. A significant difference was observed only between F1 and F2 groups ($P < 0.001$) according to the post-hoc Bonferroni test.

DISCUSSION

In this cross-sectional study, a reverse association was observed between sleep quality and liver stiffness, and in subgroup analysis, we also found a significant association between Habitual Sleep Efficiency, Subjective Sleep Quality, Total Sleep Quality Score, and liver stiffness.

Studies regarding the association between sleep disorders and NAFLD have conflicting results. Different methods used for evaluating sleep patterns may be the reason for inconsistencies in the findings. Moreover, subjective sleep quality, a self-perceived measurement, may differ due to the lack of a standard definition. PSQI is a valid and reliable questionnaire applicable in different populations, decreasing this lack of consensus in definitions and measurements.

Evaluating the fibrosis stage in patients with NAFLD is independently associated with long-term outcomes(17), however, few studies focused on liver status while working on sleep disorders in NAFLD. A recent study reported a significant association between sleep efficiency and sleep disturbance with liver stiffness in obese patients with NAFLD(17). On the other hand, Bernsmeier and colleagues found that daytime sleepiness was correlated with the severity of liver fibrosis(7). Being aware that in patients with liver cirrhosis, the risk of daytime sleepiness is high(7,18).

The underlying mechanisms of the relationship between sleep disturbance and NAFLD are not entirely understood. However, previous studies have demonstrated that poor sleep quality is associated with resistant hypertension(8), impaired glucose tolerance(17), and metabolic syndrome(18), which are the same risk factors for NAFLD. Therefore, sleep patterns could affect the liver status by altering metabolic balances. In addition, inflammatory markers are suggested responsible for causing NAFLD due to sleep disturbance(19). Finally, the liver's role in hormone regulation, such as melatonin, may affect the sleep patterns in patients with NAFLD.

There are limitations in this study: First, we could not conclude a causal relationship due to the study's cross-sectional design. Second, no data was available on age, weight, and other lifestyle differences that affect sleep quality and liver status. Finally, self-reported sleep quality could have biases(18).

CONCLUSIONS

This study supports a negative association between sleep characteristics and the severity of liver fibrosis in patients with NAFLD. Sleep quality may be related to the pathogenesis of NAFLD, and the alteration of the liver status may be affecting sleep patterns. Therefore, the identification of factors that can affect the quality of life in NAFLD is crucial.

Table 1: **Comparisons of elastography and sleep characteristics between women and men**

Variables	Total population	Women	*Men*	P value*
Elastography levels, median (IQR)	7 (5.6-9.4)	8.7 (6.7-10.3)	6.4 (4.9-8.1)	0.001
Elastography categories				
Sleep Latency				0.103
less than 5 minutes	24 (21.1)	5 (12.2)		19 (26.4)
16-30 minutes	43 (38.1)	14 (34.1)	29 (40.3)	
31-60 minutes	26 (23.0)	11 (26.8)	15 (20.8)	
more than 60 minutes	20 (17.7)	11 (26.8)	9 (12.5)	
Sleep duration				0.642
More than 7 hrs	43 (38.1)	16 (39.0)	27 (37.5)	
6-7 hrs	30 (26.5)	10 (24.4)	20 (27.8)	
5-6 hrs	21 (18.6)	6 (14.6)	15 (20.8)	
Less than 5 hrs	19 (16.8)	9 (22.0)	10 (13.9)	
Habitual sleep efficiency				0.560
More than 85%	51 (45.1)	16 (39.0)	35 (48.6)	
75-84%	46 (40.7)	17 (41.5)	29 (40.3)	
65-74%	14 (12.4)	7 (17.1)	7 (9.7)	
Less than 65%	2 (1.8)	1 (2.4)	1 (1.4)	
Sleep disturbance				0.096
0 points	3 (2.7)	1 (2.4)	2 (66.7)	
1-9 points	69 (61.1)	20 (48.8)	49 (68.1)	
10-18 points	40 (35.4)	20 (48.8)	20 (27.8)	
19-27 points	1 (0.9)	0 (0.0)	1 (1.4)	
Subjective sleep quality				0.725
Very good	23 (20.4)	8 (19.5)	15 (20.8)	
Fairy good	73 (64.6)	26 (63.4)	47 (65.3)	
Fairy bad	16 (14.2)	6 (14.6)	10 (13.9)	
Very bad	1 (0.9)	1 (2.4)	0	
Use of sleeping medications				0.073
Never	97 (85.8)	31 (75.6)	66 (91.7)	
Once a week	5 (4.4)	3 (7.3)	2 (2.8)	
Twice a week	2 (1.8)	1 (2.4)	1 (1.4)	
Three times a week	9 (8.0)	6 (14.6)	3 (4.2)	
Daytime dysfunction				0.495
0 points	74 (65.5)	28 (68.3)	46 (63.9)	
1-2 points	24 (21.2)	6 (14.6)	18 (25.0)	
3-4 points	13 (11.5)	6 (14.6)	7 (9.7)	
5-6 points	2 (1.8)	1 (2.4)	1 (1.4)	
Overall PSQI score, mean (SD)	6.3 (2.8)	7.2 (2.8)	5.8 (2.6)	0.007
<5	58 (43.3)	16 (32)	42 (50)	
5-11	69 (51.5)	28 (56)	41 (48.8)	
11-17				7 (5.2)
>17	0.0	0	0	

Table 2: Elastography levels according to different sleep categories

Variables	Liver Stiffness categories, n (%)				*P value*
	F1 (n=68)	F2 (n=41)	F3 (n=17)	*F4 (n=8)*	
Sleep latency, median (IQR)					0.067
Less than 5 minutes	16 (23.5)	3 (7.3)	6 (35.3)	3 (37.5)	
16-30 minutes	26 (38.2)	13 (31.7)	8 (47.1)	1 (12.5)	
31-60 minutes	16 (23.5)	13 (31.7)	1 (5.9)	1 (12.5)	
More than 60 minutes	10 (14.7)	12 (29.3)	2 (11.8)	3 (37.5)	
Sleep duration					0.444
More than 7 hrs.	27 (39.7)	14 (34.1)	7 (41.2)	5 (62.5)	
6-7 hrs.	23 (33.8)	9 (22.0)	3 (17.6)	1 (12.5)	
5-6 hrs.	7 (10.3)	9 (22.0)	5 (29.4)	1 (12.5)	
Less than 5 hrs.	11 (16.2)	9 (22.0)	2 (11.8)	1 (12.5)	
Habitual sleep efficiency					0.037
More than 85%	42 (61.8)	16 (39.0)	5 (29.4)	3 (37.5)	
75-84%	21 (30.9)	17 (41.5)	9 (52.9)	4 (50.0)	
65-74%	5 (7.4)	5 (7.4)	3 (17.6)	0	
Less than 65%	0	0	0	1 (12.5)	
Sleep disturbance					0.059
0 points	1 (1.5)	1 (2.4)	1 (5.9)	0	
1-9 points	44 (64.7)	19 (46.3)	10 (58.8)	7 (87.5)	
10-18 points	23 (33.8)	21 (51.2)	6 (35.3)	0	
19-27 points	0	0	0	1 (12.5)	
Subjective sleep quality					0.003
Very good	15 (22.1)	5 (7.4)	5 (29.4)	2 (25.0)	
Fairy good	46 (67.6)	30 (73.2)	10 (58.8)	1 (12.5)	
Fairy bad	7 (10.3)	6 (14.6)	1 (5.9)	5 (62.5)	
Very bad	0	0	1 (5.9)	0	
Use of sleeping medications					0.079
Never	64 (94.1)	32 (78.0)	14 (82.4)	6 (75.0)	
Once a week	2 (2.9)	3 (7.3)	1 (5.9)	0	
Twice a week	0	1 (2.4)	1 (5.9)	0	
Three times a week	2 (2.9)	5 (7.4)	1 (5.9)	2 (25.0)	
Daytime dysfunction					0.069
0 points	41 (60.3)	24 (58.5)	13 (76.5)	6 (75.0)	
1-2 points	22 (32.4)	10 (24.4)	1 (5.9)	0	
3-4 points	5 (12.2)	5 (7.4)	3 (37.5)	2 (25.0)	
5-6 points	2 (2.9)	2 (4.9)	0	0	
Overall PSQI score, mean (SD)	5.5 (2.4)	7.6 (2.7)	5.9 (2.8)	7 (3.4)	0.001

Abbreviations: hrs.: hours; n: number

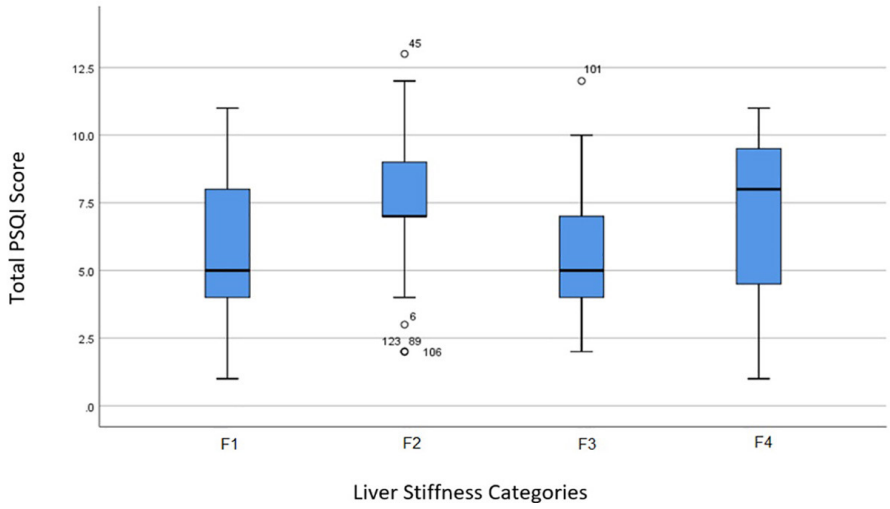

Fig.1: **Box plot of total PSQI scores in different liver stiffness categories**

Funding
None.

Authors' contributions
A.P conceived the manuscript and revised it. MH.T, A.F, E.H, and M.H did the statistical analysis, wrote the manuscript, and prepared tables and figures.

ACKNOWLEDGMENTS

We wish to thank all our colleagues in the Allied Health Sciences School, Ahvaz University of Medical Sciences.

ETHICAL APPROVE

The study was based on the approval of the Medical Ethics Committee of Jundishapur Ahvaz University (Reference Number: IR.AJUMS.REC.1398.921).

CONFLICT OF INTEREST

The authors declare no conflict of interest. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or a compared ethical strand.

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