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Insufficient nocturnal sleep was associated with a higher risk of fibrosis in patients with diabetes with metabolic associated fatty liver disease

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Abstract

Background: Metabolic associated fatty liver disease (MAFLD) refers to metabolic dysfunction associated with fatty liver disease, and liver fibrosis stage is closely connected with liver-related and all-cause mortality. This study aimed to explore the association of sleep duration with liver fibrosis in the diabetic subgroup of the MAFLD population.

Methods: This retrospective study analyzed 342 patients with MAFLD. Anthropometric measurements, clinical and biochemical markers, and lifestyle parameters were collected. Fibrosis was defined as fibrosis-4 $\geqslant$1.3. Propensity score matching (PSM) was performed to match cases. Student's *t*-test and chi-square tests were applied for group comparisons, and binary regression models were used to explore the independent risk factors of liver fibrosis.

Results: Among the 342 subjects, 87 (25.4%) were diagnosed with fibrosis and 255 (74.6%) without. Baseline characteristic comparisons showed differences in age and diabetes duration between the two groups, and adjustment was made by PSM. Ultimately, the fibrosis group and nonfibrosis group each had 87 patients. The fibrosis group had shorter duration of nocturnal sleep (6.77 $\pm$ 1.59 h) than the nonfibrosis group (7.77 $\pm$ 1.92 h, $p < 0.001$). More patients in the fibrosis group stayed up late at night (32.2% *versus* 14.9%, $p < 0.01$). Visceral adipose tissue (VAT) areas were larger in the fibrosis group than in the nonfibrosis group ($p < 0.001$). Glycemic profile, lipid profile, gamma-glutamyl transferase level, and serum uric acid level were not significantly different between the two groups. In the multivariate regression analysis, nocturnal sleep and VAT areas were independently associated with liver fibrosis, with odds ratios of 0.694 [95% confidence interval (CI) 0.551–0.875, $p < 0.01$] for nocturnal sleep and 1.031 (95% CI 1.014–1.048, $p < 0.001$) for VAT areas.

Conclusion: Insufficient nocturnal sleep was independently related to a higher risk of fibrosis. Sleep modification might be beneficial in promoting the health of patients with MAFLD.

Keywords: liver fibrosis, metabolic associated fatty liver disease, sleep duration, VAT area

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Introduction

Metabolic associated fatty liver disease (MAFLD) refers to fatty liver disease associated with metabolic dysfunction and represents the overarching umbrella of metabolism-related diseases and multiple subphenotypes.[1] The pathology of MAFLD is complicated and multifaceted: it is the result of interactions between genetic predisposition, metabolic disorders, and environmental factors,[2] and the characteristics of MAFLD are somehow different from nonalcoholic fatty liver disease (NAFLD).[3] Along with rapid urbanization, unhealthy eating, and sedentary lifestyle, the prevalence of fatty liver disease and metabolism dysfunctions is increasing in China, as well as the morbidity of MAFLD. A recent study showed

that the overall MAFLD prevalence was 35.36% for men and 26.49% for women in central China.[4] MAFLD may lead to fibrosis and eventually progress to cirrhosis, and enhance the risks of cardiovascular and cerebrovascular diseases.[5,6]

Fibrosis is a common complication of chronic liver disease, and sleep disorder has been shown to promote the progress of liver diseases.[7,8] Sleep disruption contributes to the pathogenesis of hepatic steatosis, and short sleep duration is positively associated with liver stiffness.[8] Furthermore, a study reported that insufficient sleep had negative effects on metabolic disorders including diabetes mellitus (DM), obesity, insulin resistance, and metabolic syndrome.[7] However, the relation between sleeping disorder and progression of MAFLD remains unknown.

In this retrospective study, we collected data of patients with MAFLD with type 2 DM and applied fibrosis-4 (FIB-4) score as an index to define advanced liver fibrosis. This study aimed to explore the association of nocturnal sleep duration with liver fibrosis in the DM subgroup of the MAFLD population.

Materials and methods

Subjects

Patients with type 2 DM who visited Fujian Medical University Union Hospital from 2018 to 2019 were screened for fatty liver, and those who met the diagnostic criteria of MAFLD were included.[2] This retrospective study was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2018KY072), and participants provided written informed consent for personal information collection.

Definitions

MAFLD was defined as the presence of hepatic steatosis in addition to one of the following three criteria:[2] overweight/obesity [defined as body mass index (BMI) $>25\,kg/m^2$], type 2 DM, or evidence of metabolic dysregulation. Abdominal ultrasonography was performed using a 3.5-MHz transducer (Aplio-400, Toshiba, Kyoto, Japan) by certified radiologists who were blinded to the aim of the study. Ultrasonographic diagnosis of hepatic steatosis was defined by the presence of a diffuse increase in echogenicity of the liver relative to the kidney or spleen parenchyma.[9]

The FIB-4 score was obtained using the following formula: age (years) $\times$ alanine aminotransferase (U/L)/[platelet (10^9/L) $\times \sqrt{}$ aspartate transaminase (U/L)], and fibrosis was defined as FIB-4 $\geqslant 1.3$.[10]

Smoking was defined as smoking at least one cigarette per day for at least 6 months. Physical activity was defined as >20 min of exercise per day more than three times a week over the previous 6 months. Late sleep was defined as staying up later than 0:00 am.

Measurements

Anthropometric measurements (body weight, height, and waist circumference) and lifestyle variables were collected. BMI was calculated as body weight in kilograms divided by the square of height in meters. Waist and hip circumference were measured according to a standard protocol.[11] Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas were measured by two experienced nurses using a DUALSCAN HDS-2000 machine (OMRON, Kyoto, Japan). Measurements of fasting plasma glucose (FPG), 2-h postprandial blood glucose (2hPG), fasting and 2-h postprandial C-peptide, glycosylated hemoglobin (HbA1c), alanine aminotransferase, aspartate transaminase, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were performed by standard laboratory methods.

Statistical analysis

The distribution of variables was assessed by the Shapiro–Wilk test, and data were represented by $X \pm SD$ (mean $\pm$ standard deviation) or percentage, as appropriate. Before statistical analyses, non-normally distributed variables were logarithmically transformed. Comparisons between groups were carried out by Student's *t*-test for continuous variables or chi-square test for categorical variables. Binary logistic regression was performed to evaluate the risk factors of liver disease-related and overall mortality. IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA) was used for analyses. A p value <0.05 was considered statistically significant.

Results

Participant characteristics

A total of 342 patients with MAFLD were enrolled, with 87 (25.4%) in the fibrosis group and 255 (74.6%) in the nonfibrosis group. The fibrosis group was older (64.4 ± 7.2 years *versus*

Table 1. Characteristics of patients with MAFLD before and after PSM.

	Before PSM			After PSM		
	Nonfibrosis group	**Fibrosis group**	***p***	**Nonfibrosis group**	**Fibrosis group**	***p***
Subjects, *n*	255	87		87	87	
Sex, males, *n* (%)	146 (57.3%)	50 (57.5%)	0.972	41 (47.1%)	50 (57.5%)	0.172
Age (years)	54.5 ± 11.6	64.4 ± 7.2	< 0.001	63.1 ± 7.8	64.4 ± 7.2	0.256
Diabetes duration (years)	9.6 ± 8.3	12.2 ± 7.1	0.012	13.1 ± 9.7	12.2 ± 7.1	0.461
Drug usage, *n* (%)						
Metformin	169 (66.3%)	52 (59.8%)	0.273	51 (58.6%)	52 (59.8%)	0.877
Lipid-lowering therapy	82 (32.2%)	40 (46.0%)	0.020	31 (35.6%)	40 (46.0%)	0.165
Antiplatelet therapy	33 (12.9%)	17 (19.5%)	0.132	10 (11.5%)	17 (19.5%)	0.143
Insulin therapy	233 (91.4%)	77 (88.5%)	0.428	82 (94.3%)	77 (88.5%)	0.177
Pioglitazone	149 (58.4%)	55 (63.2%)	0.432	59 (67.8%)	55 (63.2%)	0.523
BMI (kg/m^2)	26.51 ± 4.35	25.60 ± 3.20	0.073	25.01 ± 3.93	25.60 ± 3.20	0.285
Waist circumference (cm)	93.6 ± 10.3	94.9 ± 13.0	0.324	91.3 ± 9.4	94.9 ± 13.0	0.039
Hip circumference (cm)	99.1 ± 7.7	97.8 ± 6.6	0.161	97.0 ± 7.5	97.8 ± 6.6	0.436
VAT (cm^2)	98.0 ± 37.5	109.5 ± 30.3	0.010	90.1 ± 38.5	109.5 ± 30.3	< 0.001
SAT (cm^2)	196.5 ± 67.7	187.9 ± 49.7	0.279	180.3 ± 65.9	187.9 ± 49.7	0.394
Alcohol drinkers, *n* (%)	17 (6.7%)	8 (9.2%)	0.434	5 (5.7%)	8 (9.2%)	0.387
HBsAg positive, *n* (%)	12 (4.7%)	6 (6.9%)	0.429	5 (5.7%)	6 (6.9%)	0.755
MetS, *n* (%)	186 (72.9%)	56 (64.4%)	0.129	64 (73.6%)	56 (64.4%)	0.190
HbA1c (%)	9.30 ± 2.2	8.59 ± 1.95	0.007	9.05 ± 1.85	8.59 ± 1.95	0.113
FPG (mmol/L)	9.80 ± 3.41	9.42 ± 3.79	0.389	10.08 ± 3.83	9.42 ± 3.79	0.257
2hPG (mmol/L)	14.67 ± 4.63	15.19 ± 8.04	0.458	14.36 ± 4.88	15.19 ± 8.04	0.412
Fasting C-peptide (mmol/L)	0.77 ± 0.39	0.74 ± 0.40	0.616	0.76 ± 0.46	0.74 ± 0.40	0.737
Postprandial C-peptide (mmol/L)	1.65 ± 1.00	1.76 ± 1.17	0.426	1.62 ± 1.11	1.76 ± 1.17	0.430
Albumin (g/L)	42.81 ± 4.09	42.09 ± 4.40	0.165	42.22 ± 4.47	42.09 ± 4.40	0.842
TG (mmol/L)	2.32 ± 1.86	2.17 ± 1.78	0.518	2.22 ± 1.58	2.17 ± 1.78	0.845

Data are expressed as means ± standard deviation or medians (interquartile ranges) or numbers (percentage).
2hPG, 2-h postprandial plasma glucose; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; MAFLD, metabolic associated fatty liver disease; MetS, metabolic syndrome; PSM, propensity score matching; SAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue.

54.5 ± 11.6 years, $p < 0.001$) and had longer history of DM (12.2 ± 7.1 years *versus* 9.6 ± 8.3 years, $p < 0.05$) than the nonfibrosis group.

As age and duration of DM affect the development of fibrosis,[12,13] to minimize their influences, propensity score matching (PSM) analysis was performed to adjust for these two factors. Ultimately, the fibrosis group and nonfibrosis group each had 87 patients. The main anthropometric features before and after PSM are reported in Table 1.

Table 2. Lifestyle features of patients with MAFLD in nonfibrosis and fibrosis groups.

	Nonfibrosis group	Fibrosis group	*p*
Smokers, *n* (%)	26 (29.9%)	33 (37.9%)	0.262
Still at work, *n* (%)	14 (16.1%)	12 (13.8%)	0.671
Physical activity, *n* (%)	64 (73.6%)	56 (64.4%)	0.190
Daytime napper, *n* (%)	51 (58.6%)	53 (60.9%)	0.757
Daytime nap duration, h	1.20 ± 0.76	1.14 ± 0.70	0.671
Stay up late, *n* (%)	13 (14.9%)	28 (32.2%)	0.007
Nocturnal sleep duration, h	7.77 ± 1.92	6.77 ± 1.59	< 0.001
Fruits consumption, *n* (%)			0.700
<400 g per day	84 (96.6%)	83 (95.4%)	
⩾400 g per day	3 (3.4%)	4 (4.6%)	
Vegetable consumption, *n* (%)			0.759
<400 g per day	51 (58.6%)	49 (56.3%)	
⩾400 g per day	36 (41.4%)	38 (43.7%)	
Salt consumption, *n* (%)			0.696
<6 g per day	70 (80.5%)	72 (82.8%)	
⩾6 g per day	17 (19.5%)	15 (17.2%)	
Salt consumption, *n* (%)			0.598
<200 g per day	23 (26.4%)	20 (23.0%)	
⩾200 g per day	64 (73.6%)	67 (77.0%)	

MAFLD, metabolic associated fatty liver disease.

After PSM adjustment, no significant difference was found in age, sex, DM course, and use of metformin, pioglitazone, antiplatelet therapy, lipid-lowering agents, and insulin therapy between the two groups, which are factors that might influence the progress of MAFLD.[14–18] The fibrosis group had larger waist circumference (94.9 ± 13.0 cm *versus* 91.3 ± 9.4 cm, $p < 0.05$) and VAT areas (109.5 ± 30.3 cm^2 *versus* 90.1 ± 38.5 cm^2, $p < 0.001$) than the nonfibrosis group, but SAT areas showed no significant difference (Table 1).

As regards biochemical features (Table 1), glycemic profile (HbA1c, FPG, 2hPG, fasting and postprandial C-peptide values) and lipid profiles (TC, TG, HDL-C, and LDL-C values) were not significantly different between the two groups. Gamma-glutamyltransferase and serum uric acid did not differ between the two groups.

Association between sleep duration and risks of liver fibrosis in patients with MAFLD

Lifestyle data are shown in Table 2. The fibrosis group had shorter nocturnal sleep duration than the nonfibrosis group (6.77 ± 1.59 h *versus* 7.77 ± 1.92 h, respectively, $p < 0.001$), and more patients stayed up late at night (32.2% *versus* 14.0%, $p < 0.01$). Daytime nap was not significantly different between the two groups. As regards dietary intake and other lifestyle factors, no significant differences were found between the

Table 3. Association between nocturnal sleep and VAT areas and liver fibrosis risks in patients with MAFLD.

	Multivariate OR (95% CI)		
	Unadjusted model	**Model 1**	**Model 2**
Waist circumference (cm)	0.998 (0.963–1.034)	1.023 (0.976–1.071)	1.025 (0.978–1.073)
VAT (cm^2)	1.018 (1.006–1.030)**	1.032 (1.015–1.049)***	1.031 (1.014–1.048)***
Stay up late	0.601 (0.259–1.398)	0.552 (0.224–1.358)	0.553 (0.215–1.418)
Nocturnal sleep duration (h)	0.742 (0.604–0.912)**	0.709 (0.568–0.883)**	0.694 (0.551–0.875)**

Model 1: Adjusted for age, sex, BMI, and diabetes duration.
Model 2: Additionally adjusted for drug usage in evaluating the association between nocturnal sleep and VAT areas and MAFLD.
**$p < 0.01$, ***$p < 0.001$.
BMI, body mass index; CI, confidence interval; MAFLD, metabolic associated fatty liver disease; OR, odds ratio; VAT, visceral adipose tissue.

groups in terms of fruit, vegetable, fish, salt, and cigarette consumption as well as physical activities.

Multivariate binary linear regression analysis was performed to assess the influence of sleep on the risk of liver fibrosis (Table 3). Model 1 was adjusted for age, sex, BMI, and DM duration, and the odds ratios (ORs) and 95% confidence interval (CI) of liver fibrosis were 0.709 (0.568–0.883) for nocturnal sleep and 1.032 (1.015–1.049) for VAT areas ($p < 0.01$ and $p < 0.001$, respectively). Model 2 was further adjusted for drug usage, and the association between nocturnal sleep duration and fibrosis remained statistically significant, with ORs (95% CIs) of 0.694 (0.551–0.875) for nocturnal sleep and 1.031 (1.014–1.048) for VAT areas ($p < 0.01$ and $p < 0.001$, respectively).

Discussion

MAFLD represents a wide spectrum of metabolic pathological states on the basis of hepatic steatosis, the heterogeneity of which renders it necessary to stratify patients when proposing therapies. In this study, we examined features of MAFLD with type 2 DM and searched for the risk factors of advanced liver fibrosis. We found that insufficient nocturnal sleep and larger VAT areas were associated with liver fibrosis, independent of relevant confounders including age, sex, BMI, and DM duration.

Liver fibrosis stage is prognostic to the development of liver-related and all-cause mortality.[19–21] Factors contributing to the progress of fatty liver disease include enhanced inflammatory levels, dysregulated lipid metabolism, changes in gut microbiota, insulin resistance, etc.[22] The effect of sleep on the liver has been receiving attention in recent years as it regulates a series of endocrine signaling as well as the overall metabolic process. Sleep deprivation has been proven to inhibit energy production and enhance lipogenesis of hepatocytes and consequently induce hepatic steatosis and hepatic insulin resistance.[23,24] In a recent study, Peng *et al.* revealed that insufficient night-time sleep and prolonged daytime nap (>30 min) were positively linked to an increased risk of NAFLD prevalence in the middle-aged and older Chinese population.[25] Sleep disturbance or low sleep quality was also related to increased liver stiffness in patients with NAFLD, which was consistent with our findings, whereas optimal sleep (defined as sleep duration ⩾7 h and ⩽9 h/day) was found to be protective in reducing insulin resistance and liver stiffness.[8,26]

Sleep plays regulating roles in eating habits, weight gain, neuroendocrine signaling, and glucose homeostasis, and studies reported its link to higher risks of DM and worse control of glycemic levels in patients with DM.[27–29] Excessive and low-quality sleep was also harmful to metabolic health. Sleeping >9 h was shown to increase the risk of DM, cardiovascular disease, coronary heart disease, and obesity.[30,31] The MAFLD criteria contain a wider spectrum of disease rather than the pathology of an individual organ; impairments in overall metabolic homeostasis would inevitably bring further insult to the liver, and *vice*

versa. The disruption of the circadian clock is detrimental to liver functions.[32] Our study revealed that in the case of dysregulated metabolic functions, with multiple influencing factors, sleep duration was still independently related to the progress of fatty liver disease, which highlighted the importance of sleep in regulating liver metabolism and homeostasis of the metabolic environment.

Moreover, the relationship between sleep and liver disease was proven reciprocal. The prevalence of sleep-wake disturbances, such as difficulties in sleep onset and sleep maintenance, daytime sleepiness, and sleep aversion, was higher in patients with liver cirrhosis and fatty liver disease.[33] If sleep disorder is accompanied by intermittent hypoxia, which happens in obstructive sleep apnea (OSA), the activation of the sympathetic nervous system, increased cortisol secretion, and inflammatory levels would exacerbate the attacks on the liver and further heighten the risks of liver fibrosis and cardiovascular diseases.[34,35]

In our study, another factor found to be independently related to fibrosis was increased VAT area, which was consistent with the findings of previous studies.[36,37] Anatomically, VAT is connected closely and drained directly through the portal circulation to the liver, and it was reported to be more inflammatory and metabolically active than SAT, containing a larger number of immune cells and glucocorticoid and androgen receptors.[38] In obese patients, VAT deposition exposed the liver to increasing amounts of free fatty acids and proinflammatory factors, and promoted the development of hepatic insulin resistance and liver steatosis.[39] The deposition of adipose was also affected by sleep, and short sleep duration and poor sleep quality were positively related with visceral adiposity,[40] whereas a change from <6 h to 7–8 h of sleep was found to be beneficial in reducing VAT deposition.[41]

This study has several limitations. First, the sleep duration was self-reported. Nonetheless, evidence showed that self-reported sleep duration was well correlated with an objective measurement.[42] Secondly, we did not include histologic proof of liver fibrosis, but applied the noninvasive index of FIB-4, which was more acceptable by patients. The FIB-4 has a sensitivity of 0.844 and specificity of 0.685 in diagnosing liver fibrosis.[43] Thirdly, sleep apnea was not screened, as OSA was also a contributing factor to liver damage,[44] which would be complemented in further research.

In conclusion, our study revealed that insufficient nocturnal sleep and increased VAT area were associated with higher risk of liver fibrosis in patients with MAFLD. Currently, there are limited pharmacological therapies for MAFLD. Exogenous interventions like lifestyle changes have been proved to alleviate disease progression, as supported by various studies.[45] As sleep pattern influences liver metabolism and systemic metabolic health holistically, optimizing sleep duration and quality might be beneficial in promoting the health of patients with MAFLD.

Author contributions

Jiaping Zheng: conceptualization; formal analysis; investigation; writing–review and editing.

Sijie Chen: data curation; investigation; methodology; writing–review and editing.

Yuqing Cai: conceptualization; data curation; software; writing–review and editing.

Su Lin: conceptualization; project administration; writing–review and editing.

Sujie Ke: data curation; investigation; writing original draft.

Libin Liu: conceptualization; funding acquisition; project administration; supervision; writing–review and editing.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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