Observational Study

Medicine

OPEN

Association between the degree of nonalcoholic fatty liver disease and nocturnal hypertension

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Abstract

Nighttime blood pressure (BP) decreases have prognostic significance owing to circadian patterns. The prevalence of nonalcoholic fatty liver disease (NAFLD) has rapidly increased in recent years. We aimed to investigate circadian blood pressure changes in patients with NAFLD. The present study included 114 patients diagnosed with nonalcoholic fatty liver disease and no previous hypertension diagnosis. Thirty patients comprised the control group (no hepatosteatosis and no hypertension). The patients were divided into 3 groups based on nocturnal BP dipping. Blood pressure patterns using night–day ratios were classified as dipper (ratio ≤ 0, 9), nondipper (0, 9 < ratio ≤ 1, 0), or nocturnal hypertension (ratio > 1, 0). There were no significant differences in sex, age, presence of diabetes, or biochemical test results between the groups. According to the blood pressure pattern, the nondipper rate in the hepatosteatosis group was significantly higher than that in the control group. Patients were compared in terms of the presence and severity of hepatosteatosis according to night blood pressure patterns. A significant difference was observed between the groups ($P < .001$ and $P = .001$, respectively). We found an association between hepatosteatosis severity and night blood pressure patterns. Patients with nonalcoholic fatty liver disease have a higher incidence of nocturnal hypertension. We observed impaired circadian blood pressure changes in patients with nonalcoholic fatty liver disease.

Abbreviations: ABPM = ambulatory blood pressure monitoring, BP = blood pressure, NAFLD = nonalcoholic fatty liver disease.

Keywords: blood pressure, circadian pattern, nonalcoholic hepatosteatosis

1. Introduction

Systemic blood pressure (BP) exhibits diurnal variations characterized by a decrease during sleep. Millar-Craig et al[1] showed that the circadian rhythm of BP was lowest at night but highest mid-morning by continuous intra-arterial blood pressure and electrocardiogram recordings. These findings emphasized the importance of the circadian rhythm of BP in the context of therapeutic management of arterial hypertension.

The daily rhythm of BP is affected by intrinsic and extrinsic factors such as emotional state, dietary sodium intake, neurohormonal regulation, physical activity, smoking cigarettes and drinking alcohol.[2] Ambulatory blood pressure monitoring (ABPM) is a basic tool for detecting Circadian pattern of BP and determining associated cardiovascular risk factors.[3]

The night-to-day ratio is a significant predictor of outcome and allows subdivision of patients into dippers (night-day ratio ≤ 0.9 or >10% of the daytime average BP) and nondippers (night–day ratio > 0.9 or ≤10% of the daytime average BP).[4] Furthermore, nocturnal hypertension is associated with adverse cardiovascular outcome.[5–7]

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease.[8] The prevalence of NAFLD has increased rapidly in recent years and is associated with an increase in type 2 diabetes, hypertension and hypercholesterolemia.[9,10] Insulin resistance, oxidative stress, and inflammation play important roles in the pathogenesis and progression of NAFLD.[11,12] Moreover, there is a relationship between circadian clock dyssynchrony and NAFLD pathophysiology.[13]

In addition to high BP, circadian BP variability is also a predictor of target organ damage. Nondipping is linked to the progression of chronic kidney disease and is 5 times higher in end-stage kidney disease.[14,15] Circadian blood pressure changes in patients with NAFLD are unknown. Knowledge of circadian changes in blood pressure in patients with NAFLD may be important for understanding cardiovascular adverse events. We aimed to investigate the circadian BP changes in patients with NAFLD.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Astan R, Kacmaz F, Saricam E, OZYER EU, Ilkay E. Association between the degree of nonalcoholic fatty liver disease and nocturnal hypertension. Medicine 2025;104:9(e41695).

Received: 16 September 2024 / Received in final form: 7 February 2025 / Accepted: 10 February 2025

http://dx.doi.org/10.1097/MD.0000000000041695

2. Materials and methods

The present study included 144 patients diagnosed with nonalcoholic fatty liver disease and no previous hypertension. In the control group, 30 patients (nonhepatosteatosis and no hypertension) were evaluated. The data of all patients included in the study were retrospectively collected between 2021 and 2022 at the Batman Training and Research Hospital.

All patients underwent normotensive office or ambulatory daytime BP measurements. According to the results of ultrasonography, the patients were divided into 4 groups (group 1: nonhepatosteatosis; group 2: grade 1 hepatosteatosis; group 3: grade 2 hepatosteatosis; group 4: grade 3 hepatosteatosis). All patients underwent 24-hour ABPM and nighttime blood pressure patterns were evaluated. We classified nighttime blood pressure patterns as normotensive dipper, normotensive nondipper (N-ND), and nocturnal hypertension.[6,7]

The patients were divided into 3 groups according to nocturnal BP dipping. The BP patterns using night–day ratios were classified as dipper (ratio ≤ 0, 9), nondipper (0, 9 < ratio ≤ 1, 0), or nocturnal hypertension (ratio > 1, 0). Nocturnal hypertension (ratio > 1.0, average BP ≥ 120/70 mm Hg during night hours).[5–7]

The study protocol was approved by the Batman Training and Research Hospital Ethics Committee (decision number: 75144452, 929-3483, (270)/2021, 23-03-2021) and was performed in accordance with the Declaration of Helsinki. All the patients provided written informed consent to participate in the study.

Physical examination and 12-lead electrocardiography (ECG) were performed. Age, sex, smoking habits, medications used, and background information were also recorded. Patients with a history of heart failure, coronary artery disease, acute or chronic liver disease, primary and secondary hypertension, hematologic diseases, respiratory diseases, hypothyroidism or hyperthyroidism, cerebrovascular disease, acute or chronic infection, collagen tissue disease, autoimmune disease, use of steroid agents, or malignancy were excluded from the study. Sixteen patients were excluded from this study.

2.1. Twenty four-hour ABPM recordings

ABPM was performed using a Rozinn RZ250 ABP recorder (SN R 02157/0807, Glendale). The awake and sleep periods were assessed according to the patients information. Nocturnal BP dipping was calculated as follows: (%) 100 × (1–[sleep systolic BP/awake systolic BP]). The devices were programmed to perform measurements every 15 minutes between 07:00 and 23:00 (daytime) and every 30 minutes between 23:00 and 07:00 (nighttime).

2.2. Ultrasonography

The US examination of the liver was performed by a radiologist using a Versana Premier, Ultrasound device (General Electric Medical Systems, Jiangsu, China).

The diagnosis of fatty liver was established using the noninvasive method of abdominal ultrasound, followed by the exclusion of secondary causes of hepatic steatosis: a history of another known liver disease, alcohol intake of >30 g/day for males and >20 g/day for females, a positive serology for hepatitis B or C virus, or ingestion of drugs known to produce hepatic steatosis.

2.3. Echocardiographic evaluation

Transthoracic echocardiography was performed in all patients using an ultrasound machine. All measurements were performed in accordance with the American Society of Echocardiography.[16] Left ventricular hypertrophy (left ventricular mass > 95 g/m^2 for women and >115 g/m^2 for men) was excluded using echocardiography.

2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 22, IBM Corporation, Somers). The normality of the distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges, depending on the normality of their distribution. Categorical variables were interpreted using frequency tables. Categorical variables were described as frequencies and percentages. Categorical features and relationships between groups were assessed using an appropriate chi-square test. Variables that were not normally distributed were compared using the Kruskal–Wallis test. The Mann–Whitney *U* test was used when binary comparisons were required. Normally distributed variables were compared using a 1-way ANOVA variance. When overall significance was observed, pairwise post hoc tests were performed using Tukey's test. Levene's test was used to assess the homogeneity of the variances. Statistical significance was set at a 2-tailed *P* value of <.05.

3. Results

Baseline patient characteristics are shown in Table 1. There were no significant differences in sex, age, presence of diabetes, or biochemical test results between the groups. However, the sleep time relative to BP decline was significantly different between the groups (control group; 15.7 ± 3.4 [systolic] 11.6 ± 3.6 [diastolic], grade-1 NAFLD; 11.5 ± 13.7 [systolic] 8.4 ± 8.3 [diastolic], grade-2 NAFLD; 5.8 ± 9.5 [systolic] 5.6 ± 8.5 [diastolic], grade-3 NAFLD; 4.4 ± 5.8 [systolic] 4.6 ± 4.4 [diastolic], $P < .001$,$P = .001$).

Blood pressure patterns according to the hepatosteatosis classification are presented in Table 2. The nondipper rate was significantly higher in the hepatosteatosis group than in the control group.

The patients were compared in terms of the presence and severity of hepatosteatosis according to the night blood pressure patterns in Table 3. A significant difference was observed between the groups ($P < .001$ and $P = .001$, respectively).

Only the normotensive patients were compared in terms of hepatosteatosis according to the presence or absence of dippers, and a significant difference was observed between the groups ($P < .001$). This difference was only observed between the frequencies of nonhepatosteatosis and the frequency of grade-3 (Fig. 1).

4. Discussion

Here, we showed that the non-dipper rate in the hepatosteatosis group was significantly higher than that in the normal control group. Patients were compared in terms of the presence and severity of hepatosteatosis according to night blood pressure patterns. A significant difference was observed between the groups ($P < .001$ and $P = .001$, respectively). We found a relationship between hepatosteatosis severity and night blood pressure patterns. Patients with NAFLD have a higher incidence of nocturnal hypertension. Therefore, NAFLD may be a cardiovascular risk factor for nocturnal hypertension.

Circadian rhythms are composed of core cellular processes that affect organ system.[13] In mammals, the circadian pacemaker not only exists in hypothalamic structures but also in the lungs, liver, and other organs.[17,18] Therefore, endogenous functional clocks are also active in peripheral tissues.[19] For instance,

Table 1

Baseline characteristics of study group.

		NAFLD			
	No (control) (n = 30)	Grade-1 (n = 61)	Grade-2 (n = 32)	Grade-3 (n = 21)	*P*
Sex, male (%)	8 (26.7)	18 (29.5)	16 (50.0)	7 (33.3)	.178
Age (yr)	55.5 ± 15.0	55.5 ± 13.0	57.1 ± 13.3	59.8 ± 11.9	.614
Diabetes, yes (%)	8 (26.7)	10 (16.4)	9 (28.1)	5 (23.8)	.528
Office systolic BP (mm Hg)	125 (120–140)	130 (120–142.5)	130 (120–140)	120 (120–140)	.584
Office diastolic BP (mm Hg)	75 (70–85)	80 (70–90)	72.5 (70–83.8)	70 (70–85)	.713
Creatinine (mg/dL)	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.9 (0.7–1.1)	0.8 (0.7–1.0)	.006
Thyroid-stimulating hormone (mIU/L)	1.2 (0.8–2.0)	1.1 (0.54–1.62)	1.15 (0.97–1.62)	1.51 (0.58–2.1)	.550
Office pulse rate (min)	81 (70–84)	76 (68–83)	77 (74–84)	80 (78–88)	.059
White blood cell count, $10^3/mm^3$	7.4 (6.4–8.6)	7.4 (6.8–8.6)	7.4 (6.4–8.6)	7.6 (6.7–8.4)	.842
Absolute neutrophil count, $10^3/mm^3$	4.6 (4.1–5.4)	4.3 (3.6–5.4)	4.2 (3.5–5.1)	4.2 (3.8–5.0)	.573
Absolute lymphocyte count, $10^3/mm^3$	2.2 (1.5–2.6)	2.5 (1.7–2.7)	2.2 (1.7–2.7)	2.5 (2.1–2.8)	.224
C-reactive protein (CRP), mg/L	0.3 (0.1–0.7)	0.4 (0.2–0.8)	0.2 (0.1–0.7)	0.6 (0.4–1.1)	.094
Low-density lipoprotein (mg/dL)	105 ± 15.2	110 ± 28.3	114 ± 31.4	99 ± 30.6	.227
Number of hypertension medications	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–3)	.016
Systolic BP, mm Hg					
Awake	129.1 ± 13.4	129.9 ± 17.8	132.3 ± 17.5	122.8 ± 16.3	.234
Asleep	113.4 ± 11.8	119.2 ± 17.1	126.5 ± 20.4	118.4 ± 15.0	.023
24 h	125.6 ± 12.8	127.8 ± 17.0	130.9 ± 17.8	122.0 ± 15.9	.246
Diastolic BP, mm Hg					
Awake	81.2 ± 10.4	83.2 ± 13.4	80.6 ± 10.6	75.1 ± 8.9	.061
Asleep	69.6 ± 9.3	74.0 ± 12.0	75.0 ± 12.2	70.5 ± 8.4	.153
24 h	78.9 ± 10.2	80.8 ± 12.9	80.0 ± 10.3	74.2 ± 8.5	.146
Sleep time relative BP decline,					
mm Hg	15.7 ± 3.4	11.5 ± 13.7	5.8 ± 9.5	4.4 ± 5.8	<.001
Systolic	11.6 ± 3.6	8.4 ± 8.3	5.6 ± 8.5	4.6 ± 4.4	.001
Diastolic					

BP = blood pressure, CRP = C-reactive protein, NAFLD = Nonalcoholic fatty liver disease.

* Continuous variables were expressed as means ± standard deviation, or medians (interquartile ranges) and categorical variables as numbers with percentages for the description of baseline characteristics.

Table 2

Blood pressure pattern according to hepatosteatosis classification.

Blood pressure pattern	Steatozis grade	Steatozis grade	Steatozis grade	Steatozis grade
	Control	Grade 1	Grade 2	Grade 3
Dippers, n (%)	28 (93.4)	32 (52.5)	10 (31.4)	1 (4.8)
Nondippers, n (%)	1 (3.3)	25 (41)	17 (53.1)	14 (66.7)
Nocturnal, n (%)	1 (3.3)	4 (6.5)	5 (15.6)	6 (28.6)

Each subscript letter denotes a subset of steatosis categories whose column proportions do not differ significantly from each other at the 0.5 level.

Table 3

The relationship between hepatosteatosis rate and night blood pressure pattern.

Hepatosteatozis grade	Blood pressure pattern	Blood pressure pattern	Blood pressure pattern
	Dippers	Nondippers	Nocturnal
Control, n (%)	28 (39.4)	1 (1.8)	1 (6.2)
Grade 1, n (%)	32 (45.1)	25 (43.9)	4 (25)
Grade 2, n (%)	10 (14.1)	17 (29.8)	5 (31.3)
Grade 3, n (%)	1 (1.4)	14 (24.5)	6 (37.5)

Each subscript letter denotes a subset of blood pressure pattern categories whose column proportions do not differ significantly from each other at the 0.5 level.

the timing of food intake can reset the hepatic clock without affecting hypothalamic structural clock rhythms.[20]

Hepatic metabolic pathways also exhibit circadian rhythm. Circadian dyssynchrony between the hypothalamic structures and hepatic circadian clock may cause metabolic disorders, including increased adiposity, ectopic steatosis, and insulin resistance.[20–23] Interestingly, in patients with NAFLD, dysfunctional processes in the circadian clock machinery and various aspects of metabolism have been with NAFLD.[13] Dysregulation of de novo lipogenesis is an important cause of lipid accumulation in hepatocytes of patients with NAFLD.[12] The liver contains several master metabolic regulators, including adenosine monophosphate-activated protein kinase and cyclic adenosine monophosphate response element-binding protein. Several metabolic hormones, including glucagon and epinephrine, can influence the circadian clock mechanism through response element-binding protein activation.[24] Abnormalities in this process could affect cardiac circadian patterns in patients with NAFLD.

Isolated nocturnal hypertension is defined as an average BP≥ 120/70 mm Hg recorded during night hours with ABPM in people with normal daytime BP.[25–27] Moreover, it has been found to be more prevalent in men with high-normal BP and a high cardiovascular risk profile, African Americans, older individuals, and obese and diabetic patients.[28] An abnormal circadian pattern is associated with a higher risk of adverse cardiovascular outcomes.[25–27]

4.1. Limitations

This study has some limitations. This retrospective study was performed at a single center. However, we believe that the results of our study will be valuable for future research, relationships revealed herein could provide a basis for research focusing on the detection of nocturnal hypertension patterns among patients with NAFLD.

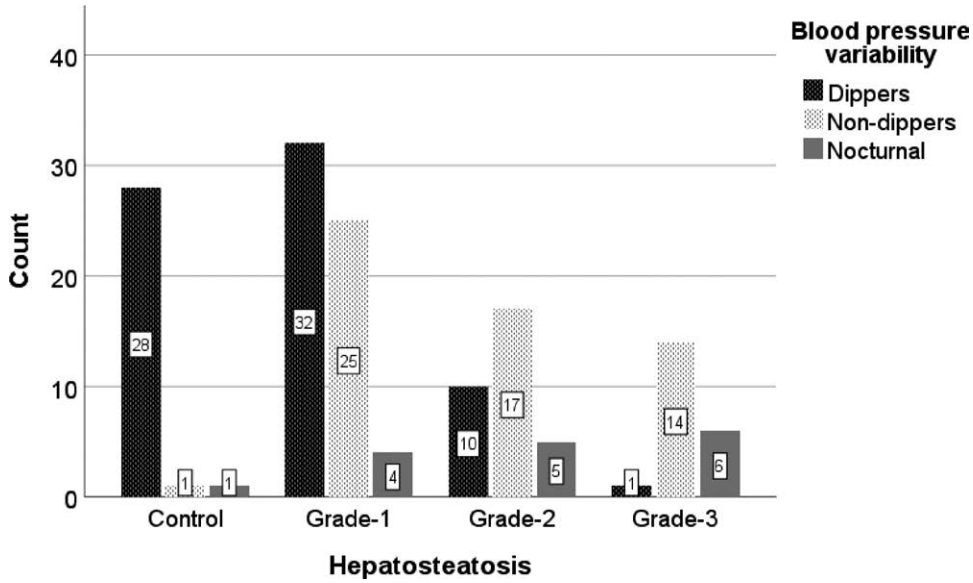

Figure 1. Comparison of blood pressure pattern according to hepatosteatosis groups.

5. Conclusion

Our study is the first study reported in the literature revealing the relationship between circadian blood pressure and NAFLD. Impaired of circadian blood pressure changes were in patients with NAFLD. Therefore, patients with NAFLD should be followed-up as follows: cardiovascular risk factor.

Author contributions

Conceptualization: Ramazan Astan, Fehmi Kacmaz, Ersin Saricam, Erdogan Ilkay.
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