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Relationship Between Monocyte/HDL Cholesterol Ratio and Urinary Protein Excretion in Patients with Primary Hypertension with Reverse Dipper Pattern

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Abstract

Objective: Ambulatory blood pressure (BP) monitoring is confronted with different clinical patterns due to diurnal changes. Rise of BP at night is known as reverse dipper, whereas it is expected to decrease at night physiologically. The monocyte/high-density lipoprotein (HDL) cholesterol ratio (MHR) is considered as a marker of inflammation and oxidative stress. The aim of the present study was to investigate the relationship between MHR and urinary protein excretion in a reverse dipper hypertension (RDHT) patient group.

Materials and Methods: Twenty-four-hour ambulatory BPs of 195 patients with primary hypertension were measured. Systolic and diastolic BP measurements were recorded. We examined the MHR and 24-hour urine protein excretion in patients with RDHT.

Results: In our study, urinary protein excretion, which is a predictive indicator of target organ damage in patients with RDHT, was found to be higher than other groups. Furthermore, MHR, an oxidative stress and inflammation marker, was found to be higher in this patient group. Stepwise regression analysis revealed that MHR was an independent predictor of urinary protein excretion in the RDHT group.

Conclusion: In patients with RDHT, except for normal physiology, high nighttime BP measurements have a negative effect on all systems. Oxidative stress and inflammation are thought to play a role in this process in terms of target organ damage.

Keywords: Monocyte/HDL ratio, reverse dipper, primary hypertension

INTRODUCTION

Hypertension is a multisystemic chronic disease that can be queried in the pathogenesis of many tissue and organ damages in the cardiovascular system. Depending on nocturnal variability of blood pressure (BP), damage may change in target organs. Rhythm of nocturnal circus is classified according to the level of variability in night BP.

In this classification made by ambulatory blood pressure monitoring (ABPM), a ≥10% decrease in BP measured at night according to the BP value measured during the day is equivalent to dipper hypertension (DHT). A fall of <10% is classified as non-dipper hypertension (NDHT)

(1, 2). Over time, extreme dipper (EDHT) and reverse dipper (RDHT) concepts have been added to the literature. In a ≥20% decrease in BP measurement EDHT, the increase in BP is defined as RDHT (3).

Patients with RDHT and NDHT have worse prognosis for cardiovascular, cerebrovascular, and renal target organ damage, which is associated with mortality (4). In a study, chronic renal damage associated with hypertension was seen in approximately 40% of patients with RDHT BP pattern. In these patients, more proteinuria and target organ damage, such as left ventricular hypertrophy, were detected compared with patients with DHT (5).

Parameters, such as carotid intima media thickness, echocardiographic evaluation, and urinary protein excretion, are performed to determine target organ damage of hypertension, but these are specialized and expensive tests that cannot be easily performed at each center. Therefore, easily identifiable markers or indices are needed to determine target organ damage.

In many studies in the literature, monocyte/high-density lipoprotein (HDL) cholesterol ratio (MHR) is considered as a prognostic marker of cardiovascular disease, which shows inflammation and oxidative stress. Specifically, MHR was found to be an independent risk factor for target organ damage due to HT (6). The aim of the present study was to investigate the relationship between MHR and urinary protein excretion in the RDHT patient group.

MATERIALS AND METHODS

Study Population
This retrospective study was conducted between July 2017 and September 2017 in the Internal Medicine Clinic, Ankara Numune Training and Research Hospital. A total of 195 patients, aged ≥18 years, who were followed up with a diagnosis of essential hypertension were included in the study.

Exclusion criteria included presence of diabetes mellitus, known secondary HT, acute or chronic renal failure, cerebrovascular disease, ischemic heart disease, congestive heart failure, acute or chronic liver disease, malignancy, inflammatory diseases, such as infections or autoimmune disorders, lipid-lowering drug use, antioxidant substance use, smoking, alcohol use, and vitamin deficiency.

The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research hospital-Number:1304/2017, Data:26-April-2017.

Biochemical Parameters
Clinical and laboratory parameters of all participants were retrospectively collected in electronic medical records at the hospital. The complete blood counts were tested using an automatic blood cell analyzer (Pentra 120 Retic Hematology Analyzer; Horiba ABX, Montpellier, France), and the monocyte count was determined as part of the routine hemogram. The reference value for monocyte in our laboratory is 2%-10%. Biochemical parameters were determined by an Automatic Biochemical Analyzer 7600-120 (Hitachi High Technologies, Japan). Total cholesterol and triglycerides were measured via the enzymatic colorimetric method, and HDL cholesterol was measuredvia the homogenous enzymatic colorimetric method using a Hitachi Modular P800 auto-analyzer (Roche Diagnostics Corp., IN, USA).

MHR (μL mg^{-1}dL) was defined as the ratio of absolute monocyte count (mL^{-1}) and HDL cholesterol level (mg dL^{-1}).

Ambulatory Blood Pressure Monitoring
The WatchBP O3 ABPM device (Microlife WatchBP AG, Switzerland) for 24-hour ABPM was evaluated for 24-hour systolic and diastolic BP (SBP and DBP) measurements.

Definitions
Participants with a reduction in SBP of ≥10% but <20% at nighttime compared with daytime were considered to have a dipping BP pattern. An extreme dipping BP pattern referred to a reduction at nighttime of >20%. A non-dipping BP pattern referred to a <10% reduction at nighttime. A reverse dipping BP pattern referred to higher SBP at nighttime than at daytime.

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Table 1. Demographic characteristics of patients					
Variables	Reverse n=35	Non-dipper n=76	Dipper n=64	Extreme dipper n=20	p
Gender					
Female	20 (57.1)	39 (51.3)	31 (48.4)	6 (30.0)	0.266
Male	15 (42.9)	37 (48.7)	33 (51.6)	14 (70.0)	
Age (year)	56.9±10.7	51.2±14.8	51.8±12.3	47.7±13.5	0.835
BMI (kg m^{-2})	30.1±3.2	29.7±5.2	30.2±5.8	29.9±5.1	0.458
SBP (mmHg)	158.2±13.9[bcd]	148.9±11.7[acd]	135.8±4.6[ab]	136.1±5.3[ab]	<0.001*
DBP (mmHg)	98.4±9.1[bcd]	92.2±8.8[acd]	85.9±4.4[ab]	86.2±5.6[ab]	<0.001*

BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure
Categorical variables were expressed as number (%).
Numerical variables were expressed as mean±standard deviation.
*p<0.05 was statistically significant.
[a]: Reverse dipper group vs other dipper groups (p<0.05).
[b]: Non-dipper group vs other dipper groups (p<0.05).
[c]: Dipper group vs other dipper groups (p<0.05).
[d]: Extreme dipper group vs other dipper groups (p<0.05).

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Table 2. Laboratory results of patients

Variables	Reverse n=35	Non-dipper n=76	Dipper n=64	Extreme dipper n=20	p
WBC (µL⁻¹)	8728.0±2544.1	8233.9±2620.1	8625±3258.8	7700.5±1391.8	0.476
Hb (g dL⁻¹)	13.1±2.3	13.6±2.1	13.4±2.4	13.9±1.9	0.548
Plt (10³µL⁻¹)	273.8±106.3	272.3±75.5	248±64.6	297.2±95.3	0.078
Monocyte (µL)	870 (280-2300)[bcd]	615 (300-1600)[a]	500 (200-1200)[a]	500 (300-900)[a]	<0.001*
BUN (mg dL⁻¹)	41 (17-147)	35.5(17-154)	32.5 (15-249)	33 (14-122)	0.482
Creatinine (mg dL⁻¹)	1.1(0.5-4.9)	1(0.4-7.6)	1 (0.5-8.2)	0.9 (0.6-564.9)	0.918
CRP (mg l⁻¹)	6 (0.9-94.9)	5 (0.1-112)	4.9 (0.7-237)	4.5 (0.2-13)	0.588
Urine prot (g 24h⁻¹)	2 (0.1-9)[bcd]	0.3 (0-0.9)[a]	0.2 (0-1.3)[a]	0.1 (0.1-1.1)[a]	<0.001*
CHOL (mg dL⁻¹)	212.5±63.9	209.3±53.8	211.9±55.2	231.1±29.1	0.463
HDL (mg dL⁻¹)	42.2±12.4[cd]	44.3±12.0[cd]	50.1±13.2[ab]	52.8±12.1[ab]	0.013*
LDL (mg dL⁻¹)	135.5±45.5	129.5±46.3	134.2±51.4	150.1±70.2	0.454
TG (mg dL⁻¹)	134 (49-417)	140 (48-703)	167 (38-654)	126 (50-707)	0.398
MHDL (µL mg⁻¹dL)	18.8 (7.1-51.1)[bcd]	15.6 (7-35.5)[acd]	11.1 (2.8-20)[ab]	9.4 (4.3-17.3)[ab]	<0.001*

WBC: white blood cell; Hb: hemoglobin; Plt: platelet; BUN: blood urine nitrogen; Urine prot: urine protein; CHOL: cholesterol; HDL: high density lipoprotein; TG: triglycerides; MHDL: monocyte/hdl ratio
Categorical variables were expressed as number (%).
Numerical variables were expressed as mean±standard deviation.
*p<0.05 was statistically significant.
[a]: Reverse dipper group vs other dipper groups (p<0.05).
[b]: Non-dipper group vs other dipper groups (p<0.05).
[c]: Dipper group vs other dipper groups (p<0.05).
[d]: Extreme dipper group vs other dipper groups (p<0.05).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows 20 program (IBM SPSS Corp.; Armonk, NY, USA). The normal distribution of data was assessed by the Kolmogorov-Smirnov test. Normal distributions of numerical variables were expressed as mean±standard deviation, and those without normal distribution as median (min-max). The ANOVA test and the Kruskal–Wallis H test were used to evaluate the differences between the numerical variables with normal distribution and the normal numerical variables. Exact chi-square test was used to compare categorical data. The relationship between numerical variables was examined by Spearman correlation analysis. Stepwise multivariable linear regression analysis was used to identify independent predictors of urinary protein and MHR. Numerical variables without normal distribution before regression analysis were transformed to normal distribution by logarithmic transformation. For statistical analysis, a p<0.05 was considered significant.

RESULTS

The study population consisted of 39% non-dipper (n=76), 32.8% dipper (n=64), 17.9% reverse dipper (n=35), and 10.3% EDHT. The mean age of the entire population was 52.0±13.3 years. In the study population, 50.8% were male, mean SBP was 144.6±13.2 mm Hg, and mean DBP was 90.7±8.6 mm Hg.

Gender, mean age (years), and mean body mass index (kg m⁻²) levels did not differ between the groups (p>0.05). Mean SBP (mm Hg) and DBP levels (mm Hg) were higher in the reverse dipper group than in the other groups (p<0.001). The mean levels of SBP (mm Hg) and DBP (mm Hg) were higher in the non-dipper group than in the dipper and EDHT groups (Table 1).

The median monocyte level (mL⁻¹) and median urinary protein excretion (g 24 h⁻¹) were higher in the reverse dipper group (p<0.001), and the mean HDL level (mg dL⁻¹) was lower (p<0.05). The median monocyte/HDL cholesterol level (µl mg⁻¹ dL) was also higher in the reverse dipper group (p<0.001) (Table 2).

In the reverse dipper group, urinary protein level (g 24 h⁻¹) had a positive correlation with SBP (r=0.391, p=0.025), DBP (r=0.520, p<0.001), white blood cell (WBC), C-reactive protein (CRP) level (r=0.532, p<0.001), and MHR (µl mg⁻¹ dL). Serum HDL level (r=−0.310, p=0.027, p=0.045) had a negative correlation with urinary protein level (g 24 h⁻¹) (Table 3). In the reverse dipper group, the ratio of monocyte/HDL cholesterol (µL mg⁻¹ dL) had a positive correlation with SBP (mm Hg) (r=0.300, p=0.040), DBP (mm Hg) (r=0.543, p<0.001), WBC (mL⁻¹) (r=0.325, p=0.027), and CRP level (mg L⁻¹) (r=0.343, p=0.018) (Table 4).

Findings related to urinary protein (g 24 h⁻¹) and monocyte/HDL cholesterol levels (µL mg⁻¹ dL) in the reverse dipper group

Table 3. Urine protein-related findings

Variables	Reverse dipper		Non-dipper		Dipper		Extreme dipper	
	r	p	r	p	r	p	r	p
Age (yr)	0.167	0.339	0.123	0.291	0.086	0.499	0.049	0.837
BMI (kg/m^2)	0.205	0.287	0.199	0.369	0.167	0.402	0.183	0.561
SBP (mm Hg)	0.391	0.025*	0.245	0.190	0.100	0.429	0.147	0.536
DBP (mm Hg)	0.520	<0.001*	0.305	0.007*	0.033	0.797	0.036	0.879
WBC (103 mL^{-1})	0.310	0.016*	0.292	0.043*	-0.216	0.087	0.050	0.835
Hb(g/dL)	-0.129	0.461	0.018	0.877	-0.172	0.175	0.228	0.334
Monocyte (mL^{-1})	0.296	0.045*	0.215	0.084	-0.244	0.079	0.032	0.893
Plt (10^3 mL^{-1})	0.099	0.570	0.094	0.422	-0.251	0.073	-0.297	0.203
BUN (mg dL^{-1})	0.162	0.353	0.098	0.397	0.192	0.128	0.258	0.121
CRP (mg L^{-1})	0.532	<0.001*	0.298	0.044*	0.162	0.200	0.263	0.116
Creatinin (mg dL^{-1})	0.339	0.011*	0.302	0.019*	0.215	0.088	0.005	0.984
CHOL (mg dL^{-1})	0.088	0.616	-0.062	0.593	-0.034	0.791	-0.275	0.178
HDL (mg dL^{-1})	-0.310	0.027*	-0.187	0.106	-0.141	0.266	-0.255	0.207
LDL (mg dL^{-1})	0.185	0.288	0.076	0.514	-0.155	0.222	-0.119	0.618
TG (mg dL^{-1})	-0.189	0.277	-0.058	0.618	0.206	0.103	0.156	0.513
MHDL (μL mg^{-1}dL)	0.495	<0.001*	0.307	0.007*	-0.162	0.201	0.203	0.391

*p<0.05 was statistically significant.
BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure
WBC:white blood cell, Hb:hemoglobin, Plt:platelet, BUN:blood urine nitrogen, Urine prot:urine protein,CHOL:cholesterol, HDL:high density lipoprotein, TG:triglycerides, MHDL:monocyte/hdl ratio

were included in the multivariate linear regression model. Before the regression model, logarithmic transformation was applied to the numerical variables without normal distribution. Accordingly, the reverse dipper group, the ratio of monocyte/HDL cholesterol (B±SE=1.280±0.450; p=0.008), log (CRP) (B±SE=1.131±0.089; p<0.001), and DBP (B±SE=0.848±0.164, p<0.001) were found to be independent predictors of log (urine protein) level. Log (urinary protein) (B±SE=0.154±0.054; p=0.001) and DBP (B±SE=0.848±0.164; p<0.001) were found to be independent predictors of log (monocyte/HDL cholesterol) ratio (Table 5).

DISCUSSION
In our study, urinary protein excretion, which is predictive of target organ damage, was found to be higher in patients with RDHT than in other groups. Furthermore, MHR, an oxidative stress and inflammation marker, was found to be higher in this group. Stepwise regression analysis showed that MHR was an independent predictor of protein excretion in the RDHT group. We did not find a study that showed a relationship between MHR and 24-hour urinary protein excretion in patients with RDHT. To our knowledge, this is the first study in this area.

Following DHT and NDHT definitions by O'Brien et al. (7), the role of diurnal BP variation in target organ damage has been studied in many studies in terms of mortality and prognosis. Ischemic cerebrovascular and cardiovascular events, such as left ventricular hypertrophy and ventricular arrhythmia, were more frequently observed in patients with NDHT. Furthermore, in patients with NDHT pattern, there was a correlation between renal dysfunction indicators albuminuria, impaired sodium uptake, and decreased glomerular filtration rate (1, 8, 9).

In a study conducted by Bin Yan et al., the frequency of RDHT patients was approximately 20% (10). In our study, this rate was found to be similar with 17.9%. We did not find a study on the frequency of RDHT among patients with hypertension in our country. This rate may be higher in a study involving more patients.

The main difference is that there is no fall in night BP when RDHT and NDHT are compared. This indicates that patients with RDHT have a higher risk of target organ damage than patients with NDHT. The prognosis of RDHT is worse, and its mortality is higher (11). In a study conducted by Minitulo et al., the RDHT and NDHT patterns were found to be independent risk factors for renal-related mortality in patients with chronic renal disease (12). In our

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Table 4. Parameters related to monocyte/HDL ratio

Variables	Reverse dipper		Non-dipper		Dipper		Extreme dipper	
	r	p	r	p	r	p	r	p
Age (yr)	0.113	0.519	0.144	0.2015	0.089	0.484	0.084	0.724
BMI (kg m^{-2})	0.186	0.405	0.203	0.387	0.216	0.392	0204	0.233
SBP (mmHg)	0.300	0.040*	0.294	0.047*	0.089	0.484	0.005	0.984
DBP (mmHg)	0.543	<0.001*	0.402	<0.001*	0.044	0.730	0.145	0.541
WBC (mL^{-1})	0.325	0.027*	0.365	0.001*	0.205	0.105	0.112	0.639
Hb (g dL^{-1})	0.128	0.463	0.103	0.376	0.252	0.045	0.147	0.535
Monocyte (mL^{-1})	0.634	<0.001*	0.823	<0.001*	0.869	<0.001*	0.836	<0.001*
Plt (10^3 mL^{-1})	-0.130	0.456	0.081	0.489	0.056	0.658	-0.062	0.795
BUN (mg dL^{-1})	-0.172	0.323	0.046	0.266	0.069	0.883	0.194	0.414
CRP (mg L^{-1})	0.343	0.018*	0.146	0.209	-0.070	0.582	0.276	0.238
Creatinin (mg dL^{-1})	0.330	0.033*	0.011	0.925	0.108	0.398	-0.169	0.476
Urineprot (g 24h^{-1})	0.495	<0.001*	0.307	0.007*	-0.162	0.201	0.203	0.391
CHOL (mg dL^{-1})	-0.106	0.543	-0.032	0.782	-0.232	0.066	-0.084	0.725
HDL (mg dL^{-1})	-0.623	<0.001*	-0.412	<0.001*	-0.400	0.001*	-0.577	0.008*
LDL (mg dL^{-1})	0.152	0.384	0.140	0.227	-0.068	0.592	0.114	0.632
TG (mg dL^{-1})	-0.124	0.477	0.036*	0.757	0.172	0.175	0.232	0.117

*$p < 0.05$ was statistically significant.
BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure;
WBC: white blood cell; Hb: hemoglobin; Plt: platelet; BUN: blood urine nitrogen; Urine prot: urine protein; CHOL: cholesterol; HDL: high density lipoprotein; TG: triglycerides; MHDL: monocyte/hdl ratio

Table 5. Independent predictor log (urine protein) level (g 24 h−1) and log (monocyte/HDL) ratio (μL mg−1 dL)

Variables	B±SE	95% CI		p
		Lower limit	Upper limit	
Log (Urine Protein)				
DBP	0.207±0.033	0.141	0.273	<0.001*
Log (Monocyte/HDL ratio)	1.280±0.450	0.364	2.196	0.008*
Log (CRP)	1.131±0.089	0.956	1.306	<0.001*
R2=0.395; p<0.001*				
Log (Monocyte/HDL ratio)				
Log (Urine Protein)	0.154±0.054	0.044	0.264	0.001*
DBP	0.848±0.164	0.513	1.182	<0.001*

R2=0.372; p<0.001*
*$p < 0.05$ was statistically significant.
B±SE, regression coefficient±standard error; CI: confidence interval; DBP: diastolic blood pressure

study, increased urinary protein excretion was found to be higher for patients with RDHT pattern. This suggests that the RDHT patient group has more severe renal system damage.

In patients with RDHT, in contrast to normal physiology, high nighttime BP measurements have a negative effect on all systems. Although etiopathogenesis is not completely known, it is

emphasized that oxidative stress and inflammation may play a role in this process in terms of target organ damage. Oxidative stress, increased especially after inflammation, plays an important role in chronic kidney injury by causing renal glomerular and tubular destruction. In addition, increased vascular permeability due to oxidative stress increases the damage of inflammatory cells to target organs cumulatively (13).

CRP, an inflammation marker, also correlates with oxidative stress in the cells. We examined the importance of the MHR, which is calculated by proportioning two different laboratory parameters. Monocyte frequency is a hematological parameter that increases during inflammation and contributes to the formation of oxidative stress (14). The HDL cholesterol level is a lipid parameter that decreases in the presence of endothelial dysfunction and atherosclerosis. Therefore, HDL has both anti-inflammatory and antioxidant properties (15). In light of these studies, MHR is also considered to be a marker of inflammation and oxidative stress.

Other studies have examined the role of the MHR in chronic kidney failure (16). An increased MHR was shown to be associated with a reduced glomerular filtration rate in patients with chronic kidney failure, and the MHR was found to be a predictor of poor cardiovascular outcomes in patients with chronic kidney failure.

In our study, a positive correlation between CRP, MHR, and WBC with 24-hour protein excretion in the RDHT patient group indicates that inflammation and oxidative stress play important roles in target organ damage. The present study also shows that MHR is an independent predictor of urinary protein excretion in the RDHT group.

Study Limitations
There are some limitations in our study. The study was conducted in one center. Furthermore, it was a cross-sectional study, and prospective randomized controlled studies are needed.

CONCLUSION
Inflammation and oxidative stress play roles in end organ damage in patients with RDHT pattern. In patients with this pattern, there is a significant association between MHR, which is a marker of target organ damage, and 24-hour urinary protein excretion, and it has been shown to be an independent predictive marker.

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