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Comparison of Dipper and Non-Dipper Hypertension Patterns According to Chronic Kidney Disease Stage

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Abstract

Introduction: Hypertension is a major cardiovascular risk factor. There is a strong relationship between blood pressure (BP) elevation and stroke, myocardial infarction, heart failure and mortality due to kidney disease. It is known that the loss of the dipping pattern in hypertension is associated with increased target organ damage. In our study, we aimed to investigate the prevalence of dipper hypertension (DHT) and nondipper hypertension (NDHT) and related factors in patients with stage 1 and 2 chronic kidney disease (CKD).

Materials and Methods: A total of 158 patients diagnosed with stage 1 or stage 2 CKD were included in the study. Demographic characteristics, anthropometric measurements, physical examination findings and laboratory results of the patients were recorded. Ambulatory BP monitoring was performed in all patients.

Results: Of the 158 patients (female n: 98), 78 (49%) were in the stage 1 CKD group and 80 (51%) were in the stage 2 CKD group. No significant difference was observed in the prevalence of DHT or NDHT between hypertensive patients in the stage 1 and 2 CKD groups. The rate of NDHT was 59.5% (94/158 patients). Female patients had more DHT in the general population and in the stage 1 group than male patients (p=0.05, p=0.01, respectively).

Conclusion: No significant difference was observed in the prevalence of DHT or NDHT between hypertensive patients in the stage 1 and 2 CKD groups. The prevalence of DHT in female patients was significantly higher in both groups than in men in both groups, but especially in the stage 1 CKD group.

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Introduction

Hypertension (HT) is a systemic disease characterized by elevated blood pressure (BP) and is a common public health problem since it is commonly seen and causes serious complications [1]. In recurrent office measurements, HT is accepted as 140/90 mmHg above the arterial BP.

Approximately 25-30% of the adult population in the United States and many European countries has HT. In several studies carried out in our country. The HT prevalence in the adult age group varies between 33% (Turkish Cardiology Association) [1], 35.9% (Turkey Endocrinology and Metabolism Association) [2] and 30.3% (CREDIT study, Turkish Hypertension and Renal Diseases Association) [3]. In summary, we can estimate the presence of HT in one of every three people in the adult age group in Turkey. Despite its high prevalence, both in the world and in Turkey, success and awareness rates are quite low.

Hypertension is a major risk factor for cardiovascular diseases and is among the leading causes of preventable mortality. There is a strong positive and sustained correlation between BP and stroke, myocardial infarction, heart failure and kidney disease-related mortality, even within normotensive limits. This correlation is more distinct as BP increases. With effective antihypertensive therapy, it was observed that the incidence of stroke, myocardial infarction and heart failure decreased by 35-40%, 20-25%, and 50%, respectively [4].

In all affected organs, the kidney is the first affected organ, and microalbuminuria, which is an early indicator of damage, is also a major cardiovascular risk factor [5]. HT is the second most common cause of end-stage renal disease (ESRD) after diabetes [6]. The risk of renal failure increases 22-fold in hypertensive patients compared to normotensive patients [7]. When renal failure develops, the risk of coronary and cerebrovascular events increases significantly [8].

Normal population studies revealed a nocturnal decrease in BP in adults. The BP pattern, in which the nocturnal decrease is between 10-20%, is called *"dipping"*, while the BP pattern with a nocturnal decline of <10% is called "*nondipping*".

Nondipping HT is associated with renal [9] and cardiac dysfunction [10]. Therefore, the *nondipping* pattern may cause target organ damage in normotensive patients as well as in hypertensive patients [11].

Hypertension is known to cause chronic kidney disease (CKD), but the etiopathogenesis of this process has not been clearly elucidated. Although a linear relationship between the stage of hypertension and kidney damage has been demonstrated, there is insufficient evidence of a relationship between the dipping pattern and nephropathy progression. The elucidation of this relationship may provide early predictability of CKD progression and delay the damage if the appropriate treatment is selected.

In our study, we aimed to investigate the prevalence of dipper hypertension (DHT) and nondipper hypertension (NDHT) and related factors in patients with stage 1 or 2 CKD.

Materials and Methods

The study was a prospective, cross-sectional study. Patients admitted to the internal medicine and nephrology outpatient clinics of our hospital between January and July 2017 were included in the study. Physical examination, medical history, and laboratory values of 310 patients were evaluated. The primary aim of the study was to identify hypertensive patients with stage 1 or 2 CKD. The secondary aim was to investigate the relationship between the dipping pattern and the stage of renal disease in these patients. A total of 158 patients (98 female) diagnosed with stage 1 or stage 2 CKD according to the KDIGO *(Kidney Disease Improving Global Outcomes*) guide (*KDIGO-Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. January 2013*) [12] were included in our study. Demographic characteristics, anthropometric measurements, physical examination findings and laboratory results of the patients were recorded by the physician. Fasting glucose, urea, creatinine, whole blood count, electrolytes, and urinalysis were analyzed. Blood pressure and glomerular filtration rate (CKD EPI formula) were recorded. Body mass index (BMI) was calculated with the weight (kg) / height (m)^2 formula.

Pregnant women, renal transplant patients, patients with stage 3 or above CKD, patients with a history of malignancy, patients with acute kidney injury and patients with secondary HT were not included in the study. A total of 152 patients were rejected for meeting these criteria.

Ambulatory BP monitoring (ABPM) was performed by putting an oscillometric-type device (Mobile-o-Graph NG Version 2.0) on the patient that automatically recorded each 24 hours at 15-minute intervals in the daytime and 30-minute intervals in the nighttime. If the difference between the two arms was less than 10 mmHg, measurements were made by placing the muff of the device on the nondominant arm; if more than 10 mmHg, measurements were made by placing the muff of the device on the high-measuring arm. In the analysis of ABPM data, measurements were discarded if systolic BP >270 mmHg, systolic BP <70 mmHg, diastolic BP >150 mmHg, diastolic BP <40 mmHg, systolic and diastolic values were equal, or systolic or diastolic BP had a 30 mmHg difference between successive measurements. Day-night BP changes were calculated using the 100x (1-nightly mean systolic BP / daily mean systolic BP) formula.

All patients were classified as DHT if systolic BP decreased more than 10% from day to night and as NDHT if systolic BP decreased less than 10%. Biochemical and hormonal investigations were studied by using a Roche Modular Analytic E170 device. The compliance of the study with the Declaration of Helsinki and the code of ethics was approved by the Lütfi Kırdar Training and Research Hospital Ethics Committee. Verbal and written consent was obtained from the participants by the physician.

Statistics

SPSS 17.0 was used for the statistical analysis of the data. An unpaired *t test* was used for statistical analysis of the measured values, and the *chi-square* test was used for the analysis of categorical data. In the results obtained from the statistical tests, a p value below 0.05 (5%) with a 95% confidence interval was considered significant.

Results

Of the 158 patients (62% female) included in our study, 78 (49%) were in the stage 1 CKD group and 80 (51%) were in the stage 2 CKD group. The age; sex; age; weight; demographic data; use of anti-hypertensive, anti-diabetic, and anti-hyperlipidemic drugs according to CKD stage and DHT-NDHT pattern; and accompanying diseases of the patients are shown in Table 1.

The mean age of the patients with stage 2 CKD (57.4 ± 8.9 years) was found to be significantly higher than the mean age of the stage 1 CKD group (45.2±12.6 years) ($p = 0.000$). Female patients had more DHT than male patients ($p = 0.05$). In the stage 1 CKD patient group, female patients were more likely to have DHT than male patients ($p = 0.01$) (Table 1).

When we examined drug use without CKD stage distinction, no significant difference was found between the DHT and NDHT groups except for the use of lipid-lowering drugs. Among patients with stage 2 CKD, the rate of NDH was found to be statistically higher in patients using lipid-lowering drugs than others ($p = 0.04$).

When we evaluated patients according to CKD stage, patients using angiotensin-converting enzyme inhibitors (ACEIs) were more likely to have the NDHT pattern in the stage 2 CKD patient group than in the stage 1 CDK group ($p = 0.02$).

When we examined the HT disease duration without CKD stage distinction, no significant difference was found between the DHT and NDHT groups. However, the stage 1 CKD group had a statistically shorter hypertension period (4.7 ± 13.1 years) than the stage 2 CKD group (7.7 ± 11.1 years) ($p = 0.034$) (Table 2).

Discussion

In our study, no significant difference was observed between the prevalence of DHT or NDHT among hypertensive patients in the stage 1 and 2 CKD groups. The rate of NDHT (59.5%, 94/158 patients) was found to be quite high. The prevalence of DHT in female patients was significantly higher in both groups than in men in both groups, but especially in the stage 1 CKD group.

In patients with NDT over fifty-five years of age, circulating free norepinephrine and peripheral vascular

Table 1. Demographic characteristics of patients according to chronic kidney disease stage and dipper/nondipper hypertension condition

	Stage 1 (n:78)		Stage 2 (n:80)		
	DHT (n: 28)	NDHT (n: 50)	DHT (n: 36)	NDHT (n: 44)	P sig*
Sex (male %)	6 (21%)	32 (64%)	10 (28%)	12 (27%)	0.05
Age (years)	45.2±12.6		57.4 ± 8.9		0.00
BMI (kg/m²)	30.8±4.5	29.9±5.2	32.3±4.7	30.5±5.2	0.20
GFR (ml/min/1.73 m2)	109.5±10.2	105.5±9.4	81.3±8.7	77.6±8.3	0.18
ACEI	6 (21%)	12 (24%)	4 (11%)	20 (45%)	0.07
ARB	6 (21%)	24 (48%)	24 (72%)	22 (50%)	0.93
Ca CB	6 (21%)	4 (8%)	8 (22%)	10 (22%)	0.43
Beta Blocker	2 (7.1%)	8 (16%)	6 (16%)	4 (9%)	0.97
Alpha blocker	0	0	0	2 (4.5%)	0.41
ASA	0	2 (4%)	6 (16%)	6 (13%)	0.89
Oral antidiabetic	12 (43%)	18 (36%)	20 (55%)	22 (50%)	0.51
Insulin	2 (7.1%)	4 (8%)	0	6 (13%)	0.22
Antihyperlipidemic drug	0	6 (12%)	2 (5.6%)	12 (27%)	0.04
Other drugs	6 (21%)	12 (24%)	3 (33%)	14 (31%)	0.76
DM	10 (35%)	20 (40%)	14 (38%)	30 (66%)	0.58
HL	4 (14%)	10 (20%)	6 (16%)	18 (41%)	0.15
CHD	0	2 (4%)	4 (11%)	6 (13%)	0.71
Thyroid disease	2 (7.1%)	6 (12%)	8 (22%)	0	0.18

DHT: dipper hypertension. NDHT: nondipper hypertension. BMI: body mass index. GFR: glomerular filtration rate. ACEI: angiotensin-converting enzyme inhibitor. ARB: angiotensin receptor blocker. Ca-CB: calcium channel blocker. ASA: acetylsalicylic acid. DM: diabetes mellitus. HL: hyperlipidemia. CHD: coronary heart disease. p *: significance level

Table 2. Comparison of ambulatory blood pressure measurements of stage 1 and 2 chronic kidney disease groups between dipper and nondipper groups

		Dipper-HT	Nondipper HT
		Mean±SD (min-max)	Mean±SD (min-max)
Stage 1 CKD	SHT	132.6±13.1 (109-148)	131.9±14.1 (110-172)
	DHT	80.9±6.4 (67-90)	82.2±9.3 (66-104)
	D-SHT	140.0±12.6 (122-160)	134.5±15.6 (100-180)
	D-DHT	84.8±6.2 (75-93)	84.1±10.3 (61-111)
	N-SHT	118.3±14.7 (99-142)	127.0±14.8 (106-162)
	N-DHT	73.4±7.8 (62-87)	77.9±9.5 (59-104)
	HT (years)	6.4±9.0 (0.0-28)	3.8±4.6 (0.0-15)
Stage 2 CKD	SHT	129.6±12.4 (104-146)	136.7±13.6 (113-177)
	DHT	79.5±6.0 (64-88)	81.4±7.9 (67-97)
	D-SHT	135.2±12.0 (110-149)	137.5±14.7 (108-177)
	D-DHT	82.9±6.5 (66-93)	83.5±7.7 (70-97)
	N-SHT	114.2±12.6 (87-140)	129.8±18.1 (95-185)
	N-DHT	70.8±8.5 (54-83)	76.5±10.0 (55-99)
	HT (years)	7.8±6.3 (0-25)	7.6±5.0 (.3-20)

CKD: chronic kidney disease. SHT: systolic hypertension. DHT: diastolic hypertension. D-SHT: daytime systolic hypertension. D-DHT: daytime diastolic hypertension. N-SHT: nocturnal systolic hypertension. N-DHT: nocturnal diastolic hypertension. HT: hypertension

resistance have been found to be increased [13]. This means there is not a sufficient nocturnal reduction in BP in these patients. Patients with NDHT have higher rates of cerebrovascular disease and left ventricular mass and increased cardiovascular mortality and morbidity [14]. NDHT is more common in the black race; advanced age, diabetes mellitus and secondary hypertension have also been reported to be associated with the development of NDHT [15]. With the definition of DHT and NDHT by O'Brian et al. [16], the places of the individual variables among the risk factors of hypertension have been questioned.

Verdecchia et al. [15] reported that the incidence of NDHT among patients with hypertension was between 10 and 40%. In a study conducted by Ersoylu et al. in our country, the rate was reported to be 43.6% (34/78) [17]. In our study, the prevalence of NDHT was found to be 59.5% (94/158 patients). The reason why this ratio was found to be higher than in the other two studies could be the selection of the patient group. Considering the data and patient sample of Verdecchia et al., the high prevalence of NDT in our study suggests that the incidence of NDHT is higher in our population as well as our particular patient group. In the study of Ersoylu et al., patients with diabetes, CKD, thyroid dysfunction or BMI > 30 kg/m^2 were not included in the study group, while these patients were included in our study group.

In the literature, the number of studies examining the relationship between CKD stage and DHT and NDHT is extremely limited. In our evaluation, we did not find any study comparing stage 1 and stage 2 CKD. Redon et al. [18] published a prospective study examining the effect of nocturnal BD on stage 3 and 4 CKD progression. The study included 79 nondiabetic patients (60% male), with a glomerular filtration rate (GFR) of 28.6 ± 14.7 ml/min. No statistically significant association was found between the calculated GFR level and the presence of NDH. Unlike previous studies, no significant relationship was found between patients' progression to ESRD or death and the *nondipping* pattern. They found that nocturnal systolic BP level could be a prognostic factor in CKD progression, as patients with nocturnal systolic BP> 130 mmHg had significantly more often reached their primary endpoint (death or ESRD).

In the study of Agarwal et al. [19], including a group of 3 nondiabetic and nondiabetic patients, systolic BP and NDHT were thought to be independent predictors of CKD progression and mortality. However, in conjunction with other risk factors leading to CKD progression, the independent prognostic value of ABPM decreased. The difference between the two studies was attributed to the fact that the patient group of Redon et al. was nondiabetic, younger and thinner than Agarwal et al.'s patient group. Most studies support the findings of Agarwal et al.

Of the 158 patients who participated in our study, 78 were in stage 1 CKD and 80 in stage 2 CKD. There was no statistically significant difference in GFR between the patients with DH and with NDH. It was determined that this was because the patients had early renal failure due to hypertension and early autoregulation mechanisms and the absence of a change in GFR between 80 and 180 mmHg of BP. In addition, it was thought that in the stage 2 CKD group, the awareness of the disease being higher and the group being more cooperative affected the results in our study.

The physiological decline in nocturnal BP decreases with age. It is thought that the possible causes of this condition may be the decrease in vascular stiffness due to aging and atherosclerosis, the deterioration of the autonomic nervous system and the vasoconstriction of the sympathetic system relative to the parasympathetic system [20].

In the study of Minutolo et al. [21], which included 459 stage 2-5 CKD patients who were divided into four groups according to their age (<55, 55-64, 65-74, ≥75 years), they found that the prevalence of NDHT increased with age, irrespective of GFR level. There was no significant relationship between age and NDHT in our study group. When the stage 1 and 2 CKD groups were examined separately, no statistically significant relationship was found between age and NDHT. This was thought to be related to the fact that the number of patients over 65 years of age was low (18%).

In our study, DHT was found to be higher in

female patients than in male patients. Most of the previous studies found no significant sex differences in ABPM. However, in a study conducted with 619 patients [22], it was shown that 24% of patients had a change of pattern (dipping or nondipping) in the second ABPM. Hypertensive pattern change was found to be especially more common in elderly women.

In a study of 658 patients that investigated the relationship between nocturnal BP reduction and BMI, it was found that overweight or obese patients had lesser nocturnal BP decreases and greater cardiac and noncardiac organ damage than the underweight group with similar BP profiles [23]. In our study, no significant difference was found in BMI between nocturnal *dipping* pattern groups or renal damage groups. This was thought to be related to patient selection. In our study, no correlation was found between CKD stage and BMI.

Autonomic neuropathy is a common complication in diabetic patients, and more glucose intolerance was detected in hypertensive patients with NDHT patterns than in the *dipper* group [24]. As a result, it has been suggested that there may be increased insulin resistance and beta cell dysfunction in the NDHT patient group. In a study by Farmer et al., diabetic nephropathy was shown to progress faster in NDHT diabetic patients [25]. In our study, no significant relationship was found between diabetes and nocturnal dipping pattern or CKD stage. This was thought to be related to patient selection, more controlled treatment of diabetic patients, and the absence of any difference in BMI between groups.

In our study, no significant relationship was found between the use of antihypertensive drugs and the use of other drug groups and the formation of NDHT. However, in patients with stage 2 CKD, a higher rate of NDHT was found in patients using ACE inhibitors ($p = 0.02$). In the literature, we did not find any study showing that the use of RAS increased the frequency of NDTH. This result may be specific to hypertensive stage 2 CKD patients but may also be due to more potent drug selection, incomplete patient treatment, noncooperative patients or a low number of patients because of higher BP in this period.

A significant positive correlation was found between CKD stage and mean age and duration of HT ($p < 0.000$, $p = 0.034$, respectively). Similar to the literature, patients with stage 1 CKD were younger and had a shorter hypertension period than those in stage 2.

Our study has certain limitations. First, it is a cross-sectional study, and factors that may affect the *dipping* pattern (psychological factors, sleep and working order, daily physical activities) could not be taken into account in long-term follow-up. Additionally, the duration of comorbid diseases such as diabetes, hypothyroidism and dyslipidemia is not known. The duration of these diseases, especially diabetes, may have affected nocturnal patterns. There was no detailed cardiac evaluation, echocardiographic findings or albuminuria values.

Although antihypertensive drugs used by hypertensive patients are generally similar among groups, they do not show a homogeneous distribution. Partially different distributions of these drugs may have affected diurnal patterns of BP. Finally, the ABPM device could be applied only once to patients due to technical limitations, but ideally, it should be applied at least 2 separate times and the average values calculated. Despite these limitations, our study is one of the few studies in the literature investigating the relationship between the NDHT pattern and stage 1 and 2 CKD.

Conclusion

No significant difference was observed between the prevalence of DHT or NDHT between hypertensive patients in the stage 1 and 2 CKD groups in our study. The rate of NDHT was found to be quite high (59.5%). As the ABPM becomes widespread, DHT-NDHT separation can be improved. Accordingly, we believe that the development of renal damage can be prevented or at least delayed by the development of treatment protocols. It is planned to make the use of ABPM more common in patients with impaired renal function in our hospital. Although the relationship between the dipping effect and early-stage renal failure could not be demonstrated, the high incidence of NDP is evidence of a higher cardiovascular risk in renal failure patients. In our study, the higher frequency of DHT in females suggests that sex may play a role in the progression of renal failure in hypertensive patients. We believe that randomized controlled prospective studies, with more

participants and well attended, should be performed.

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