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The Relationship Between Ambulatory Blood Pressure Monitoring and Uric Acid Level in Hypertensive Patients

Hipertansif Hastalarda Ambulatuvar Kan Basıncı Takibi ile Ürik Asit Düzeyi Arasındaki İlişki

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Öz

Giriş ve Amaç: Serum uric acid (SUA) pürin metabolizmasının son ürünüdür. Aşırı üretimi veya böbrek atılımının azalması hiperürisemiye sebep olur. SUA yüksekliğinin kardiyovasküler hastalıklar için risk faktörü olduğu bilinmektedir. Ürik asit yüksekliği olan hastalarda kan basıncının (KB) daha yüksek olduğu ve ürik asit düşürücü ilaç kullanımı sonrası KB düşüşünün görüldüğü bildirilmiştir.

Gereç ve Yöntemler: Hastanemize hipertansiyon (HT) sebebiyle başvuran ve ambulatuar kan basıncı monitorizasyonu (AKBM) yapılan hastalarda SUA düzeyi ile ilişkisine bakıldı. Çalışmaya 310 hasta dahil edildi. SUA düzeyi enzimatik kolorimetrik otoanalizorde belirlendi. AKBM, noninvazif multitasking KB kayıt cihazları (TM2425; A&D, Tokyo, Japonya) kullanılarak gerçekleştirildi.

Bulgular: Hastaların %49.6'sında hiperürisemi tespit edildi. Hiperürisemi olan hastalarda gündüz, gece ve 24 saatlik diastolik kan basıncı (DKB) anlamlı düzeyde daha yüksekti (p=0.021, p=0.029 p=0.005). Hiperürisemi olan hastalarda ortalama arter basıncı (OAB) ve OAB gece değerleri daha yüksekti (p=0.022, p=0.003). Hiperürisemi olan hastalarda dipper HT olanların oranı, hiperürisemi olmayanlara göre daha az olduğu görüldü (p=0.041). Hiperürisemi olan hastalarda reverse dipper HT olma oranı, hiperürisemi olmayanlara göre daha yüksek olarak saptanmıştır (p=0.022).

Sonuç: Ürik asit yüksekliği ile DKB, reverse HT ve OAB ile ilişki saptandı. SUA'nın ölçümü kardiyovasküler riskin değerlendirilmesi ve azaltılması için değerli bir araç olabilir. Ürik asit düşürülmesinin gece kan basıncının ve DKB azaltılmasına etkisini gösteren ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ambulatuar kan basıncı ölçümü, ürik asit, dipper hipertansiyon, non-dipper hipertansiyon, reverse-dipper hipertansiyon

Abstract

Aim; Serum uric acid (SUA) is the end product of purine metabolism. Excessive SUA production or decreased renal excretion causes hyperuricemia. Elevated SUA is known to be a risk factor for cardiovascular diseases. It was reported that blood pressure (BP) was higher in patients with elevated uric acid and a decrease in BP was observed after the administration of uric acid-lowering drugs.

Method; We examined the relationship between SUA levels and hypertension in patients admitted to our hospital with hypertension (HT) and undergoing ambulatory blood pressure monitoring (ABPM). A total of 310 patients were included in the study. SUA levels were determined using an enzymatic colorimetric autoanalyzer. ABPM was performed using noninvasive multitasking CR recorders (TM2425; A&D, Tokyo, Japan).

Results; Hyperuricemia was observed in 49.6% of the patients. Daytime, nocturnal, and 24-hour diastolic blood pressure (DBP) were significantly higher in patients with hyperuricemia (p=0.021, p=0.029, and p=0.005, respectively). Mean arterial pressure (MAP) and nocturnal MAP values were higher in

patients with hyperuricemia (p=0.022 and p=0.003, respectively). The rate of patients with dipper HT was lower in patients with hyperuricemia than those without hyperuricemia (p=0.041). The rate of reverse-dipper HT was found to be higher in patients with hyperuricemia compared to those without hyperuricemia (p=0.022).
Conclusion; Elevated uric acid was correlated with DBP, reverse HT, and MAP. Measurement of SUA could provide a valuable aid for the assessment and reduction of cardiovascular risk. Further studies are required to assess the effect of lowering uric acid on the reduction of nocturnal BP and DBP.

Keywords: Ambulatory blood pressure monitoring, uric acid, dipper hypertension, non-dipper hypertension, reverse-dipper hypertension

1. Introduction

Serum uric acid (SUA) is the end product of purine metabolism. It is produced by the liver and eliminated by the kidney. Excessive SUA production or decreased renal excretion causes hyperuricemia [1]. High SUA levels are often associated with lifestyle [2]. Approximately 25-40% of untreated hypertensive patients have concomitant hyperuricemia[3]. High SUA concentrations have been demonstrated to be involved in the development of hypertension, metabolic syndrome, type 2 diabetes, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, myocardial infarction, stroke, heart failure, and chronic kidney disease [4].

Several studies in the literature report relationships between SUA levels and well-known cardiovascular (CV) risk factors, including high blood pressure (BP) [5]. In the European Society of Hypertension (ESH) guideline published by the European Society of Cardiology (ESC) in 2018, it was stated that SUA level is a CV risk in hypertensive patients [6]. Many recent studies have shown that medications that reduce SUA levels, such as allopurinol and probenecid, also lower blood pressure [7].

Studies have shown that 24-hour ambulatory blood pressure monitoring (ABPM) is more definitive when compared with home or office blood pressure monitoring[8]. An important aspect of the information provided by ABPM is the ability to quantify the degree of BP variability over 24 hours, which has been shown to be a significant and independent risk factor for CV morbidity and mortality[9].

The objective of this article is to review the association of SUA with hypertension. In the present study, we investigated the relationship between ABPM and hyperuricemia in patients with hypertension. It was aimed to evaluate the importance of uric acid levels in patients with non-dipper and reverse-dipper HT, both of which are known to cause more end-organ damage in blood pressure management [10], compared to dipper patients.

2. Materials and Methods

2.1. Patient Selection

The relationship between SUA levels and hypertension (HT) was examined in patients admitted to our hospital between April 2022 and April 2023 due to hypertension and underwent ABPM. A total of 310 patients were included in the study. Of the patients, 48.3% were female and 51.7% were male. The aim of the study was explained to all participants, informed consent forms were collected, and approval was obtained from the local ethics committee with the number E1-20-1355. Inclusion criteria were as follows: age over 18 years, no diabetes, no treatment with steroids or other immunosuppressive medications, no malnutrition or active malignancy, no active infection, no myocardial infarction or cerebrovascular disease history within the last six months, unstable angina, abnormal thyroid function, obstructive sleep apnea syndrome, or other major diseases.

2.2. Evaluation of Laboratory Parameters

Venous blood samples were collected from the patients between 8:00 and 9:00 a.m. after 8-10 hours of fasting. Serum creatinine, glucose, and HbA1c values were measured using standard methods. SUA levels were determined using an enzymatic colorimetric autoanalyzer. The estimated glomerular filtration rate (eGFR) value was determined with the Modification of Diet in Renal Disease (MDRD) (11) criteria.

2.3.Ambulatory Blood Pressure Monitoring

Ambulatory BP monitoring was performed using noninvasive multitasking CR recorders (TM2425; A&D, Tokyo, Japan). Blood pressure was recorded at 15-minute intervals between 07:00 and 21:00 and at 30-minute intervals between 21:00 and 07:00. Participants were asked to continue their usual daily activities during the recording period and relax their arms during BP measurement. The mean systolic and diastolic blood pressure values were measured for each participant.Mean BP was calculated as the sum of diastolic BP and one-third of pulse pressure. Daytime and nocturnal blood pressure were obtained as mean values during the day and night periods, respectively. Then, nocturnal/daytime BP ratios were analyzed for each participant. Systolic BP (SBP) >250 mmHg or <70 mmHg, diastolic BP (DBP) >130 mmHg or <30 mmHg, pulse pressure >160 mmHg or <20 mmHg were not measured, as this may cause a technical error.

The patients were divided into 3 stages according to the blood pressure levels specified in the 2018 ESC/ESH Hypertension guideline [6]. Stage 1 HT was defined as systolic blood pressure 140-159

mmHg and/or diastolic blood pressure 90-99 mmHg, stage 2 HT as SDB 160-179 and/or DBP 100-109, and stage 3 HT as SDB ≥180 mmHg and/or DBP ≥ 110.

In this classification based on ABPM, a decrease of 10% or more in the blood pressure value measured at night compared to the daytime value was defined as dipper HT, while a decrease of less than 10% was defined as non-dipper HT, and an increase in blood pressure at night was defined as reverse-dipper HT.

2.4.Statistical Analysis

The data were analyzed with IBM SPSS. The Mann-Whitney U test was used to examine non-normally distributed quantitative characteristics by paired groups. Fisher's Exact test and Pearson chi-square test were used to analyze categorical data according to binary groups. Multiple comparisons were analyzed using Z Test with Bonferroni Correction. Factors affecting hyperuricemia status were analyzed using logistic regression analysis. The relationship between non-normally distributed uric acid values and SBP and DBP values in patients with hyperuricemia was analyzed with Spearman's rho correlation coefficient. The analysis results were presented as median (minimum - maximum) and frequency (percentage). The significance level was considered as $p<0.05$.

3. Results

A total of 310 patients were included in the study. Of the patients, 48.3% were female and 51.7% were male. The mean age of the patients was 50.72 years, and the mean duration of HT was 108.36 months. It was determined that 49.3% of the patients had stage 1 HT, 31% had stage 2 HT, and 19.7% had stage 3 HT. 72.2% of the patients were smokers. It was observed that 54% of patients had dipper, 29.2% non-dipper, and 16.6% reverse dipper HT.

Laboratory and ABPM data of the patients are presented in Table 1. The proportion of smokers was higher in male patients compared to female patients ($p<0.001$). Creatinine and SUA values of males were significantly higher than females ($p<0.001$). It was determined that the 24-hour DBP values were higher in males compared to females ($p=0.042$). No statistically significant difference was found between the other characteristics with respect to the gender of the patients ($p>0.050$).

Table 2 demonstrates the comparison of demographic, laboratory, and ABPM values of the patients in the group with and without hyperuricemia. Hyperuricemia was defined as SUA level >7.0 mg/dL in males and SUA level >5.7 mg/dL in females (12). Hyperuricemia was observed in 49.6% of the patients. Patients with hyperuricemia were older than the patients without hyperuricemia ($p=0.010$). Duration of HT was higher in patients with hyperuricemia compared to patients without hyperuricemia ($p=0.017$). In patients with hyperuricemia, the rate of patients with stage 1 HT was higher than the rate of patients with stage 2 HT ($p=0.02$). The rate of smokers was higher in patients with hyperuricemia ($p=0.003$). Creatinine was higher and eGFR was lower in patients with hyperuricemia ($p<0.001$). Daytime, nocturnal, and 24-hour DBP were significantly higher in patients with hyperuricemia ($p=0.021$, $p=0.029$, and $p=0.005$, respectively). Mean arterial pressure (MAP) and nocturnal MAP values were higher in patients with hyperuricemia ($p=0.022$ and $p=0.003$, respectively). In patients with hyperuricemia, the rate of dipper HT was lower than in patients without hyperuricemia ($p=0.041$), while the rate of reverse dipper HT was higher ($p=0.022$). No statistically significant difference was found between the other characteristics according to the hyperuricemia status of the patients ($p>0.050$).

ABPM values affecting uric acid level are presented in Table 3. Univariate and multivariate logistic regression models were utilized.

In the univariate model, it was determined that the individual effect of 24-hour DBP, nocturnal MAP, and dipper and reverse HT status on hyperuricemia was statistically significant. The likelihood of hyperuricemia increased with increasing 24-hour DBP, nocturnal MAP, and in patients with reverse dipper HT (OR:1.021, $p=0.036$; OR:1.017, $p=0.042$; OR:1.955, $p=0.030$). Dipper patients were less likely to have hyperuricemia than non-dipper patients (OR: 0.626, $p=0.042$). The effect of other variables alone was not statistically significant ($p>0.050$).

In the multivariate model, the effect of nocturnal DBP, nocturnal MAP, and reverse dipper HT status on hyperuricemia was determined to be statistically significant (OR:0.921, $p=0.042$; OR:1.130, $p=0.009$; OR:3.000, $p=0.010$).The combined effect of other variables was not statistically significant ($p>0.050$). The multivariate model correctly classified 58.8% of the cases.

A significant correlation was determined for all three values when the relationship between daytime DBP, nocturnal DBP, and 24-hour DBP values in patients with hyperuricemia was analyzed as shown in Figure 1 ($p=0.016$, $p=0.019$, $p=0.013$, respectively).

As shown in the figure, no correlation was found with daytime SBP, nocturnal SBP, and 24-hour SBP values in patients with hyperuricemia ($p>0.050$).

Table 1. Characteristics of study participants

	Female (n=150)	Male (n=160)	Total	P value
Age (years)	51 (19 - 83)	54 (18 - 82)	50.72 ± 16.63	0.826
HT duration (month)	108 (1 - 480)	36 (1 - 360)	108.36 ± 111.93	0.427
HT stage				
1	40 (52.6)	30 (45.5)	70 (49.3)	0.695
2	22 (28.9)	22 (33.3)	44 (31)	
3	14 (18.4)	14 (21.2)	28 (19.7)	
Smoke				
No	14 (58.3)	6 (12.5)	20 (27.8)	<0.001
Yes	10 (41.7)	42 (87.5)	52 (72.2)	
Glucose	93 (64 - 247)	96 (71 - 264)	105.87 ± 34.9	0.107
HbA1C	5.8 (4.4 - 10.2)	6 (5 - 54)	6.63 ± 4.17	0.063
Creatinine	0.78 (0.4 - 4.9)	1.16 (0.7 - 5.5)	1.29 ± 0.94	<0.001
eGFR	89 (1.02 - 149)	71 (0.27 - 131)	75.85 ± 34.3	0.003
Uric acid	5.6 (1.6 - 8.6)	6.4 (3.3 - 10.5)	5.99 ± 1.61	<0.001
Day DBP	78 (57 - 129)	82 (54 - 123)	80.26 ± 11.92	0.079
Night DBP	74 (54 - 120)	76.5 (54 - 122)	76.78 ± 13.21	0.311
Day SBP	126 (92 - 187)	130 (99 - 182)	129.76 ± 16.58	0.137
Night SBP	121 (88 - 209)	123 (96 - 192)	125.89 ± 19.32	0.574
24-h SBP	125 (92 - 186)	129.5 (98 - 180)	128.88 ± 16.76	0.191
24-h DBP	78 (58 - 127)	81 (54 - 120)	79.68 ± 11.87	0.042
MAP	99 (76 - 154)	102.5 (78 - 150)	102.51 ± 13.48	0.344
Day MAP	101 (75 - 155)	104 (78 - 150)	103.26 ± 13.3	0.240
Night MAP	97 (72 - 150)	97 (67 - 153)	99.36 ± 14.74	0.921
Dipper HT				
No	68 (44.2)	80 (48.8)	148 (46)	0.409
Yes	86 (55.8)	84 (51.2)	174 (54)	
Non-dipper HT				
No	108 (70.1)	116 (70.7)	228 (70.8)	0.906
Yes	46 (29.9)	48 (29.3)	94 (29.2)	
Reverse-dipper HT				
No	134 (85.9)	134 (80.7)	272 (83.4)	0.214
Yes	22 (14.1)	32 (19.3)	54 (16.6)	

Abbreviations : HT, hypertension, e GFR estimated glomerular filtration rate, DBP: diastolic blood pressure, SBP: sistolic blood pressure, MAP: mean arterial pressure, mean ± s. deviation, median (min. - max.), frequency (%)

Table 2. Characteristics of study participants with and without hyperuricemia

	Hyperuricemia		p
	No (n=156)	Yes (n=154)	
Age (years)	49.5 (19 - 83)	57 (18 - 83)	0.010
HT duration (month)	60 (1 - 360)	120 (1 - 480)	0.017
HT stage			
1	38 (54.3)[a]	30 (44.1)	0.020
2	14 (20)[a]	28 (41.2)	
3	18 (25.7)[a]	10 (14.7)	
Sex			
Female	70 (44.9)	78 (50.6)	0.309
Male	86 (55.1)	76 (49.4)	
Smoke			
No	18 (40.9)	2 (7.7)	0.003
Yes	26 (59.1)	24 (92.3)	
Glucose	95 (64 - 247)	93 (71 - 264)	0.493
HBA1C	5.8 (4.4 - 54)	6 (4.8 - 10.2)	0.538
Kreatinine	0.9 (0.46 - 4.5)	1.1 (0.4 - 5.5)	<0.001
eGFR	95 (12 - 135)	65 (0.27 - 149)	<0.001
Day DBP	78 (57 - 129)	81.5 (54 - 109)	0.021
Night DBP	72 (54 - 122)	76.5 (54 - 109)	0.029
Day SBP	127 (92 - 187)	130 (96 - 185)	0.241
Night SBP	121.5 (92 - 209)	126.5 (88 - 182)	0.067
24-h SBP	125 (92 - 186)	128 (94 - 184)	0.189
24-h DBP	76.5 (58 - 127)	80 (54 - 104)	0.005
MAP	98.5 (76 - 154)	103 (77 - 138)	0.022
Day MAP	100 (75 - 155)	104 (78 - 138)	0.081
Night MAP	93.5 (67 - 153)	99 (72 - 135)	0.003
Dipper HT			
No	64 (41)	80 (52.6)	0.041
Yes	92 (59)	72 (47.4)	
Non-dipper HT			
No	112 (71.8)	106 (69.7)	0.691
Yes	44 (28.2)	46 (30.3)	
Reverse-dipper HT			
No	138 (87.3)	120 (77.9)	0.028
Yes	20 (12.7)	34 (22.1)	

Abbreviations : HT, hypertension, e GFR estimated glomerular filtration rate, DBP: diastolic blood pressure, SBP: sistolic blood pressure, MAP: mean arterial pressure, mean ± s. deviation, median (min. - max.), frequency (%)

Table 3. Regression analysis of ambulatory BP and serum uric acid

	Univariate		Multivariate	
	OR (%95 CI)	p	OR (%95 CI)	p
Day DBP	1.016 (0.997 - 1.036)	0.105	1.01 (0.881 - 1.158)	0.883
Night DBP	1.015 (0.997 - 1.032)	0.100	0.921 (0.851 - 0.997)	0.042
Day SBP	1.006 (0.992 - 1.02)	0.387	1.023 (0.885 - 1.184)	0.756
Night SBP	1.005 (0.993 - 1.016)	0.450	0.897 (0.832 - 0.967)	0.156
24-h SBP	1.006 (0.993 - 1.02)	0.356	1.08 (0.894 - 1.304)	0.424
24-h DBP	1.021 (1.001 - 1.042)	0.036	1.111 (0.953 - 1.294)	0.178
MAP	1.014 (0.997 - 1.032)	0.108	1.042 (0.893 - 1.217)	0.602
Day MAP	1.011 (0.994 - 1.029)	0.203	0.853 (0.726 - 1.002)	0.052
Night MAP	1.017 (1.001 - 1.033)	0.042	1.13 (1.031 - 1.238)	0.009
Dipper HT	0.626 (0.399 - 0.983)	0.042		
Nondipper HT	1.105 (0.676 - 1.805)	0.691		
Reverse-dipper HT	1.955 (1.069 - 3.577)	0.030	3 (1.298 - 6.931)	0.010

OR: Odds ratio, CI: Confidance interval, Accuracy = 0.588

Factors affecting the patients' hyperuricemia status were examined with univariate and multivariate logistic regression models Abbreviations : HT, hypertension, e GFR estimated glomerular filtration rate, DBP: diastolic blood pressure, SBP: sistolic blood pressure, MAP: mean arterial pressure, mean ± s. deviation, median (min. - max.), frequency (%)

Figure 1. The relationship between diastolic blood pressures and uric acid values in hyperuricemia patients

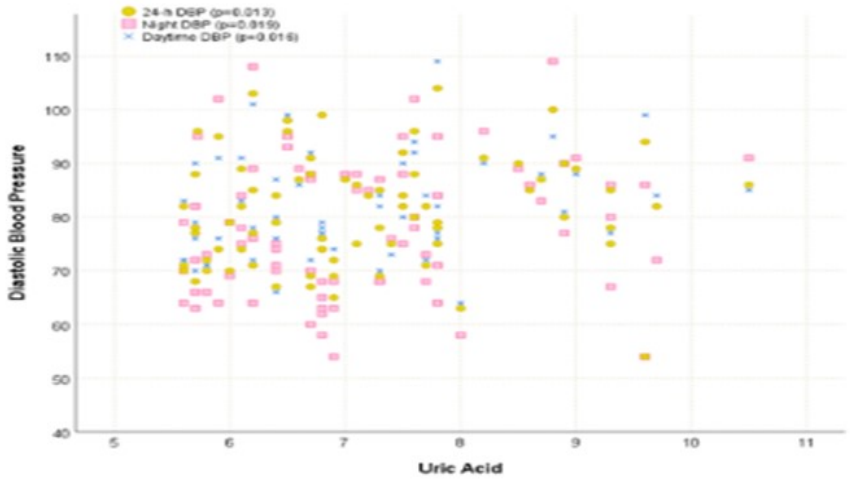
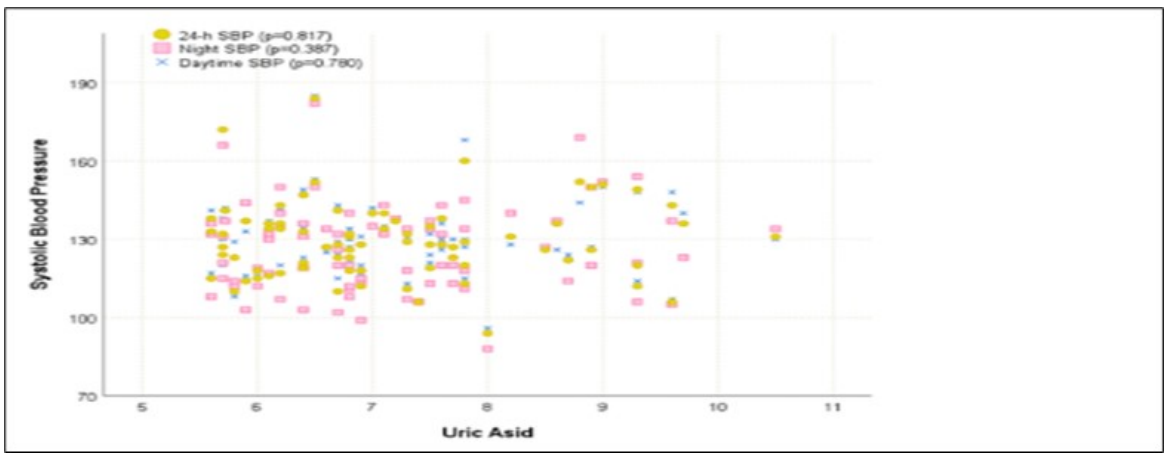


Figure 2. The relationship between sistolic blood pressures and uric acid values in hyperuricemia patients



4. Discussion

In our study, patients with elevated uric acid had higher 24-hour DBP, MAP, and nocturnal MAP values and a higher rate of reverse dipper HT, whereas the dipper pattern was lower in patients with elevated uric acid. Considering ambulatory blood pressure values affecting uric acid levels, it was determined that SUA levels were higher in patients with nocturnal BP, 24-hour BP, nocturnal MAP, and reverse dipper HT, whereas SUA levels were lower in patients with dipper pattern HT. In a study conducted by Jones et al. in which the relationship between SUA and ABPM was described, a relationship was observed between SUA level and DBP, consistent with our study (13). Similar to our study, a study conducted by Castro-Torres et al. showed a relationship between DBP and SUA (14). Sun et al. found that, among other risk factors, SBP and DBP were significantly higher in patients with hyperuricemia compared to patients with normal SUA [15].

In this study, reverse dipper pattern HT was found to be higher in patients with higher SUA levels. ABPM was utilized in our study to identify patients with a suspected diagnosis of hypertension and to detect non-dipper and reverse-dipper hypertension, which are known to pose a higher risk. This segregation of patients was based on their nocturnal blood pressure drops. Non-dipper and reverse-dipper hypertension patterns are correlated with increased cardiovascular, cerebrovascular, and renal complications[16]. A relationship with autonomic dysfunction and increased sympathetic and inflammatory activity was reported in non-dipper, and reverse-dipper hypertension, although further studies are required [17-18]. Similar to this study, Turak et al. reported a relationship between SUA elevation and non-dipper hypertension (19). In another similar study, high SUA was determined in patients with non-dipper HT in a group of 62 patients aged 30-40 years with newly diagnosed hypertension[20].

The incidence of gout and kidney stones requiring uric acid-lowering therapy is known to be higher in patients with symptomatic hyperuricemia (SUA levels >7.0 mg/dL in males and >5.7 mg/dL in females) [21]. It was also demonstrated that high SUA levels are a risk factor for high BP [22-22]. Some studies showed that the frequency of hyperuricemia in patients with uncontrolled hypertension was 40-60% [23]. In this study, a relationship was observed between the stage of hypertension and SUA levels. Sanchez-Lozada et al. also reported higher SUA levels in advanced hypertension [24].

A direct correlation between BP and SUA plasma levels was observed in animal models. In these cases, the use of medications that inhibit xanthine oxidase enzyme reduces SUA levels and BP [25]. Although uric acid-lowering medications initially lower blood pressure, there are also studies reporting that hypertension is salt-related when renal failure develops [26].

Hyperuricemia is documented to cause hypertension and subsequent preglomerular arteriolopathy. This is due to hyperuricemia causing renal vascular injury through activation of the renin-angiotensin system leading to hypertension [27]. This leads to the development of preglomerular vascular disease, which increases blood pressure[28]. It predisposes to the proliferation of vascular smooth muscle cells and endothelial dysfunction. It inhibits nitric oxide production [29]. Furthermore, uric acid was shown to cause kidney disease through afferent arteriopathy and tubulointerstitial disease [30]. In our study, we found that renal function was poorer in patients with hyperuricemia.

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