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Plasma catestatin importance and correlation in patients with dipper and non-dipper hypertension patients

Dursun Topal[1], Ferit Onur Mutluer[2], Alkame Akgumus[3], Fahri Er[4], Mehmet Demir[1], Erhan Tenekecioglu[5]

[1]Bursa University of Health Sciences, Medical School, Department of Cardiology, Bursa, Türkiye
[2]Koc University Hospital, Department of Cardiology, Istanbul, Türkiye
[3]Bandirma Education and Research Hospital, Department of Cardiology, Balikesir, Türkiye
[4]Agri State Hospital, Department of Cardiology, Agri, Türkiye
[5]Bursa Yuksek Ihtisas Education and Research Hospital, University of Health Sciences, Department of Cardiology, Bursa, Türkiye

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Abstract

Catestatin (CST) is a metabolite of chromogranin A, a soluble protein in catecholamine storage vesicles acting as a feedback inhibitor of catecholamine secretion. This study aims to investigate the correlation of catestatin with dipper and non-dipper status in hypertensive patients. Hypertensive (n=355) and healthy subjects (n=129) were randomly selected at an outpatient clinic. Blood pressure and heart rate were measured according to relevant guidelines. Plasma catestatin level, plasma glucose, lipid levels were measured. An ambulatory blood pressure monitor was performed to determine the dipping patterns in hypertensive subjects. Univariate and multivariate analyses were conducted to assess factors affecting catestatin levels. Left ventricular mass was higher among hypertensives compared with healthy controls (178±47 g versus 213±52 g in healthy controls and hypertensives, $p<0.05$), but there was no significant difference between the two hypertensive groups 205±43 g versus 228±77 g in dippers versus non-dippers, $p=0.54$). Average systolic blood pressure (SBP) and the percentage of systolic blood pressure dipping were statistically significantly negative correlated with CST ($r=-0.316$, $p<0.05$ for systolic dipping%, $r=-0.283$, $p<0.05$ for ASBP). In multivariate analysis for the prediction of catestatin levels, systolic dipping % and mean SBP were found to be independent predictors of plasma catestatin level. Plasma catestatin levels were lower among hypertensives compared to healthy controls and modest inverse correlations between catestatin and dipping percentage of systolic blood pressure and also between catestatin and average systolic blood pressure were noted. In hypertensive subjects, lower plasma catestatin levels may alert clinicians to the non-dipping status of the blood pressure.

Keywords: Hypertension, dipper, non-dipper, catestatin, biomarker

Introduction

Circulating catecholamines such as dopamine, norepinephrine and epinephrine, are produced by neuroendocrine cells actively participating in adjusting cardiovascular physiology. Increases in plasma and urine catecholamine as well as increased activity in postganglionic adrenergic nerve fibers were reported in primary HT and in some forms of secondary HT (ie. obstructive sleep apnea, obesity) [1].

Catestatin is one of the several cleavage products of chromogranin A, the principle soluble protein in catecholamine secretory granules. Catestatin inhibits catecholamine secretion via nicotinic cholinergic receptors and has vasodilatory (via NO generation) and antihypertensive effects [2]. Chromogranin A knock-out mice which exhibited severe HT were treated by administration of catestatin [3]. Plasma catestatin levels were also found decreased in patients with family history of HT as well as in their normotensive off-springs [4].

Blood pressure shows a diurnal variation with physiological nocturnal decreases. HT with ≥10% decrease in nocturnal blood pressure are labeled as "dipper" HT, whereas with <10% decrease or increase in nocturnal blood pressure are defined as "non-dipper" HT. Blunting or reversal of the dipping pattern is associated with hypertension-mediated organ damage (HMOD) as well as adverse cardiovascular events [5].

*Corresponding Author: Dursun Topal, Bursa University of Health Sciences, Medical School, Department of Cardiology, Bursa, Türkiye
Turkey E-mail: drdursuntopal@hotmail.com

The relation between catestatin levels and dipping status in hypertensive patients was not investigated previously. The aim of the present study was to investigate the relationship between plasma catestatin levels and dipping status in essential HT (EHT).

Material and Methods

Patient selection

The study was conducted at a tertiary referral hospital in Turkey between December 2017 and August 2018. Three hundred fifty-five patients, who were under follow-up for EHT in the out-patient clinic, or received diagnosis of EHT during diagnostic work-up and 129 healthy controls were consecutively and prospectively enrolled in the study. All hypertensive and healthy subjects were randomly selected from the cases who underwent coronary angiography for the investigation of coronary artery disease. Medical history, physical examination findings and laboratory data were recorded. Patients with established coronary artery disease, cerebrovascular disease or peripheral arterial disease, angina pectoris or equivalent with ECG changes, or heart failure of any class, malignancy, more than mild valvular lesion in echocardiography, other structural or congenital cardiovascular abnormality known to be associated with HTN; patients with atrial fibrillation, other sustained arrhythmia and symptoms clearly attributable to arrhythmic heart disease, any type of myocardial or pericardial disease, infectious or endocrine disease, more than mild degree renal dysfunction (Creatinine clearance ≤ 60 ml/min), patients with secondary HT following the definite diagnosis according to diagnostic work-up were excluded from the study. Diagnosis of EHT in this study was based on repeated office blood pressure measurements, according to latest guidelines and was defined as arterial blood pressure readings of ≥140 mmHg for systolic and ≥90 mmHg for diastolic values [6]. Ambulatory blood pressure monitoring was performed in all patients to classify the patients as dipper or non-dipper hypertensive. Blood sample was drawn for complete blood count, blood biochemistry and plasma catestatin measurement. Electrocardiography (ECG) and transthoracic echocardiography (TTE) were performed to assess any end-organ damage.

The study was approved by the local Ethical Committee. Written informed consent was obtained from all patients prior to participation in the study and this study was conducted in accordance with Declaration of Helsinki.

Blood pressure measurement

After 5 minutes of quiet rest in a seated position with both feet on the ground and arms supported, blood pressure was measured with a manual sphygmomanometer with an appropriate-cuff from both arms 2 times and repeated one more time if the first 2 readings varied by more than 10 mmHg. The recorded value was the higher of the 2 values obtained from the arms and average of the 2 or the latest 2 readings [6].

Ambulatory blood pressure monitorization

Ambulatory blood pressure monitorization was performed on Suntech Oscar 2 ABPM system (Suntech Medical, NC, US). Average blood pressure (MAP), systolic (SBP) and diastolic (DBP) blood pressure measurements both awake and at sleep and mean heart rates were recorded. Systolic and diastolic dipping values provided by the automated calculations of the system were recorded.

Biochemical analyses and determination of plasma catestatin level

Blood samples were drawn into EDTA tubes. Preparation of samples for catestatin assay was done according to methodology previously described [7]. Plasma samples were preserved at –80 ºC following collection and extraction until use. Catestatin level in plasma samples was determined with the use of catestatin enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Burlingame, California, USA) [8].

Fasting plasma glucose, plasma urea and creatinine levels, serum potassium and sodium levels, uric acid level, liver enzymes, thyroid function tests, hemoglobin A1c and urine analysis were routinely studied in all patients. Additional tests were ordered in an individual basis when clinical and laboratory work-up raised suspicion of secondary hypertension.

ECG

Twelve-lead ECG was obtained routinely from all patients. Signs of ischemic, valvular, arrhythmic or structural heart disease was followed by appropriate diagnostic investigations and patients who received predefined diagnoses were excluded from the study.

Transthoracic echocardiography

Two-dimensional TTE (Philips i33, Eindhoven, NL) was performed in the echocardiography laboratory following examination in the out-patient clinic. Standard apical 2-chamber, 3-chamber, 4-chamber, parasternal long-axis, short-axis and subcostal images were obtained with 2D, color and pulsed-wave Doppler echocardiography. Continuous-wave doppler images were acquired to assess valvular functions, filling characteristics and left ventricle diastolic function.

Left ventricle, interventricular septum and posterior wall diameters at end-systole and end-diastole were measured. Regional wall thickness was calculated with these variables. Left ventricular mass was estimated from diastolic left ventricular diameter, posterior wall diameters and interventricular septum diameter as defined in literature [9]. Left atrium anteroposterior diameter at end-systole and left atrium maximal volume indexed to body surface area (LAVI) were measured. Gradients and regurgitations over valves were assessed. Diastolic dysfunction was assessed with pulsed wave Doppler at mitral inflow sample and tissue pulsed-wave Doppler sampling from basal septum and basal lateral wall.

Statistical analysis

SPSS version 22 was used for statistical analysis. Continuous variables were presented as mean ± standard deviation or median (minimum-maximum) when normal distribution was not met. Independent samples t-test or Mann Whitney U test if normal distribution is not met was used to compare continuous variables between groups. Kruskal-Wallis test was used to compare means in more than two groups. Pearson's chi-square test was used to compare categorical variables. Spearman's test was used to assess correlation between various parameters and plasma catestatin

levels. Univariate and multivariate analyses were conducted to assess factors affecting catestatin levels. Areas under the receiver operating characteristic (ROC) curve, sensitivity and specificity, were calculated to assess the predictive value of the catestatin for systolic dipping percentage and average systolic blood pressure, with respective 95% confidence interval. P values of less than 0.05 were considered as statistically significant in analyses.

Results

Totally 484 patients (age 51±11, 38.6% male) were recruited into the study. The study cohort included normotensive healthy controls, dipper and non-dipper hypertensive subjects. Regarding body mass index, there was no statistically significant difference either between healthy controls and hypertensives (29.7±4 versus 30±4.2kg/m², respectively, p=0.744) or between dipper and non-dipper hypertensives (29.62±3.84 versus 30.87±4.62, respectively, p=0.57) (Table 1).

There were no significant age and gender differences between healthy subjects and hypertensives (129 healthy controls, age:51±12, 26.3% male versus 101 dipper hypertensives, age:47±10, 38.6% male and 254 non-dipper hypertensives, age:53±10, 44.8% male). However, non-dipper hypertensives were older compared to dipper hypertensives. Average systolic blood pressure (SBP) values were higher in non-dipper hypertensives, but there was no difference for average mean diastolic blood pressure (DBP) values between these 2 groups (SBP values: 139±8mmHg versus 151±17mmHg, p<0.05 and DBP values: 84±8mmHg versus 88±13mmHg, p=0.15, for dipper versus non-dipper hypertensives, respectively). There was no other significant difference for risk factors and medications between dipper and non-dipper hypertensives (Table 1).

Blood and echocardiographic parameters are summarized in Table 2. Blood count parameters, lipid panel, renal functions and fasting plasma glucose did not display any significant difference between the study groups.

Left ventricle diastolic function was significantly deteriorated in non-dipper hypertensives compared to dipper-hypertensives as displayed by mitral inflow E-wave maximal velocity (71±12cm/sec versus 87±18cm/sec, respectively, p<0.05) and mitral inflow E-wave velocity over A-wave velocity ratio (E/A) (0.82±0.24 versus 1.07±0.35, p<0.05) in transthoracic echocardiography. There was no difference between dipper and non-dipper HT groups for mitral septal E'-wave amplitudes or E/E' ratios. Left atrium volume index (LAVI) didn't differ between dipper and non-dipper hypertensive groups. Left ventricular mass (LVM) was significantly higher in hypertensives overall compared to healthy controls but there was no difference between dipper and non-dipper hypertensives (178±47 g in healthy controls, 205±43 g in dipper-hypertensives, 228±77 g in non-dipper hypertensives, p< 0.05 for healthy controls versus hypertensives, p=0.54 for dippers versus non-dippers).

In correlation analysis, average SBP and the dipping percentage of systolic blood pressure (systolic dipping %) demonstrated significant negative correlation with plasma catestatin, albeit with moderate level (r=-0.316, p<0.05 for systolic dipping %, r= -0.283, p<0.05 for average systolic blood pressure). The dipping percentage of diastolic blood pressure (diastolic dipping %) didn't display meaningful correlation with catestatin levels (r=-0.006, p=0.995). There was no significant correlation between catestatin and diastolic dysfunction parameters, E/e' (r=-0.031, p=0.778) and LAVI (rho=0.051, p=0.647) as well as with left ventricular mass indexed to body surface area (r=-0.208, p=0.06) (Table 3, Figure 1A-C).

Table 1. Clinical characteristics of study patients

	Normotensive (n=129)	Hypertensive				
		Dipper(n=101)	Non-dipper (n=254)			
	Mean±SD	Mean±SD	Mean±SD	p*	p**	p***
Age, years	51±12	47±10	53±10	0.67	**0.02**	0.07
Gender, male n, %	34 (26.3%)	39 (38.6%)	114(44.8%)	0.19	0.67	0.36
Smoking status n, %	36 (27,9%)	29(28.6%)	43(17.2%)	0.63	0.31	0.54
Diabetes mellitus n, %	22(17.2%)	21 (20,7%)	53(20.7%)	0.68	0.95	0.91
Hyperlipidemia n, %	35 (27.1%)	32 (31.6%)	79(31%)	0.70	0.93	0.93
BMI, kg/m²	29.74±4.03	29.62±3.84	30.87±4.62	0.63	0.33	0.57
Average SBP, mm Hg	121±7	139±8	151±17	**0.00**	**0.01**	**0.00**
Average DBP, mm Hg	72±5	84±8	88±13	**0.00**	0.15	**0.00**
sBP Dipping (%)	9.60±8.31	15.36±4.08	2.91±0.36	.701	.000	.000
Average HR, bpm	7±8	77±10	74±9	0.89	0.43	0.73
BB n, %	-	14 (13.8%)	61(24.1%)	**0.01**	0.35	**0.02**
CCB n, %	-	39 (38.6%)	122(48.3%)	**0.00**	0.50	**0.00**
ACE n, %	-	39 (38.6%)	79(31%)	**0.00**	0.52	**0.00**
ARB n, %	-	32 (31.6%)	79(31%)	**0.00**	0.93	**0.00**
Thiazide n, %	-	46 (45.5%)	97(38.1%)	**0.00**	0.52	**0.00**

BMI: Body mass index, CRP: C-reactive protein, HDL: High density lipoprotein; LDL: low density lipoprotein, LAVI: Left atrium volume index, BB: Beta-blocker, CCB: Calcium channel blocker, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker

* p-value for normotensive versus hypertensive patients ** p-value for dipper versus non-dipper patients *** p-value for comparison of 3 study groups

Table 2. Laboratory and echocardiographic characteristics of study patients

	Normotensive (n=129)	Hypertensive				
		Dipper(n=101)	Non-dipper (n=254)			
	Mean±SD	Mean ±SD	Mean ± SD	p*	p**	p***
Hemoglobin. g/dL	13.2±1.7	13.5±2.0	13.5±1.1	0.24	0.75	0.49
Leukocytes. /mm³	8414±2261	8696±2357	8416±2224	0.84	0.39	0.66
Platelet. /mm³	254892±56915	280481±64890	274964±70057	0.31	0.81	0.59
CRP. mg/dL	5.47±1.62	5.01±1.27	5.39±1.52	0.53	0.32	0.52
Total cholesterol. mg/dL	211±39	214±46	219±45	0.87	0.78	0.92
HDL-cholesterol. mg/dL	50±11	49±14	46±9	0.37	0.85	0.64
LDL-cholesterol. mg/dL	124±36	125±40	134±36	0.50	0.38	0.53
Triglycerides. mg/dL	191±89	185±76	225±192	0.60	0.53	0.69
Glucose. mg/dL	106±27	127±68	117±64	0.59	0.27	0.51
Creatinine clearance. ml/min	118±40	125±35	119±33	0.49	0.64	0.69
Plasma catestatin level. ng/mL	3.57±0.15	2.00±0.18	1.15±0.09	**0.00**	**0.01**	**0.01**
E (cm/sec)	81±17	87±18	71±12	0.45	**0.00**	**0.00**
E' (cm/sec)	8±2	8±2	7±2	.390	.119	.234
E/E'	10.27±2.36	10.93±2.73	9.81±2.09	0.96	0.09	0.22
E/A	0.95±0.28	1.07±0.35	0.82±0.24	0.38	**0.00**	**0.01**
LAVI (ml/m²)	24.80±5.87	24.64±8.53	27.40±6.43	0.52	0.09	0.16
Left ventricular mass	178±47	205±43	228±77	**0.00**	0.54	**0.01**

BMI: Body mass index. CRP: C-reactive protein. HDL: High density lipoprotein; LDL: low density lipoprotein. LAVI: Left atrium volume index. BB: Beta-blocker. CCB: Calcium channel blocker. ACEI: Angiotensin converting enzyme inhibitor. ARB: Angiotensin receptor blocker
* p-value for normotensive versus hypertensive patients
** p-value for dipper versus non-dipper patients
*** p-value for comparison of 3 study groups

Table 3. Correlation of Catestatin with several parameters in the study cohort

	Correlation Coefficient	Sig. (2-tailed)
Age	0.129	0.054
Body Mass Index	-0.066	0.556
Mean SBP	**-0.283**	**0.01**
Mean DBP	-0.006	0.995
Mean HR	-0.038	0.732
MAP	0.191	0.083
Systolic dipping %	**-0.316**	**0.004**
Pulse pressure	0.016	0.887
LV mass	-0.208	0.06
E/e'	-0.031	0.778
LAVI	0.051	0.647

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, MAP: mean arterial pressure, LV: left ventricle, BSA: body surface area

Table 4. Multivariate analysis for prediction of catestatin levels

	Unstandardized B coefficient	95.0% Confidence Interval for B		p value
		Lower Bound	Upper Bound	
Constant	**3.612**	**2.462**	**4.763**	**<0.05**
Mean SBP	**-0.017**	**-0.031**	**-0.003**	**<0.05**
Mean DBP	0.064	2.891	0.346	0.560
Mean HR	0.036	1.051	0.951	0.951
Body Mass Index	-0.04	1	1	1
SBP dipping	**-0.655**	**-0.431**	**-0.178**	**<0.05**
DBP dipping	-0.066	1.007	0.993	0.993
Left ventricular mass	-0.085	1.056	0.947	0.947
Age	**0.023**	**0.015**	**0.976**	**0.04**
Group	-0.145	1.256	0.796	0.796

DBP: diastolic blood pressure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, Group: healthy controls (1) versus dipper hypertensives (2) versus non-dipper hypertensives (3)

In multivariate analysis for prediction of catestatin levels, systolic dipping% and average SBP were found to be independent predictors of plasma catestatin level, albeit with modest odd ratio (O.R.) [B =-0.655 CI: -0.431- -0.178 p<0.001 for systolic dipping %; B= -0.017, CI: -0.031- -0.003, p<0.05 for average SBP]. Diastolic dipping % was not an independent predictor of plasma catestatin (B-0.066; CI: .007-0.993; p=0.993).

The ROC curve analysis showed that catestatin level was a significant indicator of systolic dipping percentage in hypertensive patients (p<0.001); the AUC of the catestatin was 0.814 (95%CI 0.742, 0.869). The optimal catestatin level cutoff point was 1.08 ng/mL with a sensitivity of 83.6% and specificity of 68.9% (Figure 2-A). During ROC curve analysis, catestatin was also significant indicator of average systolic blood pressure in our population (p<0.05); the AUC of the catestatin was 0.69 (95%CI 0.662, 0.783). The optimal catestatin level cutoff point was 2.68ng/mL with a sensitivity of 69.6% and specificity of 67.9% (Figure 2-B).

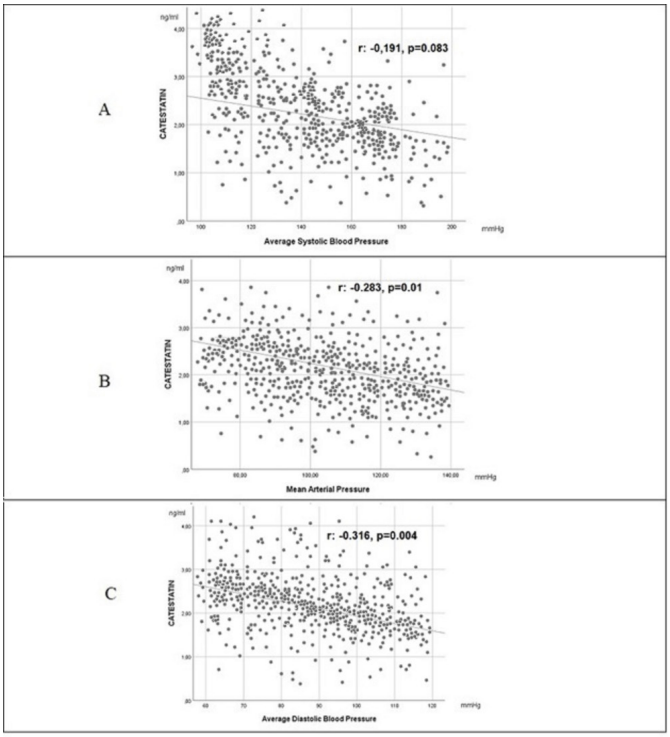

Figure 1. Plasma catestatin levels versus blood pressure parameters A. Correlation between plasma Catestatin and Systolic Blood Pressure, B. Correlation between plasma Catestatin and Mean Arterial Pressure, C. Correlation between plasma Catestatin and Diastolic Blood Pressure

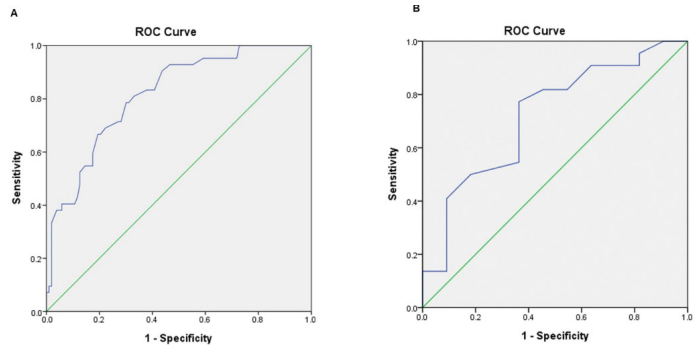

Figure 2. ROC curve analysis showed that catestatin was a good diagnostic test for both (a) systolic dipping percentage with the area under curve 0.814 (95% CI 0.742, 0.869; p=0.037) and (b) average systolic blood pressure with the area under curve 0.69 (95%CI 0.662, 0.783; p=0.043)

Discussion

The main finding of the present study was that plasma catestatin was predictor of systolic blood pressure dipping percentage and average systolic blood pressure in hypertensive subjects; there were modest inverse correlations between plasma catestatin and dipping percentage of systolic blood pressure and also between catestatin and average systolic blood pressure.

After discovery of critical role of catestatin in regulation of sympathetic output, vasomotor tonus and immune system, it was proposed and tested as a potential biomarker in various clinical conditions such as: prognostic stratification [10] and development of left ventricular remodeling in acute myocardial infarction [11], coronary collateral development in chronic myocardial ischemia [12], prediction of cardiac and all-cause mortality in chronic heart failure [13], prognosis in chronic hemodialysis patients [14] and diabetes mellitus [15]. Catestatin was also investigated as a drug target; a pharmacophore model mimicking the molecular action of catestatin on the binding sites was developed [2,16].

Characterization of the severity of EHT and prediction of HMOD was done by grading SBP and DBP readings in office and/or home blood pressure measurements. However, it was found that pattern of daily changes in BP conveyed significant additional information about the severity of the disease and related complications. Disrupted dipping pattern was associated with renal end-organ damage [17], progression of coronary artery disease [18], cerebrovascular event risk [19] and hypertension-related complications in pregnancy [20]. As a result, wide clinical use and standardization of ambulatory blood pressure monitorization was rigorously proposed [21].

Our study demonstrated lower catestatin values in hypertensive subjects compared to healthy controls. This finding contradicts previous 2 studies that found higher catestatin levels among patients with essential hypertension compared with healthy controls [7,8]. However, both of these studies were small-scale observational studies, enrolled antihypertensive-naïve patients and body mass index was relatively higher in our healthy controls compared with the cases in those previous observational studies.

Our findings support that rather than being increased along with secondarily increased catecholamine secretion due to increased blood pressures, lack of catestatin increase as a negative feedback mechanism might be associated with increased blood pressure. The significant difference in catestatin levels in dipper and non-dipper hypertensives reflect a potential role of catestatin in diurnal blood pressure variation in hypertensive subjects. Obesity is associated with increased levels of sympathetic system activity. Obese hypertensives have better prognosis compared to normal-weight hypertensive [22]. Meanwhile, the relationship between catestatin gene variations and hypertension was evident in patients with lower body mass index [23]. Our study cohort displayed higher catestatin levels compared with either study population possibly as a result of greater body mass index values in the study cohort.

Catestatin deficiency in CHGA-knockout mice produced elevated blood pressure, diminished baroreflex sensitivity, caused loss of diurnal blood pressure variation, increased plasma catecholamines, and increased left ventricular mass and dimensions, whereas external catestatin supplementation or replacement of CHGA loci

both restored baroreflex sensitivity and lowered blood pressure and catecholamines [24,25]. In addition to diminished catecholamine secretion through a negative feedback mechanism, catestatin also has potent vasodilator effects in vivo, mediated by released histamine that acts on H1 receptors [26]. Interestingly, Fung et al. [27] reported that catestatin induces vasodilation prominently in female subjects. Moreover, they found higher catestatin concentrations and lower CHGA levels in healthy females, reflecting higher conversion from CHGA to catestatin. Similarly, we observed higher catestatin concentrations in female patients, revealing another difference in cardiovascular physiology.

A blunted nocturnal BP decline is considered as a foresight marker of adverse cardiovascular events, both in hypertensives and in the healthy population. Non-dipping status is related to some diseases including metabolic disorders, obesity, sleep apnea, hypertensive target organ damage and more importantly to an increased risk of fatal and nonfatal cardiovascular events [28-34]. In the current investigation, the percentage of systolic blood pressure dipping and average systolic blood pressure were significantly associated with low catestatin levels. Low catestatin concentrations should result in resistant blood pressures in non-dipping group due to loss of vasodilator and anti-sympathetic effects. In line with our results, previously O'Connor et al reported lower catestatin levels in hypertensive subjects compared with the control group.

Regarding the clinical context, catestatin may have value in prediction of non-dipping status within hypertensives, which can alert physicians to observe their patients closely to prevent any potential end-organ damage related to resistant high blood pressure.

Another interesting and novel finding of our study is that plasma catestatin was independently related to age. Sympathetic over-activity is very important in all stages of hypertension, including the early phase [35]. Evidence suggests that sympathetic activity increases with age [36]. Since catestatin not only inhibits catecholamine secretion but also modulates autonomic activity [37,38], this association might reflect a secondary increase in plasma catestatin due to higher sympathetic activity with aging. However, since increased catestatin levels may not completely inhibit sympathetic influence, the decreased effectiveness of catestatin with aging may partially explain why elderly patients have increased blood pressure levels. Catestatin concentrations did not differ by age in the control population. Therefore, we speculate either that group size may be small or that sympathetic activity may not be as prominent as in hypertensive patients to make a difference in control subjects.

Obesity modulates sympathetic nervous system and hypertension phenotypes via obstructive sleep apnea as well as target organ involvement. The hypothesis should be tested in a normal-weight study population (ie. body mass index <25kg/m²).

Limitations of the study

Adrenergic system is an overall function of interplay between several mediators including catecholamines, adrenergic receptors and intracellular machinery attached to it, vasoactive peptides released from vesicles along with catecholamines like catestatin. Genetic mechanisms and interaction between genes increase this complexity. Studying catestatin in pathogenesis of hypertension phenotypes and cardiovascular disease necessitates concomitant assessment of plasma catecholamine levels, which was not performed in our study.

Conclusion

Plasma catestatin levels were lower among hypertensives compared to healthy controls and modest inverse correlations between catestatin and dipping percentage of systolic blood pressure and also between catestatin and average systolic blood pressure were noted. In hypertensive subjects, lower plasma catestatin levels should alert clinicians for non-dipping status of the blood pressures.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
An approval for the study was obtained from the Ethics Committee for Clinical Trials of Bursa Uludag University (2017-10/37).

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