Am J Cardiovasc Dis 2025;15(3):156-165
www.AJCD.us /ISSN:2160-200X/AJCD0164402

Original Article

Relationship between serum copeptin levels and non-invasive endothelial function indicators in dipper and non-dipper hypertensive patients

Huseyin Kandemir[1], Mehmet Tolga Dogru[1], Selcuk Ozturk[1], Muhammed Karadeniz[1], Caglar Alp[1], Ucler Kisa[2]

[1]Department of Cardiology, Kırıkkale University Faculty of Medicine, Kırıkkale, Turkey; [2]Department of Biochemistry, Kırıkkale University Faculty of Medicine, Kırıkkale, Turkey

Received March 8, 2025; Accepted June 13, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objective: Pathological changes in the endothelium are the earliest determinants of endothelial dysfunction and atherosclerosis in hypertension (HT). The diagnostic and prognostic role of copeptin in various diseases is well-recognized. This study aims to investigate the relationship between serum copeptin levels and non-invasive endothelial function indicators determined by flow-mediated dilation (FMD) and pulse wave analysis (PWA) in dipper and non-dipper HT patients. Methods: In this study, 30 dipper HT, 31 non-dipper HT patients and 30 healthy control subjects were included. Blood samples were taken for copeptin level determination. All participants underwent detailed cardiovascular and transthoracic echocardiography examinations and measurements of FMD and PWA. Results: Copeptin levels of the non-dipper HT group were significantly higher than the control group and dipper HT groups (P=.001, P=.010, respectively). No significant difference was found between the dipper and non-dipper HT groups regarding FMD and PWA measurements, and both groups significantly differed from the control group. In the whole group evaluation by partial correlation analysis, a significant correlation was found between serum copeptin levels and reflection index (RI) after adjustment for age and body mass index (r=0.24, P=.039). Stepwise linear regression analysis revealed RI as an independent predictor of copeptin (β=0.285, P=.015). Conclusion: The correlation between copeptin levels and RI in HT patients, especially in the non-dipper HT group, suggests that copeptin can be used as a biomarker to indicate endothelial dysfunction in hypertensive patients.

Keywords: Arginine vasopressin, arterial stiffness, copeptin, endothelium, hypertension, flow-mediated dilation, pulse wave analysis

Introduction

Hypertension (HT) is among the leading causes of hospital admission and death worldwide. It is a major risk factor for stroke, heart attack, kidney disease and other vascular diseases [1, 2]. Therefore, by treating high blood pressure (BP), the incidence of HT-induced complications can be reduced, and a long life can be maintained [3]. HT is a heterogeneous disease with a complex pathogenesis and is thought to be the result of disorders in several neural, renal, hormonal and vascular mechanisms that regulate BP [4]. The most important regulator of these vascular mechanisms is the endothelium. Impaired endothelial function is thought to be the earliest determinant of atherosclerosis and is also thought to play a role in the pathophysiology of HT. Non-invasive tests, such as flow-mediated dilation (FMD) and pulse wave analysis (PWA), can help us detect endothelial dysfunction at an early stage [5]. The arterial BP waveform is a complex signal determined by various physiological factors, such as left ventricular stroke volume, aortic compliance, vascular resistance and wave reflection phenomenon. PWA methods estimate cardiac output and other hemodynamic variables by mathematically analyzing the arterial BP waveform. PWA methods can be classified as invasive, minimally invasive and non-invasive methods. Digital volume pulse (DVP) measurement is a non-invasive PWA measurement method [6].

Dipper and non-dipper HT are classifications based on the circadian rhythm of BP, particu-

https://doi.org/10.62347/TSLN4765

larly the change in BP at night compared to day-time levels. If nocturnal BP decreases more than 10% of the day-time levels, it is defined as dipper HT, and if the drop is fewer than 10%, it is defined as non-dipper HT. Ambulatory BP monitoring (ABPM) can provide information about diurnal variations of BP, as well as dipper and non-dipper BP patterns [7]. The purpose of classifying HT patients into dipper and non-dipper HT is that cardiovascular morbidity and mortality are more prominent in non-dipper HT patients. The risk of target organ damage, such as left ventricular hypertrophy, congestive heart failure, myocardial infarction, stroke and kidney damage is higher in non-dipper HT patients [8]. A combination of lifestyle modifications and pharmacological agents may be used to lower BP in both dipper and non-dipper HT. Dipper HT patients who experience a normal nocturnal BP drop may benefit from standard treatments. On the contrary, non-dipper HT patients may require a more targeted approach, including medications taken at bedtime to improve the nocturnal BP decline [9].

Copeptin, a stable peptide of the arginine vasopressin (AVP), is a glycosylated 39 amino acid-long peptide molecule with a leucine-rich main body and has gained considerable popularity as a biomarker in recent years. The importance of serum levels of copeptin in diagnosing and treating cardiovascular and non-cardiovascular diseases has been shown in many different studies [10]. Copeptin has been investigated as a diagnostic and prognostic factor in various diseases, such as pneumonia, renal failure, acute coronary syndromes, heart failure, ischemic stroke, hemorrhagic and septic shock, and copeptin levels, have been found to increase in direct proportion to disease severity [10]. A recent study has also suggested that copeptin may be used in the diagnosis of masked HT and metabolic syndrome in obese subjects [11]. Indeed, to our knowledge, there is no study in the literature investigating the possible association of copeptin with endothelial dysfunction in dipper and non-dipper HT patients and the correlation between copeptin and non-invasive endothelial function parameters. In our study, we aimed to investigate the relationship between serum copeptin levels and endothelial function indicators that can be evaluated non-invasively by FMD and PWA in dipper and non-dipper HT patients.

Material and method

Study design and patient selection

This study was designed as a cross-sectional study. Following the approval of local ethics committee of the hospital (Decision Number: 09/13, Date: 04.04.2017), individuals aged 18 years and older who were evaluated with a preliminary diagnosis of HT in the outpatient clinic were invited to participate in this study. After explaining the aims of this study and obtaining written informed consent from the patients, the baseline characteristics and clinical data of the participants were recorded.

Patients aged 18 years and older with newly diagnosed HT after ABPM according to the guideline criteria published by the European Society of Cardiology in 2013 were included in the study. Patients younger than 18 years of age, diabetes mellitus, acute inflammatory and/or infectious disease, heart failure, cardiomyopathy, valvular heart disease, peripheral and/or coronary artery disease, malignancy, hormone replacement therapy, secondary HT, atrial fibrillation or flutter, use of drugs that may affect platelet function and coagulation cascades, such as antiplatelet or anticoagulants, congenital heart disease and pregnant women, were excluded. One hundred thirty-four eligible patients were evaluated and 91 were finally recruited to this study. Among newly diagnosed HT patients, patients with a decrease in night-time BP of more than 10% of day-time levels were included in the dipper HT group, whereas patients with a decrease of fewer than 10% were included in the non-dipper HT group. As a result, 61 newly diagnosed HT patients with 31 non-dipper HT and 30 dipper HT were included in the study. The healthy control group consisted of 30 volunteers who applied to the cardiology outpatient clinic for any reason, who were healthy individuals without HT and any other disease that could be included in the exclusion criteria, and who were not found to have HT in the ABPM evaluation.

Cardiovascular examination and blood tests

Demographic characteristics of all patients and healthy individuals included in the study were first recorded, and general systemic examinations were performed. Height, weight, waist circumference at the umbilicus level and body

mass index (BMI) were recorded. After resting quietly and comfortably for at least 15 minutes, BP was measured with a sphygmomanometer on the right arm in a sitting position. After physical examination, electrocardiography (ECG), lipid panel, thyroid function tests, electrolytes, renal function tests, liver function tests, biochemical tests including hormones and hemogram were performed. For copeptin level determination, 3 cc blood samples were taken into a tube containing EDTA. After centrifugation for five minutes at 5000xG at 2-8°C within 30 minutes, the supernatants were carefully collected and stored in the biochemistry laboratory of our hospital at -80°C. Hemolyzed samples were excluded from this study. Human Copeptin ELISA kit (SunRed Biological Technology Co., Catalogue No: 201-12-5463, Shanghai) was used for serum copeptin determination. The reference range of the kit was 0.07-20 ng/mL, and measurements were made by an experienced biochemist using the sandwich ELISA method.

Ambulatory blood pressure monitoring

Patients and control group individuals who gave consent to the study underwent 24-hour ABPM. A GE Tonoport (Berlin, Germany) brand device was programmed to measure BP every 30 minutes during the day (07.00-22.00) and every 60 minutes at night (22.00-07.00) and connected to the patients. As a result of ABPM, HT was diagnosed in patients by considering the 24-hour ABPM threshold values in the Arterial HT guideline published by the European Society of Cardiology in 2013. Mean day-time or awake systolic/diastolic BP measurements ≥135/85 mmHg, mean 24-hour systolic/diastolic BP measurements ≥130/80 mmHg, or mean night-time systolic/diastolic BP measurements ≥120/70 mmHg were diagnosed as HT [12]. Patients with BP recordings below these thresholds were defined as a control group. HT patients with a nocturnal BP decrease by more than 10% compared to day-time levels were included in the dipper HT group, whereas those with a nocturnal systolic BP decrease fewer than 10% compared to day-time were included in the non-dipper HT group. Office BP recordings were not considered in this study. Thirty patients (15 females, 15 males) were diagnosed as dipper HT, 31 patients (13 females, 18 males) were diagnosed as non-dipper HT, and 30 healthy volunteers (18 females, 12 males) were included as a control group.

Non-invasive evaluation of endothelial function

Flow-mediated dilation: A GE Vivid E9 (General Electric, Horten, Norway) ultrasonography device and a 12 L Doppler ultrasonography probe were used for brachial artery Doppler ultrasonography. FMD assessment was performed using the method described by Mućka *et al.* [5]. The diameter of the brachial artery and blood flow velocity were determined through Doppler ultrasonography after a 10-minute resting period while the patients were in the supine position. The measurement site was marked. Then, the cuff of the sphygmomanometer was wrapped 5 cm above the measurement site, and the cuff was inflated to 40 mmHg above the systolic pressure of the patient. The cuff was rapidly deflated after five minutes in this position. Brachial artery diameter and Doppler flow measurements were taken 30 seconds after the cuff was deflated and recorded as the hyperemia phase. The FMD rate value was obtained by dividing the difference between the hyperemia phase vessel diameter and basal vessel diameter to the basal vessel diameter [5].

Pulse wave analysis: PWA measurements were performed using photoplethysmography (Pulse Trace PCA 2, Micro Medical, Rochester, UK). Stiffness index (SI), reflection index (RI), and pulse propagation time (PPT) values were obtained from DVP recordings of the initial pulse wave generated by BP on the vessel wall followed by its reflection wave (**Figure 1**). The SI, which is related to the stiffness of the large arteries, is calculated by dividing the height of the waveform of the first pulse generated by BP on the vessel wall by the PPT. RI, which is related to peripheral arterial resistance and vascular tone, was calculated as the height of the waveform of the first pulse generated by BP on the vessel wall divided by the height of the waveform of the reflection pulse of the first pulse (**Figure 1**) [13, 14].

Statistical analysis

Statistical tests were performed using Statistical Package for Social Sciences (SPSS) 20.0 (Inc., Chicago, Illinois, USA) statistical analysis software. The distribution pattern of

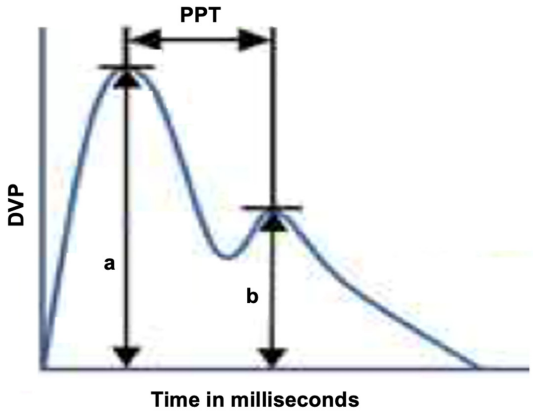

Figure 1. Digital Volume Pulse (DVP) waveform obtained through pulse wave analysis (PWA). The waveform of the first pulse generated by blood pressure on the vessel wall in PWA is defined as a and the waveform of the reflection pulse of the first pulse depending on the tone of the vessel wall is defined as b. The time difference between the waveforms of b and a is defined as pulse propagation time (PPT). Stiffness index = a/PPT, Reflection index = b/a.

the variables was analyzed using the one-sample Kolmogorov-Smirnov test. All variables were abnormally distributed and expressed as median (interquartile range, 25^{th}-75^{th}), and comparisons between groups were made by using Mann-Whitney U or Kruskal-Wallis tests. The correlation of copeptin levels with non-invasive endothelial function indicators and systolic and diastolic dipping ratios were tested by Spearman's correlation analysis. Afterwards, partial correlation analysis was performed, and the results were reported as the corresponding r correlation coefficients and *p*-values. Stepwise linear regression analysis was used to evaluate the main parameters associated with copeptin levels. Non-invasive endothelial function parameters, including RI, SI, PPT and FMD rate, and variables that reached statistical significance in group comparisons and could be associated with copeptin, such as age, BMI and waist circumference, were included in the analysis. In all analyses, *p*-value below .050 value was considered statistically significant.

Results

Study population

One hundred thirty-four patients who applied to Kırıkkale University Faculty of Medicine Department of Cardiology and diagnosed with HT were included in this study. After the application of the exclusion criteria, there remained 91 people (46 females and 45 males), including 61 HT patients and 30 healthy control group. Participant ages ranged from 19 to 82 years, and the mean age of the study population was 48.3±15.5 years.

Comparison of patient and control groups

The comparison of all individuals included in this study as patient and healthy volunteer control groups is shown in **Table 1**. There was no significant difference between the groups in terms of height. However, age, weight, BMI and waist circumference were significantly higher in the patient group than control group (P<.001 for all). In addition, both systolic and diastolic BPs were higher in the patient group (P<.001 for all). Basal FMD measurement and FMD measurements during the hyperemia phase was significantly higher in the patient group (P<.001, P=.032, respectively), whereas FMD rate was significantly lower in the patient group (P<.001). Regarding endothelial function parameters obtained through PWA and DVP, RI and SI were significantly higher and PPT was significantly lower in the patient group than the control group (P<.001 for all). The median of serum copeptin levels was significantly higher in the patient group than the control group 6.95 (5.25-14.65), 4.51 (3.44-10.10), P=.003, respectively.

Comparison of dipper HT, non-dipper HT, and control group

The comparison of dipper HT patients, non-dipper HT patients and the control group is shown in **Table 2**. Height measurements and FMD measurements during the hyperemia phase were similar between the three groups. Other anthropometric data, BP measurements, FMD, PWA and DVP parameters significantly differed between groups (P<.001 for all). There was a statistically significant difference between the control group, dipper HT and non-dipper HT patient groups in terms of median serum copeptin levels 4.51 (3.44-10.10), 6.09 (4.58-12.83), 7.81 (5.88-17.29), P=.001, respectively. When the groups were compared among themselves in terms of serum copeptin values, there was no significant difference between the control group and the dipper HT patient group (P=.101). When the control group and

Table 1. Comparison of patient and control groups

Parameter	Control group (n=30)	Patient group (n=61)	*p* value
Age	36.5 (30.5-47.5)	54 (43.5-64.5)	<.001
Height (cm)	168.5 (161.5-172)	165 (160-172)	>.050
Weight (kg)	68.5 (64.75-74)	83 (74-90)	<.001
Body mass index (kg/m^2)	24.27 (22-27.48)	29.71 (27.26-33.22)	<.001
Waist circumference (cm)	84.5 (79.5-89)	106 (100-114.5)	<.001
Systolic Blood Pressure (mmHg)	120 (110-126.25)	160 (155-170)	<.001
Diastolic Blood Pressure (mmHg)	70 (65-80)	95 (85-100)	<.001
Flow mediated dilation (Basal) (cm)	0.39 (0.34-0.42)	0.43 (0.40-0.49)	<.001
Flow mediated dilation (Hyperemia) (cm)	0.45 (0.39-0.49)	0.48 (0.43-0.53)	.032
Flow mediated dilation rate	0.16 (0.11-0.19)	0.06 (0.04-0.11)	<.001
Stiffness index (m/sec)	7.23 (6.92-8.49)	11.28 (9.86-12.85)	<.001
Reflection index	57 (44.25-64.5)	70.5 (62-78.75)	<.001
Pulse propagation time (msec)	228.5 (190.75-242.50)	150 (132-175.25)	<.001
Copeptin level	4.51 (3.44-10.10)	6.95 (5.25-14.65)	.003

All variables were abnormally distributed, and expressed as median (interquartile range, 25th-75th), and comparisons between groups were made by using Mann-Whitney U test. In all analyses, *p* value below .050 was considered statistically significant.

Table 2. Comparison of the data of dipper and non-dipper hypertension patient groups and control group

Parameter	Control (n=30)	Dipper Hypertension (n=30)	Non-dipper Hypertension (n=31)	*p* value
Age	36.5 (30.5-47.5)	52 (38.75-63.25)	58 (48-66)	<.001
Height (cm)	168.5 (161.5-172)	165 (160-171.25)	168 (160-174)	>.050
Weight (kg)	68.5 (64.75-74)	83 (71.5-86.5)	83 (74-90)	<.001
BMI (kg/m^2)	24.27 (22-27.48)	28.89 (27.30-33.15)	29.90 (26.54-33.46)	<.001
Waist circumference (cm)	84.5 (79.5-89)	106.5 (100-115)	103 (100-114)	<.001
Systolic Blood Pressure (mmHg)	120 (110-126.25)	160 (155-170)	165 (155-175)	<.001
Diastolic Blood Pressure (mmHg)	70 (65-80)	97.5 (85-100)	95 (85-100)	<.001
Flow-mediated dilation (Basal) (cm)	0.39 (0.34-0.42)	0.43 (0.39-0.50)	0.44 (0.40-0.49)	<.001
Flow-mediated dilation (Hyperemia) (cm)	0.45 (0.39-0.49)	0.48 (0.43-0.53)	0.48 (0.44-0.53)	>.050
Flow-mediated dilation rate	0.16 (0.11-0.19)	0.06 (0.04-0.16)	0.06 (0.04-0.10)	<.001
Stiffness index	7.23 (6.92-8.49)	10.71 (8.38-12.27)	11.62 (10.32-13.28)	<.001
Reflection index	57 (44.25-64.5)	71.5 (62-81)	69.50 (62-78.75)	<.001
Pulse propagation time (msec)	228.5 (190.75-242.50)	154.5 (135-190.25)	147 (131.5-163.5)	<.001
Copeptin level	4.51 (3.44-10.10)	6.09 (4.58-12.83)	7.81 (5.88-17.29)	.001

All variables were abnormally distributed, and expressed as median. (interquartile range, 25th-75th), and comparisons between groups were made, using Kruskal-Wallis test. In all analyses, *p* value below .050 was considered statistically significant.

non-dipper HT group and dipper HT and non-dipper HT groups were compared among themselves, the median of serum copeptin values of non-dipper HT patients were significantly higher than both groups (P=.001, P=.010, respectively) (**Figure 2**).

Correlation of copeptin and non-invasive endothelial function indicators

Correlation analyses of copeptin levels with non-invasive endothelial function indicators are given in **Table 3**. Among tested parameters, there was a significant correlation only between copeptin and RI (r=0.29, P=.014) (**Figure 3**). Copeptin levels significantly correlated with the systolic dipping ratio (r=-0.38, P=.002) at a moderate level but did not correlate with the diastolic dipping ratio (r=-0.24, P=.057) in HT patients. Afterwards, age and BMI were adjusted for partial correlation analysis in the whole group and a significant correlation was found between serum copeptin levels and RI (r=0.24, P=.039). When the groups were evaluated with-

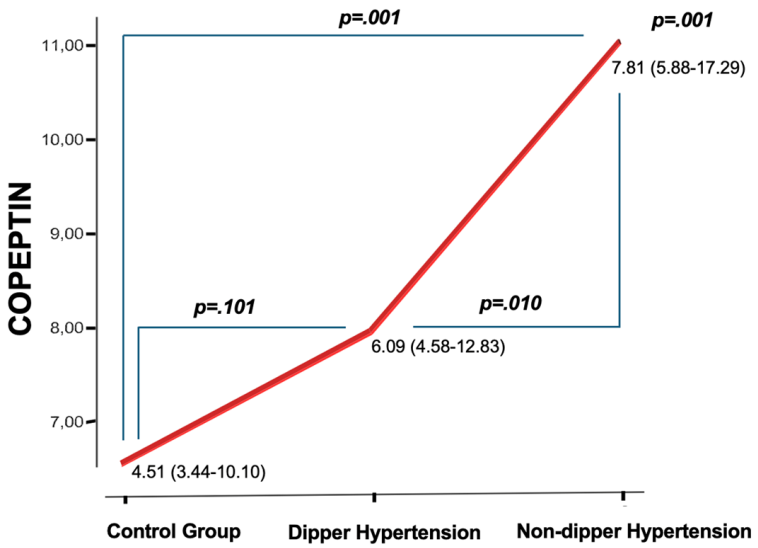

Figure 2. Graph showing the difference of copeptin levels as ng/mL among groups.

Table 3. Correlation of copeptin with non-invasive endothelial function indicators

Variables	Copeptin	
	r coefficient	*p* value
Flow mediated dilation (Basal)	0.16	.129
Flow mediated dilation (Hyperemia)	0.15	.149
Flow mediated dilation rate	-0.16	.122
Stiffness index	0.20	.079
Reflection index	0.29	.014
Pulse propagation time	-0.22	.059

r coefficient = Spearman's rho. *p* value below .050 was considered statistically significant.

in themselves, this correlation was more prominent but with no statistical significance especially in the non-dipper HT patient group (r=0.44, P=.050). No correlation was observed between copeptin and other non-invasive endothelial function parameters measured by FMD, PWA and DVP. When the groups were evaluated separately by partial correlation analysis, it was found that the significant correlation between copeptin levels and RI persisted after adjustment for age in the non-dipper HT patient group (r=0.43, P=.048).

Linear regression analysis for copeptin

The results of the stepwise linear regression analysis for copeptin are demonstrated in **Table 4**. RI emerged as an independent predictor of copeptin (β=0.285, P=.015), but there were no significant associations of other variables included in the model, such as SI, PPT, FMD rate, age, BMI and waist circumference, and copeptin.

Discussion

In this study, the relationship between non-invasively measured endothelial function-related parameters and copeptin levels in newly diagnosed dipper and non-dipper HT patients and a healthy volunteer control group was investigated. Among the many parameters evaluated in the study, it was shown that RI measurement, which was measured non-invasively by PWA, had a more prominent association with copeptin levels.

There is no robust evidence in the literature about the most appropriate method to detect endothelial dysfunction. Kelly *et al.* measured endothelial dysfunction through endothelium-dependent vasodilatation activity in humans [15]. Andrew Stiegler demonstrated the relationship between high BP and endothelial dysfunction through acetylcholine activity [16]. Nathan S. Bryan and Asker *et al.* detected endothelial dysfunction by measuring plasma nitric oxide concentration [17, 18]. Poredos *et al.* aimed to detect and measure endothelial dysfunction through imbalance of vasoactive substances [19]. Among diverse methods currently used and described in the literature, measurement of FMD of the brachial artery by ultrasonography is the fastest, easiest and most widely utilized method for detecting endothelial dysfunction. Furthermore, it correlates well with coronary flow-induced dilation and is a non-invasive procedure [20, 21]. Similar to FMD, the waveform obtained through DVP, which provides non-invasive endothelial function measurement, is independent of local changes in the vascular structure. It helps

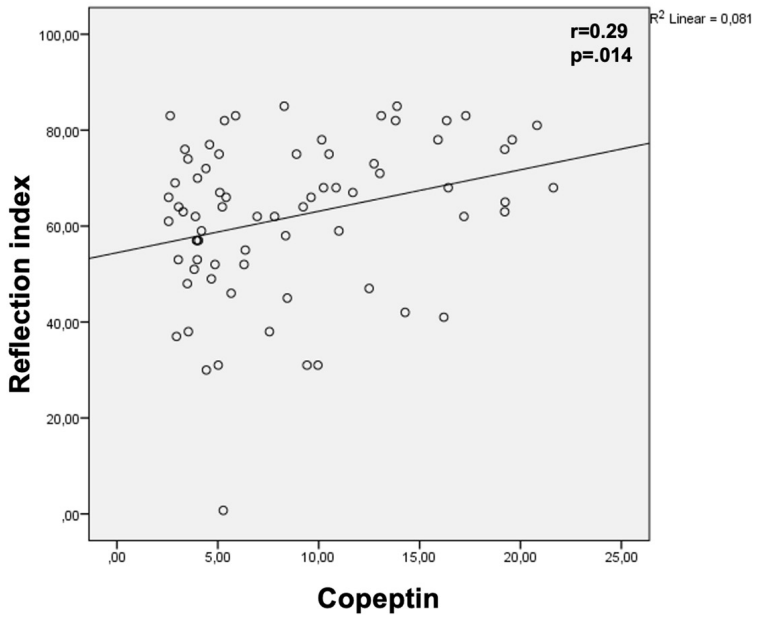

Figure 3. Correlation between copeptin levels and reflection index.

Table 4. Stepwise linear regression analysis for copeptin

Variables	Copeptin Level	
	Standardized regression coefficient (β)	*p* value
Age	0.086	.481
Body mass index	0.041	.723
Waist circumference	0.066	.594
Flow mediated dilation rate	-0.166	.171
Stiffness index	-0.019	.871
Reflection index	0.285	.015
Pulse propagation time	-0.109	.423

A *p* value below .050 was considered statistically significant.

determine RI, which provides information about vascular tone, and SI, which yields information about large artery stiffness [14]. Indeed, arterial stiffness is known to be an indicator of target organ damage in HT patients [22].

There is an increasing number of studies showing that endothelial dysfunction has an important role in the pathophysiology of many diseases, especially cardiovascular diseases and HT. Endothelial dysfunction in HT can be reversed by both pharmacological and non-pharmacological approaches. Studies showed that regular aerobic exercise improves endothelium-dependent vasodilatation in the forearm microcirculation of HT patients [18]. In the study by Landmesser *et al*., improvement in endothelium-dependent vasodilation was observed in HT patients after treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and dihydropyridine group calcium channel blockers [23]. For a long time, it has been investigated why, in some hypertensive patients, BP does not decrease at night. Studies showed that some biological and hormonal mechanisms are more active in non-dipper HT patients. It is thought that the "dipping" mechanism is impaired due to impaired autonomic nervous system function and decreased nocturnal suppressive effect and interaction of the renin-angiotensin-aldosterone system with the sympathetic system [23, 24].

Copeptin has been demonstrated to reflect endogenous stress levels better than cortisol. Since there is a positive correlation between copeptin levels and disease severity and clinical outcomes, it has been suggested that copeptin can be used as a prognostic marker in acute diseases [25]. On the other hand, copeptin has been investigated as a diagnostic and prognostic biomarker in various diseases, such as pneumonia, acute coronary syndromes, heart failure, renal failure, hemorrhagic and septic shock, and copeptin levels, increased in direct proportion to disease severity [26]. Consistent with our study results, previous studies found that copeptin levels are elevated in HT patients, and this elevation may be associated with poor outcomes [27-29]. In this context, in our study, we investigated the copeptin levels in HT patients among dipper and non-dipper HT patients and healthy control groups and the relationship of these levels with non-invasive endothelial dysfunction indicators. In our study, the increase in copeptin levels in the non-dipper HT patient group was

statistically significant compared to the copeptin levels of the dipper HT patient group and the healthy control group. However, no statistically significant difference was found between the healthy control group and the dipper hypertensive patient group regarding copeptin levels. This finding indicates that non-dipper HT patients have a more severe risk of complications and cardiovascular disease compared to other HT groups. It suggests that treatment and follow-up should be done more seriously and closely in this group of patients.

Uzun *et al.* found that higher serum copeptin levels predict the non-dipping pattern in newly diagnosed HT patients [30]. In a similar manner, Altın *et al.* found higher serum copeptin levels in non-dipper HT patients and suggested that high copeptin levels are linked with poor prognostic course [31]. Similar to aforementioned studies, we found higher copeptin levels in non-dipper HT patients than dipper HT patients and control group. There are many underlying mechanisms for the association between increased copeptin and dipping status. Relative hyperosmolarity due to increased sodium uptake may increase AVP and copeptin levels and cause hypervolemia [32]. Imbalance between the sympathetic and parasympathetic nervous tone can cause excessive fluid overload that results with AVP secretion and non-dipper HT due to prominent volume shift that occurs at night. Increased stressful life status, which is associated with non-dipper HT, can also disrupt hypothalamic-pituitary-adrenal axis, increases sympathetic activity and adrenergic hormones that stimulate AVP release [33].

In our study, when the FMD and DVP waveform parameters were analyzed, it was found that the difference between the healthy volunteers and HT patient groups was statistically significant. When this difference was compared separately between the dipper HT and non-dipper HT patient groups and the control group, a statistically significant difference was found in both patient groups compared to the control group. However, no significant difference was found between the dipper and non-dipper HT patient groups. This finding is consistent with other studies we observed in the literature suggesting endothelial dysfunction occurs significantly in HT patients [21]. It is worthwhile mentioning that HT group patients, both including the dipper and non-dipper groups, had higher baseline brachial artery diameters. However, we think this occurs due to the higher BMI of the HT patient group compared to the control group patients. HT patients did not have adequate vasodilatation capacity due to underlying endothelial dysfunction, and FMD rates were lower in the HT patient group than the control group. This finding is in line with a previous study that showed similar baseline brachial artery diameters but reduced dilatation response to hyperemia in hypercholesterolemic subjects than control subjects [34]. On the other hand, dipper and non-dipper HT patients had similar FMD rates, suggesting the contribution of diverse mechanisms in the pathophysiology of HT and endothelial dysfunction rather than dipping status only, which deserves to be investigated in future studies. We also keep in mind that these discrepancies might occur due to abnormal distribution of the variables in the study. At this point, it should also be mentioned that serum copeptin levels increase progressively as we move from controls to dippers and non-dippers. However, we do not see such a trend with respect to FMD and PWA measurements within HT patients, which we think again is due to abnormal distribution of these parameters. However, none of the parameters except RI correlated with copeptin in the study.

In our study, higher copeptin levels in the non-dipper HT patient group were more strongly correlated with RI. This result suggests that copeptin, which can be used as a biomarker to evaluate treatment and prognosis in chronic diseases, can be used as an effective marker to show that arterial atherosclerosis and vascular tone are affected and endothelial functions are impaired in HT patients. In previous studies, endpoints, such as death and hospitalization, were significantly higher in non-dipper HT patients, and copeptin levels were shown to be higher in patients with poor prognosis compared to those with good prognosis [30]. In our study, significantly higher copeptin levels and non-invasive endothelial function correlation in the non-dipper HT patient group suggest that HT patients, especially non-dipper HT patients, constitute a risky group in terms of endothelial dysfunction and the significant increase in copeptin levels suggests that the prognosis of this patient group might be worse.

There are many limitations of the study that should be mentioned. The small number of patients and the inclusion of patients from a single center limit the generalizability of the results. The fact that extreme dipper, reverse dipper and normotensive non-dipper individuals were not included in the study also stands out as a limitation. Because we diagnosed HT according to ABPM and did not consider office BP measurements, we could not classify and stage severity of HT. Since the study design was cross-sectional and there was no follow-up of the patients, it is unknown whether copeptin elevation and endothelial dysfunction improve with treatment and its effect on prognosis. The study design is also insufficient to explain the cause-and-effect relationship. For example, it is unknown whether non-dipper HT develops due to endothelial dysfunction or endothelial dysfunction develops due to non-dipper HT. Therefore, there is a need for further studies in which these limitations are considered.

In conclusion, our findings suggest that endothelial dysfunction was more advanced in HT patients, especially in the non-dipper HT group. Significantly higher copeptin levels in these patients suggest that the prognosis of this patient group may be worse. Elevated copeptin levels in this patient group showed a significant correlation with RI, one of the parameters of endothelial dysfunction. Copeptin can be used as a biomarker in determining the degree of arterial stiffness and evaluation of endothelial dysfunction.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Huseyin Kandemir, Department of Cardiology, Kırıkkale University Faculty of Medicine, Kırıkkale, Turkey. Tel: +90-538-351-6691; ORCID: 0000-0002-4462-7425; E-mail: dr_hsynkndmr@hotmail.com

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