RESEARCH ARTICLE

Serum pentraxin-3 levels and flow-mediated dilation in dipper and non-dipper hypertension

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Background: Endothelial dysfunction is one of the main pathological processes of hypertension. The association of serum pentraxin-3 (PTX3) levels and endothelial dysfunction becomes a more interesting scientific research issue due to high potential of PTX3 as a diagnostic and prognostic biomarker. We aimed to investigate the relationship between serum PTX3 levels and flow-mediated dilation results in patients with dipper and non-dipper hypertension.

Methods: This study included 90 hypertensive patients were divided into two groups based on 24 hours ambulatory blood pressure monitoring (ABPM): 38 patients with a dipper pattern and 52 patients with non-dipper pattern. Noninvasive evaluation of the endothelial functions was performed using flow-mediated dilation (FMD) method.

Results: Serum pentraxin-3 levels were higher in patients with non-dipper HT compared to dipper hypertension ($P = 0.028$). In addition, we found negative correlation between serum PTX3 and FMD basal/FMD hyperemia ratio ($r = -0.297$, $P = 0.05$ for FMD basal/FMD hyperemia ratio, respectively).

Conclusions: Serum PTX3 levels are closely related with the measures of indirect noninvasive evaluation methods (FMD) in both DH and NDH patients.

KEYWORDS

ambulatory blood pressure monitoring, dipper hypertension, flow-mediated dilation, non-dipper hypertension, pentraxin-3

1 | INTRODUCTION

Hypertension is one of the most common diseases worldwide.¹ Although there are several etiological factors which may cause high blood pressure, endothelial dysfunction is one of the main pathological processes of hypertension.^{2,3} In clinical practice, there is no direct method to measure endothelial functions. However, some of indirect and practical methods can aid to evaluate the endothelial functions via measurement of responses to shear stress. Among them, flow-mediated dilation (FMD) is the most practical and effective method.^{4,5} Flow-mediated dilation depends on measuring the dilation ratio of the brachial artery. Dilation of the brachial artery is induced by enhanced nitric oxide (NO) levels in response to augmented vessel wall shear stress.³⁻⁵

In recent years, the association of serum pentraxin-3 (PTX3) levels and endothelial dysfunction becomes more interesting scientific research issue due to high potential of PTX3 as a diagnostic and prognostic biomarker for endothelial dysfunction.^{6,7} Several studies have shown that elevated PTX3 levels are associated with high blood pressure levels in hypertensive patients.^{8,9} Yasunaga et al¹⁰ have also suggested that PTX3 is more valuable than C-reactive protein (CRP) to show endothelial dysfunction. However, there is a limited number of data regarding the relationship between serum PTX3 levels and circadian blood pressure alterations.

In the present study, we aimed to investigate the relationship between serum PTX3 levels and FMD in patients with dipper and non-dipper hypertension.

2 | MATERIAL AND METHODS

In this cross-sectional study, a total of 240 patients who were admitted to the Cardiology Department of Kirikkale University Medical Faculty with high blood pressure and associated symptoms between June 2013 and July 2014 were screened. The study protocol was approved by local Ethics Committee (13.01.2014/02.01). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.1 | Patient selection

Exclusion criteria were as follows: acute coronary syndromes, systolic heart failure (ejection fraction [EF] <50%), coronary and peripheral artery disease, secondary hypertension, congenital heart disease, moderate to severe valvular heart disease, thoracic/abdominal aortic aneurysms, acute-onset carotid artery stenosis or a previous history of carotid artery stenosis and relevant treatments applied, chronic renal dysfunction (serum creatinine level >1.5 mg/dL), diabetes mellitus (fasting blood glucose level ≥ 126 mg/dL), malignancies, morbid obesity (body mass index [BMI] ≥ 40 kg/m²), asthma or chronic obstructive lung disease, infections, connective tissue disorders, neurological problems, psychiatric diseases (psychosis, major depression, and anxiety disorder), endocrine disease, alcohol and drug abuse, and use of medications for hormonal treatment.

Based on these exclusion criteria, a total of 150 patients were excluded, and 90 patients were included in the study.

2.2 | Laboratory analysis

A fasting blood sample was drawn between 09.00 AM and 10.00 AM from each patient. Laboratory workup included detailed biochemistry analysis with complete blood count, fasting blood glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum lipid profile including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride.

2.2.1 | Quantification of serum PTX levels

We used human PTX 3/TSG-14 (PTX3, Long) enzyme-linked immunosorbent assay (ELISA) No: E-EL-H1574 Elabscience® (Sandiwh-ELISA method). Blood samples (2-3 cc) were collected into tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were, then, centrifugated at 5000 g at 2-8°C for 30 minutes. After five min, the supernatants were carefully assembled. After hemolyzed products were eliminated, the remaining products were stored at -80°C, until analysis.¹¹

2.3 | Cardiological examination

After obtaining detailed medical history, physical examination including blood pressure measurement in both arms using an aneroid

sphygmomanometer was performed in all patients. Standard 12-lead electrocardiography (ECG) recording and transthoracic echocardiography (Ge-Vivid 7 Pro; General Electric; FL) were applied to all study participants.

2.3.1 | Ambulatory blood pressure monitoring

Diagnosis of essential hypertension was established by ambulatory blood pressure monitoring (ABPM; GE Tonoport, Berlin, Germany). The ABPM device was programmed to perform the measurements per 30 minutes at daytime (between 06.00 AM and 10.00 PM) and per 60 minutes at nighttime (between 10.00 PM and 06.00 AM). After 24-hour blood pressure monitoring, recordings were processed by Ge Tonoport Programme®. Blood pressure levels were assessed according to the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) 2013 guidelines.¹² Once the diagnosis of hypertension was made, all patients were divided into groups according to the decline in the blood pressure at nighttime: the patients with a decline of >10% during the nighttime were classified as dipper hypertensive patients (DH; n = 38), while those with a decline below 10% were classified as non-dipper hypertensive patients (NDH; n = 52).¹²

2.4 | Noninvasive evaluation of endothelial functions

Noninvasive evaluation of endothelial functions was performed by using FMD.

2.4.1 | FMD method

Flow-mediated dilation measurements were performed by Ge-Vivid 7 Pro, 12 L Doppler probe (General Electric, Florida, USA) according to the method of Celermajer, DS et al¹³

In addition, we used the following parameters to measure FMD:

- FMD basal (cm): baseline brachial artery diameter
- FMD hyperemia (cm): brachial artery diameter at hyperemic phase
- FMD ratio (%): (FMD hyperemia- FMD basal)/FMD basal

2.5 | Statistical analysis

Statistical analysis was performed by using the SPSS version 20.0 software (IBM Corp., Armonk, NY). The normally distributed data were expressed in mean $\pm$ standard deviation (SD), while abnormally distributed data were expressed in median (25%-75%). For continuous variables, Student's *t* test was used to compare data with normal distribution. The Mann-Whitney *U* test was used to compare abnormally distributed data. The Pearson and Spearman tests were used for the correlation analysis. Univariate analysis was also performed to evaluate the factors influencing serum PTX3 levels. A *P* value of <0.05 was considered as statistically significant.

TABLE 1 Demographic data of study groups

	Dipper HT N = 38	Non-dipper HT N = 52	P
Age	57.50 ± 12.58	55.40 ± 13.04	NS
Height	165.58 ± 8.66	164.42 ± 10.05	NS
Weight	79.37 ± 12.89	80.90 ± 12.9	NS
BMI	29.15 ± 5.65	29.95 ± 4.99	NS
Systolic BP	141.3 ± 15.8	143.6 ± 14.9	NS
Diastolic BP	84.5 ± 9.9	88.3 ± 10.8	NS

NS, statistically non-significant.

3 | RESULTS

Totally 90 patients were recruited to present study. Of them, 44 were males with a mean age of 58 ± 12 years and 46 were females with a mean age of 54 ± 12 years. Mean age of all patients was 56 ± 12 (range: 23-89) years. There were 38 patients (42%) with DH and 52 patients (58%) with NDH. There were no significant differences in the anthropometric measurements between the patient groups. Demographic data of the study groups are also shown in Table 1.

3.1 | Laboratory results

There was no significant difference in biochemical test results between patients with DH and NDH, except for serum PTX3 levels. Patients with NDH had higher serum PTX3 levels than DH patients ($P = 0.028$; Table 2).

TABLE 2 The statistical comparison about biochemical blood analysis including serum pentraxin-3 levels of patients with dipper and non-dipper hypertension

Patient characteristics	Dipper hypertension (DH) N: 38	Non-dipper hypertension (NDH) N: 52	P
Hemoglobin (mg/dL)	14.0 ± 1.5	13.7 ± 2.4	NS
Glucose (mg/dL)	102.0 ± 15.0	109.2 ± 14.8	NS
Urea (mg/dL)	32.9 ± 13.7	35.2 ± 14.4	NS
Creatinine (mg/dL)*	0.71 (0.6-0.9)	0.72 (0.65-0.94)	NS
ALT (U/L)	20.7 ± 7.7	21.19 ± 10.5	NS
AST (U/L)	21.1 ± 5.3	23.5 ± 13.9	NS
Total cholesterol (mg/dL)	203.0 ± 33.3	205.7 ± 35.7	NS
HDL (mg/dL)	51.4 ± 11.7	46.8 ± 10.6	NS
LDL (mg/dL)	122.5 ± 26.7	121.2 ± 35.3	NS
Triglyceride (mg/dL)*	135 (97.2-177.2)	142 (109.7-106.5)	NS
TSH (μIU/mL)*	1.96 (1.21-2.97)	1.53 (1.10-2.45)	NS
CRP (mg/L)	4.75 (2-5)	4.70 (2.5-6)	NS
Pentraxin-3*	3.96 (3.14-5.45)	5.02 (3.76-8.60)	0.028

NS: statistically non-significant.

Student's *t* test, Mean ± SD, $P < 0.05$.

*Mann-Whitney *U* test, Median (25%-75%), $P < 0.05$.

3.2 | FMD results

There was no significant difference between DH and NDH patients in basal FMD values and FMD values after hyperemia (Table 3).

3.3 | Correlation analysis of serum PTX3 levels and FMD measurements

We performed correlation analysis between serum PTX3 levels and FMD results of the all study participants (Table 4).

Beside a correlation between serum PTX3 levels and FMD values, we also found a negative correlation between serum PTX3 levels and FMD basal/FMD hyperemia ratio ($r = -0.297$, $P = 0.05$; Table 4).

In addition, we repeated the correlation analysis of serum PTX3 levels and FMD results in both DH and NDH patients. Although we did not find any significant correlation between serum PTX3 levels and FMD values in DH patients, there was a statistically significant negative correlation between serum PTX3 levels and FMD hyperemia ($r = -0.427$, $P = 0.002$) and FMD hyperemia/FMD basal ratio values ($r = -0.401$, $P = 0.001$).

4 | DISCUSSION

In the present study, we found a negative correlation between serum PTX3 levels and FMD hyperemia and FMD hyperemia/FMD basal ratios. We also found that the difference in FMD results between DH and NDH patients was statistically non-significant.

Hypertension is one of the most common conditions, which involves both endothelial dysfunction and inflammation.¹⁴⁻¹⁷ Additionally, some clinical forms of hypertension have a higher

	Dipper hypertension (DH) N:38	Non-dipper hypertension (NDH) N:52	P
FMD basal (cm)	0.42 ± 0.10	0.39 ± 0.6	NS
FMD hyperemia (cm)	0.47 ± 0.11	0.46 ± 0.7	NS
FMD basal/FMD hyperemia ratio (%) [*]	9.10 (3.88-18.23)	7.33 (4.97-14.97)	0.045

NS, statistically non-significant.

FMD basal (cm): basal brachial artery diameter.

FMD hyperemia (cm): brachial artery diameter at Hyperemia phase.

Student's *t* test, Mean ± SD, *P* < 0.05.

^{*}Mann-Whitney *U* test, Median (25%-75%), *P* < 0.05.

Bold values signifies FMD basal/FMD hyperemia ratio was higher in DH patients.

TABLE 3 The statistical comparison about FMD measurements of patients with dipper and non-dipper hypertension

TABLE 4 Correlation of pentraxin-3 levels with FMD

	FMD basal/FMD hyperemia ratio (%) [*]
Pentaxin-3	R: -0.297 P:0.05

^{*}Correlation is significant at the 0.05 level (2-tailed) Pearson correlation analysis.

tendency to cause target organ damage than those of the others. The existence or nonexistence of dipping in blood pressure is one of the main factors for morbidity, target organ damage, and clinical complications in hypertensive patients.¹⁷

Pentaxin-3 is a novel biological marker of inflammatory processes. Many diseases which have some inflammatory characteristics and have potential to cause endothelial dysfunction can lead to increased serum PTX3 levels.¹⁸⁻²¹ Pentraxin-3 is involved in a variety of molecular mechanisms which can eventually lead to endothelial dysfunction, inflammation, and increased arterial stiffness in hypertensive patients.²¹ In a study, it was shown that PTX3 induced dysfunction and morphological changes in the endothelial layer through a P-selectin/matrix metalloproteinase-1 pathway.²² In the aforementioned study, it was suggested that the same pathophysiological mechanism could prevent the detachment of endothelial NO synthase from caveolin-1, thereby leading to impaired NO signaling. Higashi et al²³ also demonstrated that endothelium-dependent vasodilation was blunted through a decline in the NO release in non-dippers, compared to those with DH. These data are also consistent with our study findings. According to our results, there was a statistically significant difference between the dipper and non-dipper patients by means of serum PTX3 levels. In addition, there was a statistically significant negative correlation between serum PTX3 levels and flow-mediated and NO-dependent arterial vasodilation capacity in all groups. More important, this negative correlation was still statistically significant after adjusting for potential confounding factors such as age, sex, BMI, and systolic and diastolic blood pressures.^{24,25} In a study conducted by Tomohiko Yasunagan et al, the relationship between high-sensitive CRP and pentraxin-3 levels and FMD as endothelial dysfunction markers was evaluated in patients with coronary

artery disease. A negative correlation between FMD and pentraxin-3 was found to be more apparent than the correlation with high-sensitive CRP. This relationship is attributed to the structural properties of PTX3 molecule.

Furthermore, our data are also consistent with the literature findings which have shown the potential importance of serum PTX3 levels as compared to some other markers in the determination of clinical diagnosis and prognosis of endothelial dysfunction and inflammation. According to our study findings, it seems that the patients with NDH have a higher serum PTX3 levels than the others. This can be attributed to the fact that NDH patients have more apparent endothelial dysfunction and more pronounced vascular inflammation.

Nonetheless, there are some limitations in our study. Main limitation of the present study was the lack of measurement of serum NO levels, and the second limitation was a relatively small sample size. Therefore, further large-scale studies are required to reveal the clinical importance of PTX3 in hypertensive patients.

5 | CONCLUSION

In conclusion, this study results suggest that serum PTX3 levels are closely related with the measures of endothelial dysfunction parameters in both DH and NDH patients. In addition, serum PTX3 levels are positively correlated with increased arterial resistance, decreased arterial elasticity, and increased strength of large arteries.

Although there was no difference in CRP levels between in groups, the difference in serum PTX3 levels may suggest that PTX3 may be a more sensitive marker than CRP in determining endothelial dysfunction.

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