RESEARCH ARTICLE

F.U. Med.J.Health.Sci.
2024; 38 (1): 37 - 43
http://www.fusabil.org

Comparisons of the Serum Osteopontin Levels of Patients with Dipper and Non-Dipper Hypertension

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Hypertension (HT) is a preventable significant cause of morbidity and mortality that affects millions of people worldwide. Inflammation plays an important role in the pathophysiology of cardiovascular diseases (CVD) and non-dipper hypertension (NDHT). Hypertension has a circadian rhythm. The aim of this study was to examine the difference in the levels of osteopontin (OPN), an inflammatory mediator, between the DHT and NDHT groups.

Materials and Methods: Patients with hypertension who admitted to the cardiology outpatient clinic were evaluated in this cross-sectional study. HT was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or the patient receiving anti-hypertensive treatment. A 24-hour ambulatory blood pressure monitoring was performed for participats then patients were separated into two groups according to their results as DHT and NDHT. All the patients underwent echocardiography, and serum OPN level was measured with the ELISA method.

Results: We enrolled 40 DHT and 40 NHDT patients in this study. Serum OPN levels were significantly different between two groups (NDHT=215.50±114.44, DHT=152.12±92.76, p=0.008). The left ventricle mass index and left atrium diameter were significantly higher in NDHT group compared to DHT group (IVS; NDHT=11.60±1.24, DHT=10.30±1.55 p<0.001 LV Mass; NDHT=175.35±40.75, DHT=159.36±36.32 p<0.001, LA; NDHT=37.90±3.90, DHT=33.55±3.32 p<0.001). The total cholesterol level was found to be significantly higher in the NDHT group than in the DHT group (NDHT=209.15±28.24, DHT=189.72±33.25 p=0.006).

Conclusion: Our study showed that serum OPN levels were higher in the NDHT group than in the DHT group.

Key Words: *Dipper, non dipper, hypertension, osteopontin, inflammation*

Dipper ve Non Dipper Hipertansiyonu Olan Hastaların Serum Osteopontin Düzeyinin Karşılaştırılması

Amaç: Hipertansiyon dünyada milyonlarca insanı etkileyen önlenebilir önemli bir mortalite ve morbidite sebebidir. İnflamasvon, kardiyovasküler hastalıklar ve dipper olmayan (NDHT) hipertansiyon patofizyolojisinde önemli bir yer tutar. Bu çalışmada, ambulatuvar kan basıncı izlemi yaptığımız ve dipper hipertansiyon (DHT), NDHT grubu olarak ayırdığımız hipertansiyon hastalarında, birçok biyolojik süreçte rol alan ve aynı zamanda inflamatuvar bir mediyatör olan osteopontin (OPN) düzeyinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu kesitsel çalışmada kardiyoloji polikliniğine başvuran hipertansiyon hastaları değerlendirildi. Ofiste ölçülen kan basıncı değerlerinin; sistolik kan basıncı ≥140 mmHg ve/veya diyastolik kan basıncı ≥90 mmHg olması ya da hastanın antihipertansif tedavi alması hipertansiyon olarak tanımlandı. Tüm hastaların 24 saatlik ambulatuvar kan basıncı ölçümü yapıldı. Hastalar DHT ve NDHT olarak iki gruba ayrıldı. Hastaların ekokardiyografisi yapıldı ve bu hastalardan alınan kan örneklerinde serum OPN düzeyi Elisa yöntemi ile ölçüldü.

Bulgular: Çalışmaya 40 DHT ve 40 NHDT olan hasta dahil edildi. Bu hastalarda serum OPN düzeylerinde anlamlı farklılık saptandı (NDHT: 215.5±114.4, DHT: 152.1±92.7 p=0,008). NDHT grubunda, DHT grubuna göre sol ventrikül kütlesinde ve sol atriyum çapında istatiksel olarak anlamlı bir fark saptandı (İnterventriküler septum; NDHT: 11.6±1.2, DHT: 10.3±1.5 p<0.001 sol ventrikül kütlesi; NDHT:175±40.7, DHT: 159.3±36.3 p<0.001, sol atriyum; NDHT: 37.9±3.9, DHT: 33.5±3.3 p<0.001). NDHT grubunda, DHT grubuna göre total kolesterol düzeyi istatiksel açıdan anlamlı olarak daha yüksek bulundu (NDHT: 209.1±28.2, DHT: 189.7±33.2 p=0.006).

Sonuç: Çalışmamızda NDHT grubunda, serum OPN düzeyinin DHT grubuna göre daha yüksek olduğu saptanmıştır.

Anahtar Kelimeler: *Dipper, non dipper, hipertansiyon, osteopontin, inflamasyon*

Received : 06.07.2023
Accepted : 14.12.2023

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Introduction

Hypertension is a chronic disease, and well known risk factor for cardiovascular diseases (CVD) (1). In hypertensive patients, a circadian change in systolic and diastolic blood pressure is known as dipper hypertension, and a fall of >10% is expected during sleep compared to daytime. When this circadian variation does not occur, it is known as non-dipper hypertension (NDHT) which means a decrease in blood pressure of <10% during sleep (2). Uncontrolled HT is an important risk factor for CVD and increases

morbidity and mortality (3, 4). Many studies have reported that NDHT is a stronger marker than DHT for adverse cardiovascular outcomes (5, 6). Inflammation has a significant role in the pathophysiology of NDHT (7, 8). Other studies have also shown that inflammatory markers could be associated with variability in blood pressure (9).

Rather than the classic cardiovascular risk factors, other risk factors such as inflammation, pro-thrombotic factors, and gene mutations have recently been shown as treatment targets for CVD (10, 11). In a series of experimental animal studies, an increase was observed in osteopontin (OPN) expression in aortic tissues with HT, and OPN expression was shown to be related to systolic blood pressure (12). OPN also plays an important role in the correction of cardiac hypertrophy with matrix metalloproteinase (MMP) as a response to chronic pressure loading (13, 14). OPN has a functional role in ischaemic heart diseases, hypertension, heart failure, dilated cardiomyopathy, atherosclerosis and various cardiomyopathies, and several other cardiac diseases. Many stimuli, including cytokines (IL-10, MCSF), oxidized LDL, angiotensin II, hyperglycemia, hypoxia, and epigenetic mechanisms stimulate the expression of OPN (15-19).

OPN is a pro-inflammatory cytokine and is effective in the formation of the cell-mediated immune response (20-23). In the light of these data, the aim of this study was to investigate the potential relationship of serum OPN levels with changes in nocturnal blood pressure values in DHT and NDHT patients.

Materials and Methods

Research and Publication Ethics: Approval for this study was granted by our local ethics committee (decisionn no:09-06, dated 17.12.2013). We also obtained an informed consent from all participants.

Subjects: This case-control study was conducted by evaluating patients with who admitted to the Cardiology outpatient clinic between and were newly diagnosed or had been previously diagnosed with hypertension.

Before measuring the blood pressure (BP) of the patients, they were asked for at least 10 minutes of rest and had been instructed to avoid physical exercise, eating, and smoking for at least 30 mins. HT was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or the patient receiving anti-hypertensive treatment. 24-hour ambulatory BP monitorisation was applied to these patients. With the measurements performed with the ambulatory blood pressure monitoring, the diagnoses were made of DHT when there was a decrease of ≥10% in the nocturnal BP value compared to the daytime value, and NDHT when the decrease was <10%. All participants were devited in to two groups as DHT and NDHT. Study exclusion criteria were; coronary artery disease history, chronic renal failure (serum creatinine level > 2.0 mg/dL), diabetes mellitus (type 1 or type 2), ejection fraction <50%, cardiomyopathies (ischemic and other cardiomyopathies), secondary hypertension (eg. pheochromocytoma, aorta coarctation, renal parenchymal and renovascular diseases, endocrine diseases), familial hyperlipidemia, liver failure (acute or chronic), cerebrovascular diseases (ischemic or hemorrhagic), significant heart valve diseases (regurgitation or stenosis), atrial fibrillation, patients with active infectious disease or inflammation and patients for whom ambulatory BP measurements could not be performed for technical reasons (extremely obese).

Laboratory Measurements: In newly diagnosed patients, the average of 3 consecutive measurements taken at 5-min intervals was accepted as the clinical BP value. The BP measurement was taken using a mercury blood pressure device with an appropriately sized cuff. Ambulatory 24-hour BP was monitored in all the patients. Together with the BP records, venous blood samples were taken from the patients after at least 8 hours fasting. Plasma glucose, creatinine, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and full blood count were examined from the blood samples. Then, transthoracic echocardiographic measurements were performed for all the patients.

Ambulatory Blood Pressure Measurement: The blood pressure measurements were taken with a portable digital recording device by placing an appropriatly sized cuff on the upper part of the left arm in an appropriate position (AND A&D Medical Doctor Pro3 1-243 Asahi, Kitamo-shi, Saitama 364-8585 JAPAN). The device was set to take measurements every 20 mins from 08:01 to 22:59 and every 30 mins from 23:00 to 08:00. The device was also set to automatically reduce pressure at the rate of 3 mmHg. It was explained to the patients that they should continue with normal daily activities, avoid intense exercise, and remain still while the measurement was taken. Patients were also asked to record unusual events and duration of sleep during the day.

Blood Sample Collection: The blood samples were withdrawn into tubes not containing anticoagulant. After being left at room temperature for a minimum of 30 mins and maximum 2 hours, the tubes were centrifuged at 4000 xg for 15 mins. The serum samples obtained were placed in Eppendorf tubes and stored at -80°C until assay of the biochemical parameters.

The OPN levels in the serum samples were examined with the ELISA method according to the manufacturer's instructions (Sunred Biotechnology Company. Human Osteopontin ELISA Kit, Catalog Number: 201-12-1526).

Statistical Analysis: Data obtained in the study were analyzed statistically using SPSS vn. 21 software (Statistical Package for Social Sciences). Descriptive statistics were stated as arithmetic mean±standard deviation (SD) for numerical variables and as number (n) and percentage (%) for categorical variables. Conformity of the variables to normal distribution was assessed with the Kolmogorov-Smirnov test. The parametric

independent samples t-test was used in the comparisons of variables showing normal distribution. The Chi-square test was used in the comparisons of categorical data. A value of $p<0.05$ was accepted as statistically significant in all the analyses.

We calculated our sample size before enrollment of participants and found 80 participants were enough for 0.5 type-1 error and 95% confidence interval with 80% of power.

Results

The study included a total of 80 patients, who were evaluated in the Cardiology outpatient clinic and met the study inclusion criteria, as 40 patients with DHT and 40 patients with NDHT. The baseline characteristics of the patients are shown in Table 1. Age, gender, body mass index, and waist circumference ratio valves were similar between study groups.

In the echoocardiographic evaluation, a significant difference was determined between the groups in respect of left ventricular systolic and end diastolic diameter, and ejection fraction. The interventricular septum (IVS) and posterior wall (PW) thickness values, left atrium diameter, LV mass, and LV mass index values were significantly higher in the patients with NDHT compared to the DHT group (Table 2).

Table 1. Demographic characteristics of the patients

	Dipper HT (n= 40)	Non-dipper HT (n=40)	p value
Age (years)	49.8±12.6	55.7±14.8	0.061
Female n (%)	33 (82.5%)	27 (67.5%)	0.064
Body mass index (kg/m^2)	27.82±1.81	28.23±1.92	0.340
Waist circumference (cm)	102.56±6.14	103.70±6.90	0.773
Smoker	13 (32.5%)	17 (42.5%)	0.052
Impaired fasting glucose	7 (17.5%)	9 (22.5%)	

Table 2. Echocardiographic parameters

	Non-dipper (n= 40)	Dipper (n= 40)	p value
Ejection fraction (%)	60.20±4.72	61.60±4.78	0.142
Left ventricle systole end diameter (mm)	30.10±3.60	29.40±1.90	0.336
Left ventricle diastole end diameter (mm)	46.40±2.82	46.30±2.21	0.484
Interventricular septum thickness (mm)	11.60±1.24	10.30±1.55	<0.001
Posterior wall thickness (mm)	10.80±1.20	9.50±1.20	<0.001
Left atrium (mm)	37.90±3.90	33.55±3.32	<0.001
LV Mass	175.35±40.75	159.36±36.32	<0.001
LV Mass Index	93.25±21.55	85.70±20.95	0.003

Table 3. Ambulatory blood pressure values

Clinic data	Non-dipper (n= 40)	Dipper (n= 40)	p value
24-hour systolic blood pressure (mmHg)	152.05±6.35	154.45±7.21	0.125
24-hour diastolic blood pressure (mmHg)	86.65±9.25	91.85±9.60	0.012
Daytime systolic blood pressure (mmHg)	154.15±6.66	159.52±7.72	0.010
Daytime diastolic blood pressure (mmHg)	87.02±12.5	95.65±12.34	0.003
Nocturnal systolic blood pressure (mmHg)	145.45±6.20	134.55±7.71	<0.001
Nocturnal diastolic blood pressure (mmHg)	85.50±8.44	78.82±9.15	0.001
Clinical systolic blood pressure (mmHg)	159.60±14.25	147.65±16.54	0.001

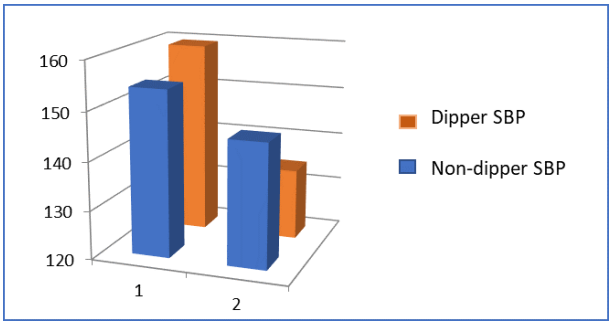

Figure 1. Change in systolic blood pressure between the groups

The mean of 24-hour systolic BP was 152.05 mmHg (±6.35) in the NDHT group, and 154.45 mmHg (±7.21) in the DHT group (p=0.125). The mean of 24-hour diastolic BP was 86.65 mmHg (±9.25) in the NDHT group, and 91.85 mmHg (±9.60) in the DHT group (p=0.012). The groups were evaluated in terms of mean daytime and nocturnal systolic and diastolic BP. The daytime mean systolic BP was 154.15 mmHg (±6.66) in the NHDT group, and 159.52 mmHg (±7.72) in the DHT group (p=0.010). The daytime mean diastolic BP was 87.02 mmHg (±12.5) in th NHDT group, and 95.65 mmHg (±12.34) in the DHT group (p=0.003). The nocturnal mean systolic BP was 145.45 mmHg (±6.20) in the NHDT group, and 134.55 mmHg (±7.71) in the DHT group (p<0.001). The nocturnal mean diastolic BP was 85.50 mmHg (±8.44) in the NHDT group, and 78.82 mmHg (±9.15) in the DHT group (p=0.001) (Table 3 and Figure 1).

A statistically significant difference was found between the groups in respect of total cholesterol and triglyceride levels. The total cholesterol level was determined to be 209.15 (±28.24) mg/dL in the NDHT group, and 189.72 (±33.25) mg/dL in the DHT group (p=0.006). The triglyceride level was 184.67 (±61.10) mg/dl in the NDHT group, and 143.45 (±60.52) mg/dL in thee DHT group (p=0.003) (Table 4).

The mean OPN value was 215.50 (±114.44) pg/ml in the NDHT group and 152.12 (±92.76) pg/ml (p=0.008) in the DHT group, which was significantly higher in the NDHT group when compared (Table 5 and Figure 2).

Table 4. Comparisons of the laboratory parameters of the groups

	Non-dipper (n= 40)	**Dipper (n= 40)**	**P value**
Total cholesterol (mg/dL)	209.15±28.24	189.72±33.25	0.006
Triglycerides (mg/dL)	184.67±61.10	143.45±60.52	0.003
HDL- cholesterol (mg/dL)	44.23±9.14	46.45±10.16	0.310
LDL- cholesterol (mg/dL)	126.67±31.30	115.14±27.75	0.088
Fasting glucose (mg/dL)	97.13±13.90	94.88±13.34	0.442
Hemoglobin (mg/dL)	13.81±1.40	13.25±1.69	0.091
Hematocrit (%)	41.93±3.84	40.56±4.53	0.155
WBC (mcL)	7.25±1.62	6.91±1.98	0.395
MCV (fL)	87.63±6.00	87.95±5.35	0.601
Urea (mg/dL)	32.56±8.94	30.63±9.95	0.362
Creatinin (mg/dL)	0.76±0.15	0.69±0.17	0.065

HDL; high-density lipoprotein, LDL; low-density lipoprotein, WBC; white blood cells, MCV; mean erythrocyte volume.

Table 5. Osteopontin levels of the groups

	Non-dipper (n= 40)	**Dipper (n= 40)**	**P value**
Osteopontin (pg/mL)	215.50±114.44	152.12±92.76	0.008

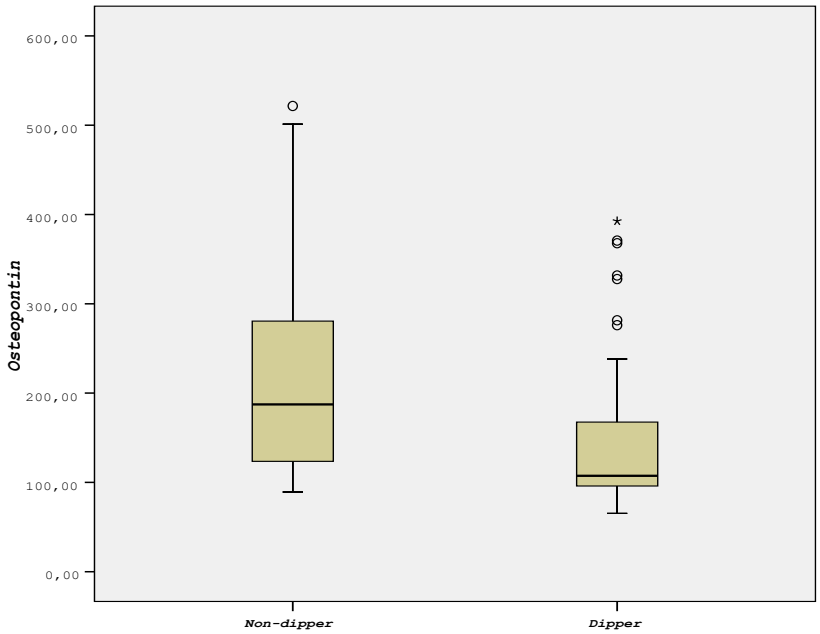

Figure 2. Osteopontin levels of the groups

Discussion

The results of this study demonstrated that the OPN level was affected by nocturnal blood pressure. A fall of <10% in nocturnal BP compared to the daytime BP value is referred to as NDHT pattern, and this is always associated with autonomic dysfunction (24).

The circadian blood pressure changes occur due to the hormones that form the autonomic nervous system (sympathetic and parasympathetic nervous system, vasopressin, acetylcholine, adrenocorticotropic hormone, cortisol, insulin, ghrelin, adiponectin, and leptin, and partially the renin-angiotensin-aldosterone system). These fluctuations in hormone levels are responsible for higher BP during the day and lower BP at night. There are several potential mechanisms that are responsible for nocturnal hypertension; increased sympathetic nervous system activity, hyperactivity of the renin-angiotensin-aldosterone system, sodium retention, renal dysfunction, obstructive sleep apnea syndrome and other sleep disorders, obesity, inflammation, ageing, stress, and diabetes. Nocturnal hypertension may be the first symptom of sympathetic hyperactivity, and this is generally associated with adverse cardiovascular events (stroke, coronary artery disease, heart failure) or other target organ damage (renal failure, cognitive disorder, peripheral artery disease) (25).

Target organ damage and endothelial dysfunction are seen more often in nocturnal hypertension. Therefore, the determination of the risk factors and treatment directed at the potential mechanisms of nocturnal hypertension are extremely important in respect of morbidity and mortality.

OPN is a matricellular protein without collagen that is mainly located in the bone matrix and encoded by the SPP1 gene. OPN plays a role in the proliferation and migration of smooth muscle and the re-shaping of endothelial cells. It functions as a chemotactic molecule to encourage migration of inflammatory cells to an injured region, and as an adhesive protein to keep the cells in the region. At the same time, OPN functions as a pro-inflammatory cytokine, and can modulate the immune response by increasing the expression of Th 1 cytokines and matrix degrading enzymes (26).

Inflammation and immune system activation have been shown to lead to high blood pressure (27). The plasma level of OPN, which is a pro-inflammatory mediator, has been reported to be associated with systolic blood pressure (9).

In many studies, OPN has been shown to be effective in remodelling the heart in clinical conditions such as myocardial infarction and heart failure (28, 29). Moreover, OPN plays an important role in mediating remodelling caused by hypertension has been revealed in the literature (30). Some studies have shown that OPN is expressed in various cell types, including cardiac myocytes, fibroblasts, and myofibroblasts (31). Therefore, OPN has been associated with pathophysiological processes such as CVDs, the inflammatory process, biomineralisation, cell vitality, and wound healing (32). OPN is also known to increase cardiac atrophy and heart failure because of myocardial remodelling probably due to biomechanical stress (29).

It has been reported that because of the nocturnal pressure burden, patients with NDHT are at greater risk of developing left ventricular hypertrophy, left atrial

dilatation, and left ventricular diastolic dysfunction (33). In the echocardiography examinations of this study, it was found that the interventricular septum and posterior wall thicknesses and the left atrial dimensions were significantly higher in the NDHT group. LV mass and LV mass indices wewre also significantly higher in the NDHT group.

Our study has some limitations. First of all, this was a single-center study, so our sample size was relatively small. As a second limitation, inflammatory markers other than OPN were not measured; and lastly, this was a cross-sectional study therefore we could not speculate about pathogenetic relationship or prognostic effect of OPN in patients with NDHT. The actual mechanism of OPN or its potential prognostic effect have to be studied by prospective and randomized trials.

In conclusion, we found that serum OPN levels were significantly higher in NDHT group compared to DHT group. Future studies are warranted for OPN's role as a potential marker in this particular population.

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