

Original Article

Influence of circadian blood pressure alterations on serum SCUBE-1 and soluble CD40 ligand levels in patients with essential hypertension

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Abstract: Background: Dipper and non-dipper hypertension are different clinical forms of essential hypertension. In this study, the effect of circadian blood pressure changes on serum SCUBE-1 and soluble CD40 ligand (sCD40L) levels was investigated in patients with hypertension. Methods: A total of 100 participants aged 23-89 years were included in the study. Patients with essential hypertension were followed up by ambulatory blood pressure measurement. Results: Serum SCUBE1 levels were significantly higher in the non-dipper group than in the normal group ($P < 0.001$). Dipper and non-dipper patients had significantly higher serum sCD40L levels when compared to the normal group ($P = 0.048$ and $P = 0.035$, respectively). We also found a positive correlation between SCUBE1, sCD40L levels and 24-hour mean systolic blood pressure levels ($r: 0.232$, $p: 0.034$ and $r: 0.241$, $p: 0.027$, respectively). Conclusion: Serum SCUBE1 and sCD40L levels were higher in hypertensive patients than normal participants. Serum SCUBE1 levels were higher in patients with non-dipper compared to other participants.

Keywords: SCUBE1 protein human, sCD40L protein, hypertension, blood pressure monitoring

Introduction

Hypertension is one of the most important public health problems [1]. Hypertension is a complex clinical, pathological condition that includes endothelial dysfunction, autonomic imbalance, volume overload, increased arterial resistance. In addition, acute and chronic complications and comorbid pathologies can easily have a detrimental effect on organ systems [2]. However, some studies have shown that some types of hypertension have more complications than other forms. At this point, deterministic clinical characteristic is not only having a higher blood pressure than those of the other patients, but also blood pressure changes during 24 hours could be important for managing hypertension [3, 4]. Cardiovascular parameters such as blood pressure, heart rate and coronary tone vary during the day. According to ambulatory blood pressure monitoring (ABPM) data, the blood pressure of healthy individuals is maximum in the morning, decreases slowly dur-

ing the day and is minimum in the night [4]. In ABPM classification, 10% or more decrease in BP at night is defined as “dipper hypertension” and less than 10% decrease is defined as “non-dipper hypertension” [2, 4, 5]. Most studies have shown that patients with non-dipper hypertension have more target organ damage and related complications [2, 3, 6]. Under normal physiological conditions it is known that there is excessive platelet activity and aggregation, increased vasospastic tone, heart rate and blood pressure in the morning [7].

Autonomic and metabolic processes manage cardiovascular circadian rhythm and platelet activity changes. There are also some serum proteins with activator or regulatory missions for platelet activity [8]. Recently, it has been shown that SCUBE1 (containing the protein-1 domain containing the signal peptide-cub-egf domain) and soluble CD40 ligand (sCD40L) are important for regulating platelet activation. SCUBE-1 has been shown to play a role in the

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pathogenesis of cardiovascular diseases and increase platelet aggregation [8-10]. On the other hand, CD40L is a member of the tumor necrosis factor family. 90% of serum sCD40L is obtained from platelets; CD40L on the surface of platelets begins to synthesize when platelets are activated [9, 10].

In this study, we aimed to investigate the effects of circadian blood pressure changes on serum SCUBE-1 and sCD40L levels in patients with essential hypertension. In this context, serum SCUBE-1 and sCD40L levels in patients with dipper and non-dipper hypertension and the differences were examined.

Material and methods

The study is cross-sectional. The study population consisted of healthy subjects and patients diagnosed with hypertension by 24-hours ABPM. A total of 250 consecutive patients aged 18-75 years between January 2014 and July 2014 were selected. Hypertension was diagnosed based on the ESC/ESH 2013 Hypertension Guidelines [2]. The study design was approved by the local ethics committee (04.06.2014-16/08). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient selection

Exclusion criteria were acute coronary syndromes, systolic heart failure (EF < 50%), coronary and peripheral artery disease, secondary hypertension, congenital heart disease, moderate and severe valvular heart disease, thoracic or abdominal aortic aneurysm, acute or a history of treatment for or diagnosis of carotid artery stenosis, chronic renal dysfunction (serum creatinin level > 1.5 mg/dl), diabetes mellitus (fasting blood glucose level \geq 126 mg/dl), malignancies, morbid obesity (body mass index [BMI] \geq 40 kg/m²), asthma or chronic obstructive pulmonary disease, infections, connective tissue disorders, neurological problems, psychiatric diseases (psychotic and major depressive patients and the patients with anxiety disorders), endocrine disease, alcohol and drug abuse and use of medications for hormonal treatment. One hundred fifty patients were excluded because of progression of any exclusion criteria during the study period. A total of 100 participants (Minimum age: 23, maximum age: 89, mean age: 55.7 \pm 12.7 years) were enrolled into the study.

Laboratory

Fasting blood samples were taken between 09.00 and 10.00 in the morning. As laboratory tests; detailed biochemical analyzes including complete blood count, fasting blood glucose, urea, creatinine, thyroid-stimulating hormone (TSH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum lipid profile (total cholesterol, High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), triglyceride) were performed.

Required blood samples for SCUBE1 and sCD40L measurements were taken 2-3 cc into EDTA tube. Supernatants were collected carefully after centrifuged at 1000XG 2-8°C within 30 min. Samples were stored at -80° C after products with hemolysis were excluded. All these subjects were applied 24-hours ABPM and measurements were recorded.

Determination of SCUBE-1 level

Serum signal peptide-Cub-Egf domain-containing protein-1 (SCUBE1) level (SCUBE-1L): Human SCUBE1 (Signal Peptide, CUB and EGF-like Domain-containing Protein 1) ELISA (Enzyme-linked immunosorbent assay) Elabscience® kits made in China ELISA were used with Sandwich-ELISA technique.

Determination of sCD40L level

Human CD40L/TNFSF5 (Cluster of Differentiation 40 Ligand) ELISA KIT Elab science® ELISA (Enzyme-linked immune-sorbent assay) KIT Elab science® made in P.R.C. tests were used with Sandwich-ELISA technique.

Cardiac evaluation

After obtaining detailed medical history; physical examination including blood pressure measurement in both arms by using sphygmomanometry was done in all subjects. 12-channel electrocardiography (ECG) recordings and transthoracic echocardiography (Ge-Vivid 7 Pro, General Electric; FL, USA) were performed. We diagnosed essential hypertension using ABPM (GE Tonoport, Berlin, Germany). The ABPM device is programmed to measure at 30 minute intervals (06:00-22:00) during the day and at 60 minute intervals at night (22:00-06:00). After 24-hour blood pressure monitoring, recordings were processed using Ge Tono-

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Table 1. Anthropometric characteristics of patients

Patient Characteristics	Mean \pm Standard Deviation
Age (years)	56.29 \pm 12.83
Height, cm	165.00 \pm 9.65
Weight, kg	80.17 \pm 12.59
Body Mass Index (BMI), kg/m ²	29.95 \pm 7.03
Waist Circumference, cm	100.17 \pm 14.74

portProgramme®. Day and night systolic and diastolic blood pressure values were evaluated according to ESC/ESH 2013 hypertension guidelines [2]. On the other hand, all participants were grouped according to the decrease in blood pressure levels at night. During the night; patients with blood pressure drops > 10% were classified as “dipper hypertension” and the rest as “non-dipper hypertension” [2-4].

The individuals included in the study were examined in three groups. In order to compare the data, group 1 consisted of 24 healthy individuals, and according to nighttime systolic blood pressure decline; group 2 of 30 individuals with dipper hypertension and group 3 of 46 individuals with non-dipper hypertension.

Statistical analysis

All statistical analysis was performed using SPSS version 20.0 (SPSS; Chicago, IL, USA). The normally distributed data are presented as mean \pm standard deviation (SD) and non-normally distributed data are expressed as median (25%-75%). For continuous data Student t test with was used for comparing normally distributed data. MannWhitney U test was used for comparing non-normally distributed data. Partial correlation analysis was used for correlation analysis. Multivariate analysis of covariance (MANCOVA) was also performed for the evaluation of the factors which were of important associations with serum SCUBE1 and sCD40L levels. A *p* value of < 0.05 was accepted as statistically significant.

Results

A total of 100 individuals (49 male, 51 female) were included in the study (Minimum age: 23, maximum age: 89, mean age: 55.7 \pm 12.7 years). Dipper hypertension group consisted of 30 (30%) patients, non-dipper hypertension

group 46 (46%) patients and 24 (24%) were the healthy control group. Anthropometric characteristics of patients are given in **Table 1**. The groups were similar in terms of demographic characteristics, fasting plasma glucose, creatinine, hemoglobin, hematocrit, white blood cell count, platelet count, mean platelet volume, AST, ALT, TSH, total cholesterol, LDL-C, HDL-C and triglyceride levels (**Table 2**).

Comparison of measurements about serum SCUBE1 and sCD40L levels among normal participants, the patients with dipper hypertension and non-dipper hypertension

There was statistically significant difference about serum SCUBE1 levels among the study groups ($P < 0.001$, Kruskal Wallis Test), (**Table 2**). When we performed Bonferroni adjustment, we found that the serum SCUBE1 levels were significantly higher in non-dipper hypertension group compared to healthy controls ($P < 0.001$). While SCUBE1 values tended to elevate in non-dipper hypertension group compared to dipper group, the difference was not statistically significant ($P > 0.05$). There was also statistically significant difference on serum sCD40L levels between the groups ($P = 0.025$, One Way ANOVA Test). There was significantly higher serum sCD40L levels in the patients with dipper and non-dipper hypertension compared to control group ($P = 0.048$ and $P = 0.035$, respectively), (**Table 2**).

Partial correlation analysis

In partial correlation analysis, after controlling the effects of age, gender, weight, height and waist circumference, we found positive correlation between serum SCUBE1 and sCD40L levels ($r: 0.456$, $P < 0.001$). There was a positive correlation between serum SCUBE1, sCD40L levels and 24 hour mean systolic blood pressure ($r: 0.232$, $p: 0.034$ and $r: 0.241$, $p: 0.027$, respectively).

Results of multivariate analysis of covariance (MANCOVA) of SCUBE1 and sCD40L

In multivariate analysis of covariance (MANCOVA) model including age, gender, systolic and diastolic blood pressure, body mass index, platelet count, daytime and nighttime diastolic and systolic blood pressure differences, to determine the effective factors on the serum levels of SCUBE1 and sCD40L; a statistically

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Table 2. The comparison of anthropometric characteristics, biochemical blood analyses, serum SCUBE1 and SCD40L levels among the study groups

Patient Characteristics	Normal Group N:24	Dipper Hypertension Group N:30	Non-dipper Hypertension Group N:46	P
Age, years	51.5 ± 10.7	58.1 ± 13.1	56.4 ± 13.1	NS
Height, cm	168.04 ± 8.06	163.50 ± 8.30	164.39 ± 10.62	NS
Weight, kg	78.13 ± 8.31	80.00 ± 14.00	81.35 ± 13.55	NS
Body Mass Index, kg/m ²	27.53 ± 4.31	29.71 ± 5.74	31.36 ± 8.54	NS
Waist Circumference, cm	95.96 ± 13.58	102.56 ± 14.17	100.80 ± 15.51	NS
Glucose, mg/dl	95.66 ± 14.46	100.26 ± 20.97	104.87 ± 11.68	NS
Urea, mg/dl	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	NS
Creatinine, mg/dl*	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	NS
ALT, U/L	20.12 ± 7.3	22.03 ± 10.00	21.04 ± 10.67	NS
AST, U/L	21.54 ± 6.77	21.59 ± 5.77	23.43 ± 14.41	NS
Total cholesterol, mg/dl	203 ± 34.5	203.9 ± 34.27	204.5 ± 34.7	NS
HDL, mg/dl	47.8 ± 11.1	51.9 ± 10.9	47.9 ± 11.6	NS
LDL, mg/dl	122.5 ± 31.4	123.1 ± 26.6	119.8 ± 34.7	NS
Triglyceride, mg/dl*	135 (97.2-177.2)	142.5 (109.3-106.5)	152.5 (114.3-234.0)	NS
TSH, µIU/mL*	1.87 (1.18-2.74)	1.53 (1.19-2.86)	2 (1.26-2.98)	NS
Red Blood Cell count (10 ⁶ /µL)	4.79 ± 0.46	4.83 ± 0.54	4.83 ± 0.76	NS
Hemoglobin, mg/dl	14.2 ± 1.5	14.0 ± 1.5	13.5 ± 2.5	NS
Hematocrite (%)	42.15 ± 4.58	41.66 ± 4.37	40.92 ± 4.69	NS
White Blood Cell count (10 ³ /µL)	7.55 ± 1.44	7.21 ± 2.7	7.88 ± 2.25	NS
Platelet count (10 ³ /µL)*	318.133 ± 53.901	261.838 ± 84.180	244.565 ± 56.476	NS
MPV	9.17 ± 0.95	8.88 ± 1.29	8.67 ± 0.93	NS
SCUBE1 ng/dL	1.19 (0.71-1.65)	1.68 (0.94-3.90)	2.30 (1.47-5.32)	< 0.001
SCD40L ng/dL	707.70 ± 160.24	864.21 ± 190.93	858.80 ± 245.40	< 0.05

One Way ANOVA, Mean ± SD, *Kruskal Wallis test, Median (%25-%75). NS: Not significant (P ≥ 0.05), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-Density Lipoprotein Cholesterol, LDL: Low-Density Lipoprotein Cholesterol, TSH: Thyroid-Stimulating Hormone, MPV: Mean platelet volume, SCUBE1: Signal peptide-cub-egf domain-containing protein-1, SCD40L: Soluble CD40 Ligand.

significant association was found between serum levels of SCUBE1, sCD40L and daytime and nighttime diastolic and systolic blood pressure differences [F (Wilks-Lambda): 3.124, p: 0.049 and F (Wilks-Lambda): 3.041, p: 0.050, respectively).

Discussion

Study group was composed of the newly diagnosed hypertension patients in our clinic and any of were taking anti-coagulant or anti-hypertensive treatment which could influence SCUBE1 and sCD40L levels. Consequently, serum SCUBE1 and sCD40L levels were found to be significantly higher in dipper and non-dipper hypertension groups than the control group. There was no statistically significant difference in serum sCD40L levels between dipper and non-dipper hypertension groups. On the other

hand, patients with non-dipper hypertension had higher serum SCUBE1 levels than other participants.

Hypertension is one of the most important risk factors for atherothrombotic complications and endothelial dysfunction. Endothelial dysfunction and vascular injury are the triggers of platelet activation [10-12]. Chronic high blood pressure; increase in vascular bed resistance and shear stress cause target organ damage, and most of these pathological changes may also cause abnormal platelet activity, leading to atherothrombotic events [12]. Patients with hypertension have decreased nitric oxide bioavailability and increased levels of serum reactive oxygen products and vascular endothelial growth factor [13-15]. Recently, some authors have suggested that some new biomarkers, previously shown as indicators of inflammation and

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platelet activity, may also play a role in the process of hypertension [15-17].

SCUBE1 is a cell surface glycoprotein which is present in platelet and endothelial cells. Furthermore, SCUBE1 and SCUBE2 deposition was detected immune-histo-chemically in sub-endothelial matrix of athero-sclerotic lesions. It is known to increase platelet agglutinations and thereby play a pathologic role in endothelial adhesion molecule and cardio-vascular biology [18-21]. sCD40L which belongs to TNF family has a soluble form released from activated platelets. Recent studies indicate that activated platelets play an important role in inflammation and coagulation cascade by causing interference between CD40 and CD40L in endothelial cells [21-23]. Dai et al. [24] found significantly higher plasma levels of sCD40L and SCUBE1 in acute ischemic stroke and acute coronary syndrome group. However a significant difference was not found between chronic coronary artery disease (CAD) patients and healthy subjects. This condition supports that SCUBE1 and sCD40L levels are good biomarkers for platelet activation. Soluble CD40 ligand is expressed from surface of activated platelets. SCUBE1 plasma levels may be expected to elevate in hypertension patients and correlate with sCD40L [25-28]. Özkan et al. [29] compared SCUBE1 and sCD40L levels with office measurements in newly diagnosed hypertension patients and found them significantly elevated in hypertension group. On the other hand, diagnosis of hypertension was based on office measurements in these patients. Blood pressure values show daytime variations and patients with paroxysmal blood pressure elevation may be evaluated insufficiently by using only office measurements. Besides, dipper and non-dipper hypertension patients have different prognosis. Cardiovascular event risk was shown to increase significantly in non-dipper hypertension patients [30]. Dai et al. [24] did not find a significant difference at SCUBE1 and sCD40L levels between chronic CAD patients and control group. However 62% of chronic CAD group was composed of hypertension patients in that study. In the study of Dai et al., there was no data on whether patients had blood pressure changes during the day or whether BP values were regulated. Therefore, higher serum SCUBE1 may be associated with decreased platelet activation as a result of decreased BP induction and improved endothelial function.

According to our data, high serum SCUBE1 and sCD40L levels in patients with hypertension suggest that these serum biomarkers may be affected by high BP averages. However, only serum SCUBE1 levels seem to be affected by daytime blood pressure changes. At this point, our data on SCUBE1 were consistent with the literature in the context of non-dipper hypertension, which is known to be more risky than dipper hypertension in cardiovascular events.

Study limitations

The most important limitations of our study are the fact that it is a single-center study and has small sample size.

Conclusion

Novel platelet activation markers, serum SCUBE1 and sCD40L levels increase in “newly diagnosed” hypertension patients. This increase was shown both in dipper and non-dipper hypertension groups. In our study, SCUBE1 levels were higher in the patients with non-dipper hypertension than those of other participants. However, further studies are needed, which may be supported by similar results.

Disclosure of conflict of interest

None.

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