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ORIGINAL ARTICLE

Plasma SCF/c-kit Levels in Patients with Dipper and Non-Dipper Hypertension

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Key words: ambulatory blood pressure monitor; dipper hypertension; non-dipper hypertension; stem cell factor; c-kit

Objective The aim of this study was to investigate the relationship between peripheral plasma stem cell factor (SCF)/c-kit levels and the types of dipper and non-dipper hypertension in hypertensive patients.

Methods This cross-sectional study included newly diagnosed hypertensive patients who underwent 24-hour ambulatory blood pressure monitor (ABPM) between January 2009 and 2012 in Jiangning city. Patients were divided into the dipper group and the non-dipper group according to ABPM measurements. The levels of SCF and its receptor c-kit, tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6) in peripheral blood were measured *via* enzyme-linked immunosorbent assays. The serum levels of glucose and lipid were examined as well. The levels of SCF/c-kit were compared between the dippers and the non-dippers; and their correlation with 24-hour mean systolic blood pressure (MSBP), 24-hour mean diastolic blood pressure (MDBP), TNF- α and IL-6 were investigated using linear regression analyses statistically.

Results A total of 247 patients with newly diagnosed hypertension were recruited into the study, including 116 non-dippers and 131 dippers. The levels of peripheral plasma SCF were higher in non-dipper group (907.1 ± 52.7 ng/L *vs.* 778.7 ± 44.6 ng/L; $t=2.837$, $P<0.01$), and the levels of c-kit were higher in non-dipper group too (13.2 ± 1.7 μ g/L *vs.* 9.57 ± 1.4 μ g/L; $t=2.831$, $P<0.01$). Linear regression analysis revealed that SCF/c-kit levels were significantly positively correlated with MSBP, MDBP, plasma TNF- α , and IL-6 levels (all $P<0.01$).

Conclusions Peripheral plasma SCF/c-kit levels are higher in patients with non-dipper hypertension than those with dipper one, and significantly correlate with 24-hour MSBP, 24-hour MDBP, serum TNF- α and IL-6 levels.

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THE prevalence of hypertension is rapidly increasing. The onset and progression of hypertension have complicated pathophysiology. Ambulatory blood pressure monitoring (ABPM) has been increasingly used in recent years to assess the circadian pattern of blood pressure (BP).¹ This pattern is considered an important predictor of both target-organ damage and cardiovascular events.²⁻⁴ There have been many evidences indicating that vascular endothelial dysfunction is the most critical phase in the development of hypertension.⁵ Stem cells, such as mesenchymal stem cells, endothelial progenitor cells and peripheral blood stem cells, are mobilized to promote vascular repair when the endothelium is activated.⁶ Stem cell factor (SCF), the ligand of c-kit, belongs to a super family of tyrosine kinase receptor, where the members of this family are cardinal regulators of cellular fate in the mammalian body.⁷ SCF/c-kit is a principal regulator for survival and function of a multitude of neural crest-derived cell types, particularly for those involved in smooth muscle contraction and inflammation.⁸⁻¹⁰ Our previous study found that peripheral serum SCF/c-kit levels increase in pre-hypertensive and hypertensive patients.¹¹ However, the relationship between SCF/c-kit and the type of hypertension (dipper or non-dipper) remains unclear. The present study explores the plasma SCF/c-kit levels in patients with dipper and non-dipper hypertension. We propose that the non-dipper hypertension should be paid more attention, and SCF could become a new approach for the treatment of hypertension.

MATERIALS AND METHODS

Study protocol and subjects recruitment

This study was conducted in the Second People's Hospital of Jiangning from March 2009 to July 2012. The study was approved by the Institutional Review Boards, and written informed consent forms were acquired from all patients prior to the enrollment.

Patients who were newly diagnosed with hypertension by inpatient and outpatient clinics were the candidates of the study. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg in an office setting, and SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg based on the mean 24 h circadian ABPM.¹² All candidates completed a questionnaire on general information (age, sex, height, weight, drinking and smoking history, and disease history). Body mass index (BMI) was calculated as the ratio of body weight in kilograms to height squared.

The exclusion criteria were as follows: recent infections, history of cancer, liver disease, chronic kidney disease, diabetes mellitus, secondary hypertension, or chronic degenerative diseases; history of anti-hypertensive medications or anti-diabetic medications that affect glucose and/or lipid metabolism; those with sympathetic activation; and history of coronary heart disease, heart failure, stroke, severe alular disease or other concomitant disease.

According to ABPM measurement, all enrolled subjects were assigned into two groups: dipper HP patients and non-dipper HP patients. Hypertensive subjects who showed a reduction of SBP $< 10\%$ from daytime to nighttime were defined as "non-dippers", and those who had a reduction of SBP $\geq 10\%$ from daytime to nighttime were defined as "dippers".¹²

Clinical BP and ABPM measurements

SBP and DBP were measured 10 minutes after patients arriving at the clinics. Three BP measurements were obtained every five minutes, and the average was recorded. The blood pressure was recorded at Korotkoff phase's I and V. ABPM was measured over a period of 24 hours using a Spacelab's monitor (90207, Spacelabs Medical Inc, USA). The device was set to measure BP at a 15-minute interval during the daytime (6 am to 10 pm) and at a 30-minute interval during the nighttime (10 pm to 6 am). The cuff was put on the right side, and kept the ABPM arm at rest during each measurement. Patients were instructed to act and work normally, and their sleeping time and waking time were recorded.

Laboratory examination

Peripheral venous blood was sampled in the morning after overnight fasting. The blood samples were centrifuged, and the supernatants were stored at -20°C till use. The heparinized samples were used to measure SCF and c-kit with enzyme-linked immunosorbent assay kits (Quantikine, R&D Systems, USA). The samples in the tube containing disodium EDTA were used to measure plasma IL-6 and TNF- α by immunoradiometric assay (Biotechnology Institute of Beijing, China). Serum creatinine, free plasma glucose, uric acid, urea nitrogen, cholesterol, triglyceride (TC), high density lipoprotein (HDP) and low density lipoprotein (LDP) were measured using an automatic biochemical analyzer (D240, SINNOWA, China) on the day of sampling. All the samples were free of hemolysis.

Statistical analysis

The data were calculated and analyzed by Stata (version 7.0, Stata corp. USA) and Excel software. Measurement

data were expressed as mean $\pm$ SD. The parameters of the dipper group and the non-dipper group were compared using a one-way ANOVA. The relationships between SCF/c-kit, TNF- α , IL-6 and BP type were analyzed using simple linear regression. A *P* value of <0.05 was considered statistically significant; and *P* <0.01 was considered highly significant.

RESULTS

Demographic characteristics

A total of 247 patients, aged from 38 to 76 years old, with newly diagnosed hypertension were recruited into the study, including 116 non-dippers and 131 dippers. The dippers contained 61 males and 70 females, with a mean age of 53.1 $\pm$ 14.6 years old; and the non-dipper contained

53 males and 63 females, with a mean age of 54.3 $\pm$ 14.1 years old. There were no significant difference between the two groups regarding the age (*t*=0.841, *P*=0.401) and the gender (χ^2 =0.019, *P*=0.991).

Baseline characteristics and serum levels of SCF, c-kit, TNF- α , and IL-6

Baseline characteristics of dipper and non-dipper hypertension patients are presented in Table 1. Compared to the patients with dipper hypertension, non-dipper hypertensive patients had significantly higher levels of SCF, c-kit, TNF- α and IL-6 (all *P*<0.01). The night-time SBP and DBP were significantly higher in non-dippers than in dippers (both *P*<0.01); The non-dippers had significantly less nocturnal reductions in SBP and DBP compared to the dippers (both *P*<0.01).

Table 1. Comparison of clinical characteristics and serum measurements between dipper and non-dipper hypertension[§]

Variable	Hypertension patients		<i>t</i>	<i>P</i>
	Dipper (<i>n</i> =131)	Non-dipper (<i>n</i> =116)		
Smokers (%)	25 (19.1)	22 (19.0)	0.951	0.378
Drinkers (%)	57 (43.5)	52 (44.8)	0.679	0.491
BMI (kg/m ²)	23.6 $\pm$ 3.2	24.0 $\pm$ 3.1	0.748	0.452
Urea nitrogen (mmol/L)	5.0 $\pm$ 1.2	5.1 $\pm$ 1.2	1.020	0.210
Creatinine (mmol/L)	67.6 $\pm$ 12.4	68.6 $\pm$ 13.3	0.810	0.412
Uric acid (mmol/L)	266.7 $\pm$ 76.5	270.4 $\pm$ 72.5	1.127	0.301
Systolic BP (mmHg)				
Clinic	151.9 $\pm$ 13.8	152.4 $\pm$ 14.8	0.751	0.443
24-hour	131.1 $\pm$ 11.8	133.3 $\pm$ 13.8	1.872	0.043
Day time	136.6 $\pm$ 12.3	135.0 $\pm$ 14.0	1.567	0.135
Night time	115.0 $\pm$ 11.2	128.5 $\pm$ 14.4	2.641	0.009
Nocturnal reduction (%)	15.7 $\pm$ 4.1	4.7 $\pm$ 4.9	2.793	0.005
Diastolic BP (mmHg)				
Clinic	93.0 $\pm$ 9.6	92.2 $\pm$ 10.4	0.849	0.413
24-hour	81.2 $\pm$ 9.1	80.2 $\pm$ 10.2	1.279	0.215
Day time	85.6 $\pm$ 9.5	82.2 $\pm$ 10.4	1.578	0.129
Night time	68.2 $\pm$ 8.7	74.5 $\pm$ 10.3	2.703	0.008
Nocturnal reduction (%)	20.4 $\pm$ 5.6	9.1 $\pm$ 6.4	2.656	0.009
FPG (mmol/L)	4.9 $\pm$ 0.3	5.0 $\pm$ 0.5	1.420	0.229
Cholesterol (mmol/L)	4.6 $\pm$ 1.0	4.7 $\pm$ 1.1	1.300	0.211
LDL (mmol/L)	2.8 $\pm$ 0.9	2.9 $\pm$ 0.9	1.001	0.301
HDL (mmol/L)	1.4 $\pm$ 0.8	1.4 $\pm$ 0.9	0.957	0.379
Triglycerides (mmol/L)	1.2 $\pm$ 0.9	1.5 $\pm$ 1.0	1.592	0.112
TNF- α (ng/L)	11.6 $\pm$ 4.2	14.7 $\pm$ 3.9	2.751	0.007
IL-6 (mg/L)	15 550 $\pm$ 447.3	26 860 $\pm$ 249.5	2.827	0.006
SCF (ng/L)	778.7 $\pm$ 44.6	907.1 $\pm$ 52.7	2.837	0.005
c-kit (μ g/L)	9.57 $\pm$ 1.4	13.2 $\pm$ 1.7	2.831	0.005

§: Plus-minus values are means $\pm$ SD.

FPG, Free Plasma glucose; LDL, Low-density-lipoprotein; HDL, High-density-lipoprotein. TNF- α , tumor necrosis factor- α ; SCF, stem cell factor; IL-6, interleukin 6; BMI, body mass index.

Linear regression analysis of SCF/c-kit, TNF- α , and IL-6

Figure 1 Show the relationships between the peripheral serum SCF/c-kit level and MSBP, MDBP, TNF- α and IL-6. There was a significantly positive correlation between the SCF level and MSBP ($r=0.866$; $P<0.01$), MDBP ($r=0.769$;

$P<0.01$), TNF- α ($r=0.756$; $P<0.01$) and IL-6 ($r=0.905$; $P<0.01$). Plasma with higher concentration of c-kit showed higher MSBP ($r=0.824$; $P<0.01$), and higher MDBP ($r=0.672$; $P<0.01$). Plasma concentration of c-kit was positively correlated with TNF- α level ($r=0.699$; $P<0.01$) and IL-6 level ($r=0.711$; $P<0.01$).

Figure 1. Linear regression analysis of relationships of SCF/c-kit with MSBP, MDBP, TNF- α and IL-6.

A. SCF vs. MSBP; B. SCF vs. MDBP; C. c-kit vs. MSBP; D. c-kit vs. MDBP; E. SCF vs. TNF- α ; F. SCF vs. IL-6; G. c-kit vs. TNF- α ; H. c-kit vs. IL-6.

DISCUSSION

In this study, we demonstrated that non-dipper hypertensive patients had higher plasma SCF/c-kit level than the dippers. Furthermore, plasma SCF/c-kit level of hypertensive patients increased with the increases of MSBP, MDBP, plasma TNF- α and IL-6.

The SCF/c-kit mechanism may involve the following signaling molecules: Phosphatidylinositol 3-kinase, extra-cellular regulated protein kinases signal transducers and activators of transcription, phospholipase C and the tyrosine-protein kinase Src. Biological signals are initiated to regulate survival, proliferation, differentiation, apoptosis, motility and migration of c-kit bearing cells.¹³ It is widely acknowledged that functions of vascular system, kidneys and sympathetic nervous system are critical for control and maintenance of BP.¹⁴ Stiffness, vascular resistance, remodeling, and endothelial dysfunction are hallmarks of hypertension.^{15,16} The clinical relevance of a non-dipping status in hypertensive patients increases the risk for cardiovascular events.¹⁷ The endothelium-dependent vasodilatation is much more impaired in non-dippers. A nocturnal non-dipping pattern is a situation accompanied by inflammation and endothelial dysfunction.¹⁸ The blunted decline of nighttime BP is also considered as a prognostic marker for cardiovascular events in hypertensive subjects.¹⁹ Many studies showed that left ventricular hypertrophy and carotid intima-media thickness were much more prevalent in non-dipper hypertension than in dipper hypertension.²⁰ Hollenbeck *et al* showed that SCF/c-kit was released from the combined membrane of vascular smooth muscle cells through matrix metalloproteinases-9, and the expression of c-kit was significantly increased after bubble injury to the carotid artery in mice.²¹ Wang *et al* reported that SCF/c-kit played important roles in anti-apoptosis of vascular smooth muscle cells and inhibiting endothelial membrane hyperplasia.²² Endothelial progenitor cells were increasingly mobilized in the circulation to promote endothelial recovery, and they might be an independent risk factor for ischemic damage.²³ The SCF/c-kit system may be involved in repairing damaged blood vessels. To summarize aforesaid studies, inflammation and endothelial dysfunction may help to explain the higher levels of SCF/c-kit in patients with non-dipper hypertension.

The current study also demonstrated that both IL-6 and TNF- α were positively correlated with SCF/c-kit. TNF- α and IL-6 are produced by multiple cells including immune cells, vascular cells and T cells.^{24,25} Insulin resistance and endothelial dysfunction have both been implicated in the

pathogenesis of hypertension. Circulating IL-6 and TNF- α levels were found to be consistently elevated in insulin-resistant individuals.^{26,27} Mice lacking TNF- α gene and mice treated with TNF- α antagonist did not develop hypertension.²⁸ Mice treated with IL-6 not only had increased vascular AT1 receptor expression but also had induced vasoconstriction, oxidative stress and impaired endothelial function.²⁹ IL-6 and TNF- α might be a dynamic biomarker of endothelial activation in a hypertensive state. The level of SCF/c-kit that promotes endothelial recovery increases with the elevation of IL-6 and TNF- α . These associations indicated the central role that SCF/c-kit may play in the treatment of hypertension.

This study has a few potential limitations. Absence of a normal control group constitutes the major limitation of our study. Secondly, this study didn't use the inflammatory cytokine, endothelin-1(ET-1), one of the most potent vasoconstrictor peptides, as a vascular endothelial injury marker. The underlying mechanism need to be further confirmed by large-scale studies with follow-up data.

In summary, peripheral plasma levels of SCF/c-kit were higher in non-dipper hypertension than the dipper hypertension. Non-dipper hypertensive patients experience more endothelial damage due to exposure to a hypertensive state throughout day and night. Endothelial dysfunction and inflammatory response may play a key role in the pathogenesis of non-dipper hypertension, which is a large and intricate network system. The results of our study provided further evidence for the altered circadian patterns in BP variability, and will help to establish proper therapeutic strategies for non-dipper hypertensive patients.

Conflict of interest statement

The authors declared no conflict of interests.

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