ORIGINAL ARTICLE

Expression of Serum Vascular Endothelial Growth Factor and Angiopoietin Receptor Tie-2 in Essential Hypertension

AK Filiz[1], E Ozdemir[1], H Gunes[1,2], MB Yılmaz[2]

ABSTRACT

Objective: *To investigate the serum levels of a vascular endothelial growth factor (VEGF), an angiogenic factor and a soluble angiopoietin receptor Tie-2 (sTie-2) in patients with essential hypertension.*

Methods: *In the present study 90 individuals (56 males and 34 females, mean age 48 ± 7 years) have been divided into 3 groups: 30 patients with hypertension, 30 healthy individuals with a family history of hypertension and 30 healthy individuals with no family history of hypertension. All individuals have been evaluated in terms of blood pressure and biochemical parameters. The levels of VEGF and Tie-2 receptor have been evaluated by using the enzyme-linked immunosorbent assay method.*

Results: *The findings suggested that the serum VEGF, sTie-2 receptor, low-density lipoprotein and triglycerides levels in the hypertensive patients were significantly higher than those in the control group (*$p < 0.05$*). However, the level of high-density lipoprotein cholesterol in the patients was significantly lower than in those in the control group (*$p < 0.05$*). In correlation analysis, a positive correlation was found statistically significant between the values of VEGF and sTie-2 (*$r = 0.405$*,* $p = 0.026$*).*

Conclusion: *As a result of this study, our data indicate that serum levels of VEGF and Tie-2 receptor may be related to the primary hypertension. This study could inspire to further studies to explore the roles of VEGF and Tie-2 receptor in essential hypertension.*

Keywords: Angiopoietin receptor, endothelial disfunction, hypertension, Tie-2 receptor, vascular endothelial growth factor

INTRODUCTION

Hypertension is an important medical problem because constant high blood pressure has harmful effects on target organs such as the heart and kidney, bringing about severe cardiovascular disease and renal failure (1). However, the pathophysiological mechanisms of essential hypertension are not exactly elucidated. Essential hypertension is associated with altered function and structure of vessels, as well as altered platelet function and insulin resistance and imbalance in angiogenesis (2, 3). Angiogenesis, the formation of new blood vessels from pre-existing vessels, is the physiological process that occurs in response to tissue cell hypoxia and other stimuli (4). Enhanced nitric oxide (NO) in several processes and cardiovascular disorders increases angiogenesis, and reduced NO biosynthesis disrupts angiogenesis in several tissues (5). Angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), induce NO biosynthesis. Several studies indicate that angiogenesis is impaired in arterial hypertension (6, 7).

Evidence encourages a novel view of hypertension as a disease of insufficient or abnormal responses to angiogenic growth factors such as VEGF. Hypertensive patients have decreased microvascular density, with some evidence supporting a significant role for rarefaction

From: [1]Department of Physiology, School of Medicine, Sivas Cumhuriyet University, Sivas, Turkey and [2]Department of Cardiology, School of Medicine, Sivas Cumhuriyet University, Sivas, Turkey.

Correspondence: Dr E Ozdemir, Department of Physiology, School of Medicine, Sivas Cumhuriyet University, 58140 Sivas, Turkey. Email: ercan_ozdemir@hotmail.com

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in hypertension (8). Changes in different angiogenic markers have been shown in essential hypertension. For instance, serum levels of VEGF are increased in hypertension, and correlate with cardiovascular risk and normalize with treatment (9), demonstrating a relation between pro-angiogenic factors and arterial blood pressure.

Angiopoietins are pro-angiogenic factors indispensable for vascular development and maturation in angiogenesis (10, 11). Angiopoietin-1 (Ang-1) and its antagonist angiopoietin-2 (Ang-2) bind to the tyrosine kinase receptor (Tie-2) which is particularly expressed on vascular endothelial cells (12, 13). Angiopoietin-1 is released by vascular smooth muscle cells and pericytes in blood vessels and stabilizes the development of newly formed blood vessels by recruiting vascular smooth muscle cells and pericytes. In addition, this angiogenic factor supports the structural integrity of mature vessels (14). Ang-1 has robust vascular protective effects. It suppresses plasma leakage, prevents vascular inflammation and inhibits endothelial cell death. On the other hand, this molecule has also been implicated in the induction of angiogenesis and pulmonary hypertension (10). Vascular endothelial growth factor and the angiopoietins/Tie-2 receptor system are important regulators of angiogenesis that are stimulated by a lot of factors, including markers of hypoxia and inflammation (15–17). It is likely that in arterial hypertension, which is related to the rarefaction of the small vessels, these factors are increased as a compensative mechanism for the hypoxia that is resulted from rarefied small vessels (6). Accordingly, it has been suggested that Ang-2 and its receptor Tie-2 are increased in the presence of relative hypoxia (18, 19).

In the presence of VEGF, Ang-2 may play an important role in stabilizing vessels, sprouting and regression for pathophysiological angiogenesis (20). Chen *et al* (21) suggested that the angiopoietins/Tie-2 system is essential for the protection of vascular system integrity, vessel remodelling and induction of angiogenesis. The role of Ang-1 and Ang-2 in the reorganization of angiogenesis is dependent on other growth factors (VEGF, FGF and platelet-derived growth factor).

Otherwise, it is known that the angiopoietin/Tie-2 system influences vascular smooth muscle hyperplasia in primer pulmonary hypertension (22). However, the pathophysiological role of VEGF and the angiopoietin/Tie-2 signalling pathway in essential hypertension has not been studied in humans. In the light of this information, our aim of the study was to investigate the serum levels of VEGF and soluble angiopoietin receptor Tie-2 (sTie-2) in patients with essential hypertension.

SUBJECTS AND METHODS

Study population and design

A total of 30 patients previously diagnosed with essential hypertension, 30 healthy individuals with no family history of hypertension (control group 1) and 30 healthy individuals with a family history of hypertension (control group 2) admitted to the Cardiology Department of Cumhuriyet University Education and Research Hospital between March 2012 and April 2013 were included in the study. The volunteer subjects were informed about the procedures. The study protocol was approved by the Cumhuriyet University School of Medicine Ethics Committee (Ethic No: 2011/061), and written informed consent was obtained from all participants in accordance with the Helsinki Declaration.

The participants with a history of anti-hypertensive drug use, peripheral artery disease, cancer, diabetes mellitus, atherosclerotic heart disease and heart failure were not included in the study. The demographic characteristics (age, gender, body weight and height) of the volunteers were recorded and measurements of body mass index (BMI) were carried out separately. Fasting blood glucose, serum electrolytes and lipids were measured, and renal function tests were performed.

Measurement of blood pressure

The participants rested for about 10 minutes before arterial blood pressure was measured. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the same time every day for 7 days to identify hypertensive patients. Hypertension stages were determined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). The blood pressure defined four categories in the JNC-7 guidelines (23): normal blood pressure (SBP < 120 mmHg and DBP < 80 mmHg), prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg), Stage I hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg) and Stage II hypertension (SBP > 160 mmHg or DBP > 100 mmHg).

Biochemical parameters

Fasting blood glucose by the enzymatic hexokinase method; creatinine, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride by the

enzymatic colorimetric method; and blood urea nitrogen by the kinetic test were measured.

Measurement of VEGF and soluble Tie-2 receptor

Venous blood samples (3 ml) were collected from each hypertensive patient and healthy individual. All blood samples were drawn during routine blood tests on the same day and processed within 1 hour. Serum was separated by centrifugation at 4000×g for 5 minutes at 4°C, and sample aliquots were immediately stored at −70°C until assayed. Serum concentrations of VEGF ($VEGF_{165}$) and sTie-2 were measured in duplicate with a quantitative enzyme-linked immunosorbent assay technique (Boster Biological Technology Co. Ltd. Fremont, CA, USA) according to the manufacturer's guidelines.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows version 17.0 (SPSS, Chicago, IL, USA). Results are expressed as mean with standard deviation (SD) or as median with inter-quartile range for the normally distributed data and skewed data respectively. Baseline characteristics of groups were compared using the Chi-square test. Non-parametric tests (the Kruskal–Wallis test for three independent samples and the Bonferroni-corrected Mann–Whitney test for statistical difference between the two groups) were used to compare the three groups. Spearman's correlation test was used for correlation analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the study population

Demographic characteristics of 90 subjects ($n = 30$ for all groups) are summarized in Table 1.

There was no statistically significant difference between the mean ages (50.13 ± 6.32 years) of the patients of control 1 (48.86 ± 7.03 years) and control 2 (47.33 ± 8.14 years) groups. Bodyweight (kg) and height (m) showed no difference between all study groups. Regarding body mass index (BMI), the difference was not statistically significant ($p > 0.05$) in all the groups.

Comparison of the biochemical parameters of the hypertensive subject with controls

Differences between serum creatinine, fasting blood glucose, sodium, potassium, calcium and blood urea nitrogen (BUN) levels in patients with hypertension were not statistically significant compared to the control group (Table 2). The HDL cholesterol (mg/dL) level of the patients with hypertension (37.80 ± 8.93) was significantly lower ($p < 0.05$) than those in the control 1 (43.03 ± 7.58) and control 2 (42.93 ± 4.38) groups groups. However, the patients' serum LDL cholesterol (mg/dL) (93.37 ± 27.30) and TG (139.20 ± 80.30) levels were significantly higher ($p < 0.01$) in the control 1 (69.80 ± 14.72; 83.06 ± 16.32, respectively) and control 2 (71.30 ± 10.94; 79.26 ± 18.96, respectively) groups.

Serum levels of VEGF and sTie-2 receptor in patients with hypertensions and control groups

The serum levels of VEGF in patients with hypertension (51.91 ± 7.83) were significantly higher ($p < 0.01$) than those in the control 1 (35.03 ± 3.71) and control 2 (27.19 ± 3.21) groups (Fig. 1).

Table 1: Baseline demographic and clinical characteristics of all subjects

Characteristics	Patient (n = 30)	Control 1 (n = 30)	Control 2 (n = 30)	*p*
Gender (M/F)	19/11	21/9	16/14	
(%)	(63/37)	(70/30)	(53/47)	0.182
Age (years)	50.13 ± 6.32	48.86 ± 7.03	47.33 ± 8.14	0.512
Body weight (kg)	78.40 ± 19.32	77.28 ± 21.06	73.50 ± 18.30	0.634
Height (m)	1.68 ± 0.07	1.67 ± 0.08	1.68 ± 0.10	0.781
BMI (kg/m^2)	27.65 ± 3.90	27.60 ± 3.67	26.06 ± 2.63	0.247
SBP (mmHg)	148.50 ± 17.42	109.83 ± 5.16	106.50 ± 7.08	0.020*
DBP (mmHg)	95.33 ± 11.05	66.00 ± 6.07	59.50 ± 8.02	0.003**

Control 1 = participants with no family history of hypertension; Control 2 = participants with a family history of hypertension. Data were expressed as mean ± SD. BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; *$p < 0.05$ and **$p < 0.01$= the differences between the patient group and the control groups.

Table 2: Biochemical parameters of patients and the control group

	Patient (n = 30)	Control 1 (n = 30)	Control 2 (n = 30)	*p*
Ca^{2+} (µmol/L)	8.81 ± 0.50	8.85 ± 0.48	8.78 ± 0.44	0.827
FBG (mg/dL)	85.0 ± 10.50	87.9 ± 10.70	86.4 ± 10.30	0.216
BUN (mg/dL)	13.2 ± 2.70	12.8 ± 3.10	14.5 ± 4.40	0.105
Cr (mg/dL)	0.82 ± 0.20	0.80 ± 0.20	0.84 ± 0.20	0.911
Na^+ (mmol/L)	140.2 ± 2.30	139.5 ± 3.60	141.2 ± 0.40	0.780
K^+ (mmol/L)	4.5 ± 0.40	4.5 ± 0.30	4.5 ± 0.40	0.683
HDL cholesterol (mg/dL)	37.80 ± 8.93	43.03 ± 7.58	42.93 ± 4.38	0.023*
LDL cholesterol (mg/dL)	93.37 ± 27.30	69.80 ± 14.72	71.30 ± 10.94	0.009**
TG (mg/dL)	139.20 ± 80.30	83.06 ± 16.32	79.26 ± 18.96	0.004**

BUN = blood urea nitrogen; Cr = creatinine; FBG, fasting blood glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride. *$p < 0.05$ = compared to control groups 1 and 2; **$p < 0.01$ = compared to patients with hypertension.

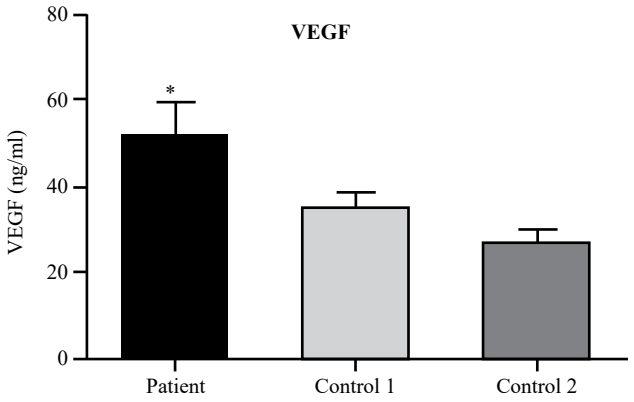

Fig. 1. Serum levels of VEGF in patients with hypertension and control groups. Data are given as mean ± SD. VEGF = vascular endothelial growth factor. *$p < 0.01$ compared with control 1 and control 2 subjects.

Similarly, the sTie-2 receptor levels of patients (193.13 ± 41.38) were statistically significant higher ($p < 0.05$) than those in the control 1 (116.11 ± 9.02) and control 2 (104.30 ± 16.60) groups (Fig. 2).

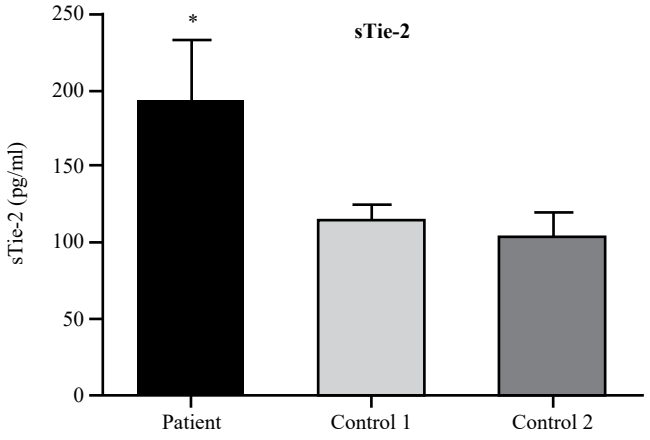

Fig. 2. Serum levels of sTie-2 receptor in patients with hypertension and control groups. Data are given as mean ± SD. sTie-2 = soluble Tie-2 receptor. *$p < 0.05$ compared with control 1 and control 2 subjects.

Serum VEGF and sTie-2 levels according to the stage of hypertension in patients

VEGF values were evaluated according to the stages of hypertension in the patients. The serum levels of VEGF in the patients of the stage 2 group (53.20 ± 12.17) were higher than those with pre-hypertension (39.71 ± 6.78) and those in the stage 1 group (45.68 ± 10.23). However, the difference between groups was not statistically significant (Fig. 3, $p > 0.05$).

Comparing the concentration of sTie-2 receptor according to the stage of hypertension, the levels of sTie-2 in stage 2 group (251.55 ± 39.94) were significantly higher than in prehypertension (78.02 ± 13.26) and stage 1 group (115.89 ± 26.69) [Fig. 4; $p = 0.001$, $p = 0.032$, respectively].

Correlation analysis levels of serum VEGF and sTie-2 receptor in patients with hypertension

A positive correlation was found statistically significant between the values of VEGF and sTie-2 ($r = 0.405$, $p = 0.026$, Spearman's test) (Fig. 5).

DISCUSSION

To the best of the authors' knowledge, this is the first comprehensive study on circulating VEGF and sTie-2 receptor in essential hypertension. The decisive results are (a) compared with healthy or disease controls; hypertensive patients are characterized by an excess of circulating sTie-2 and VEGF; (b) the concentrations of sTie-2 receptor in stage 2 group were significantly increased; (c) the levels of VEGF were correlated with the sTie-2 receptor in patients; (d) in accordance with hypertension, HDL cholesterol levels in patients were found to be extremely low. These findings have implications for the role of angiopoietins in the pathogenesis of arterial hypertension.

Hypertension is a widespread but poorly understood disease. There are many explanations for pathophysiological mechanisms in essential hypertension, including increased adrenergic activity, impaired renin–angiotensin–aldosterone system, constitutional and environmental factors (24). Obtained pieces of evidence support a novel view of hypertension as a disease of insufficient or abnormal responses to angiogenic factors and its associated vascular rarefaction and remodelling (8, 25).

At the present time, the best way to prevent or decrease cardiovascular complications in hypertension is lowering the blood pressure. For all that, several studies have demonstrated that controlling blood pressure does not fully prevent vascular or renal complication in essential hypertension (26). For this reason, we need more understanding regarding the vascular changes related to blood pressure, endothelial dysfunction or vascular remodelling and about the angiogenic factors in the pathophysiological mechanism in hypertension (6, 26). Kim *et al* suggested that Ang-1, as an angiogenic factor, has the miscellaneous vascular effects on microvascular rarefaction and target organ damage in hypertension (27). It is involved in angiogenesis and increases endothelial stabilization by boosting vascular integrity. In addition, the specific characteristic of Ang-1 is the formation of a tight vascular network, compared

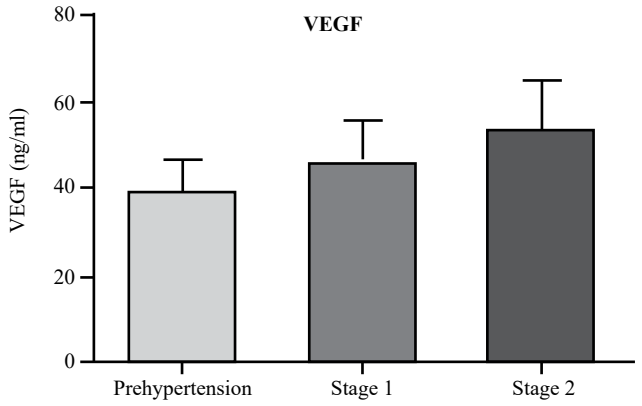

Fig. 3. Serum levels of VEGF in patients with hypertension. Data are given as mean ± SD. n = 8, prehypertension; n = 11, stage 1 and n = 11, stage 2. VEGF = vascular endothelial growth factor.

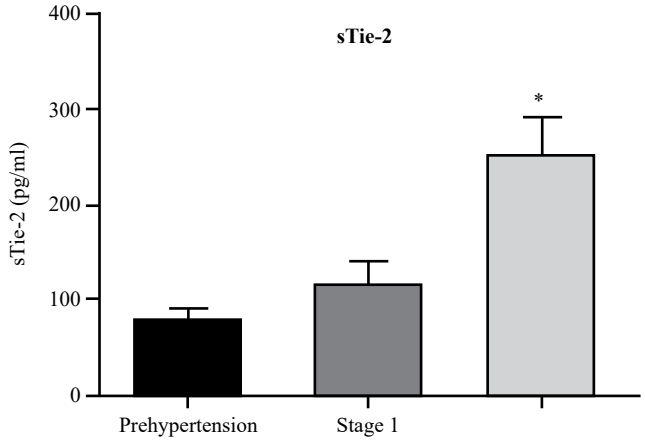

Fig. 4. Serum levels of sTie-2 in patients with hypertension. Data are given as mean ± SD. sTie-2 = soluble Tie-2 receptor. *$p < 0.05$ compared with prehypertension and stage 2 subjects (n = 8, prehypertension; n = 11, stage 1 and n = 11, stage 2).

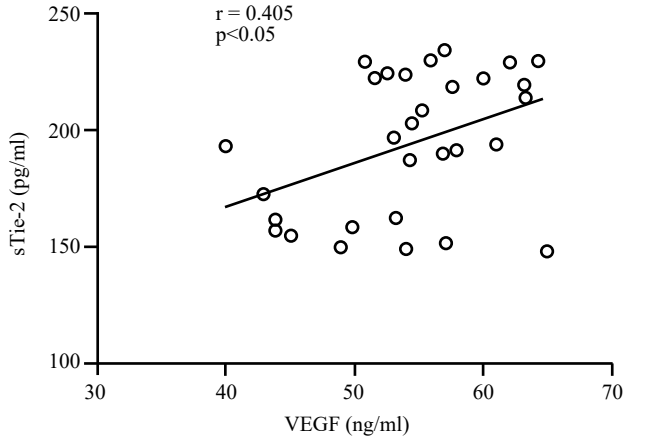

Fig. 5. The correlation between VEGF and sTie-2 parameters in patients with hypertension. (n = 30). $r = 0.405$, $p = 0.026$ (Spearman's test). sTie-2 = soluble Tie-2 receptor; VEGF = vascular endothelial growth factor.

with VEGF (28, 29). Angiopoietin and its receptors (Tie-1 and Tie-2) have important roles in the late stages of vascular development, where they control the stabilization and formation of the vessels. Therefore, Ang-1 is required for the excellent organization and maturation of newly formed vessels and supports the stability and structural integrity of vasculature (10). Ang-2 demonstrates very different features of angiogenesis. Ang-1 stimulates the Tie-2 receptor, whereas Ang-2 can inhibit this receptor. Ang-2 demonstrates angiogenic activity only in the presence of VEGF (27).

Tie-2 is an angiopoietin receptor and is extensively expressed on the endothelial cells. This receptor also plays a significant role in angiogenesis (30). The Tie-2 receptor seems to be important for vascular stabilization and angiogenic remodelling that occur after the effects of VEGF (31, 32). Several reports indicate that the Ang-1/Tie-2 signalling pathway is involved in endothelial cell–matrix interactions (33). Therefore, this signalling pathway also helps stabilize new vessel formation, and the alterations of all these three in hypertensives reflect the abnormal angiogenesis that is seen here. The sTie-2 receptor in plasma has been identified both in diseased and healthy humans (32). However, the exact role of sTie-2 in essential hypertension is not known completely. Plasma levels of sTie-2 are increased in malignant tumours (34) and congestive cardiac failure (35). In the present analysis, we have demonstrated that sTie-2 levels elevated in patients with hypertension. On the other hand, Lee *et al* (28) suggested that Ang-1 prevents hypertension and targets organ damage through its interaction with vascular endothelial Tie-2 receptor. Ang-1 was found to be effective in preventing hypertension and reducing target organ damage in hypertensive rats. In addition, Ang-1 was shown to increase the plasma level of NO through the endothelial-specific Tie-2/endothelial NO synthase signalling pathway (29). Circulating NO plays a significant role in controlling arterial blood pressure by regulating vasodilation and is also important for sustaining endothelial homeostasis.

Consistent with our findings, an analysis of 248 patients with hypertension demonstrated a positive correlation between more severe hypertension and higher VEGF levels (2). Bevacizumab, a recombinant human monoclonal antibody to VEGF, has been attempted as anti-angiogenic treatment of various cancers including renal cell and colorectal carcinoma (36, 37). However, it has been indicated that bevacizumab treatment induces hypertension in patients with cancer (38).

In conclusion, our findings suggested that the changes in serum levels of VEGF lead to hypertension, and the increased sTie-2 receptor level may be associated with essential hypertension. In the light of these findings, it may be concluded that serum VEGF and the angiopoietin/Tie-2 signalling system play an important role in essential hypertension.

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