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OPEN

Inverse Correlation Between Plasma Adropin and ET-1 Levels in Essential Hypertension

A Cross-Sectional Study

Xiaosong Gu, MD, PhD, Hui Li, MD, Xinyi Zhu, MD, Haibo Gu, MD, Jianchang Chen, MD, PhD, Luchen Wang, BS, Pamela Harding, PhD, and Weiting Xu, MD

Abstract: Adropin is a recently identified bioactive protein that promotes energy homeostasis by affecting glucose and lipid metabolism. Recently, adropin has also been reported to be associated with endothelial dysfunction. Also, ET-1, as a biomarker for endothelial dysfunction, is a key regulator in hypertension. Accordingly, the aim of the present study was to detect the relationship between plasma adropin and ET-1 levels in hypertension.

A total of 123 participants, diagnosed with primary hypertension on the basis of World Health Organization criteria (systolic blood pressure [SBP] ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg), and 58 normotensive subjects were enrolled in the cross-sectional study from October 2011 to December 2013. All study participants were older than 18 years of age. Adropin and ET-1 levels were measured by enzyme-linked immunosorbent assay (ELISA).

We found that plasma adropin levels were significantly lower in hypertensives compared with controls (3.18 ± 1.00 vs 4.21 ± 1.14 ng/mL, $P < 0.001$). Plasma ET-1 levels were higher in hypertensives than controls (2.60 ± 1.14 vs 1.54 ± 0.66 pg/mL, $P < 0.001$). Adropin had a negative correlation with DBP ($r = -0.40$, $P < 0.001$), SBP ($r = -0.49$, $P < 0.001$), and adjusted for age, body mass index, SBP, DBP, glucose, TC, TG, LDL, and Cr, there was a negative correlation between ET-1 and adropin ($r = -0.20$, $P = 0.04$). In multivariate logistic regression analysis of the variables, ET-1 (odds ratio [OR], 3.84; 95% CI, 2.16–6.81; $P < 0.001$) and adropin (OR, 0.99; 95% CI, 0.99–1.0; $P < 0.001$) were found to be independent predictors for hypertension.

In conclusion, decreased plasma adropin levels are associated with increased blood pressure in hypertension. Adropin is an independent predictor for hypertension, and may influence blood pressure by protecting endothelial function.

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Abbreviations: BMI = body mass index, CKD = chronic kidney disease, Cr = Creatinine, DBP = diastolic blood pressure, ET-1 = Endothelin 1, LDL = low-density lipoprotein, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

INTRODUCTION

Hypertension contributes greatly to the global burden of disease and in many patients current treatments are often inadequate. Endothelial dysfunction plays an important role in the progression of hypertension.¹ Endothelin-1 (ET-1) is elevated in hypertensive subjects and is a potential marker of endothelial dysfunction.² ET-1 is a potent vasoconstrictor that is implicated in the pathogenesis of hypertension,^{3,4} and reduced ET-1 levels have been shown to decrease systolic blood pressure (SBP).⁵ In the context of the strong association between hypertension and chronic kidney disease (CKD),⁶ ET-1 was also found to have a close relationship with renal dysfunction induced by hypertension.⁷ Thus ET-1, as a biomarker for endothelial dysfunction, is a key regulator in hypertension.

Endothelial dysfunction is an important manifestation of diabetes. Increased production of ET-1 mediates many pathophysiological events contributing to the development of vascular complications in diabetes mellitus.⁸ Adropin, encoded by the energy homeostasis-associated (*ENHO*) gene, participates in the maintenance of energy homeostasis and the response to insulin.⁹ Recently, adropin has also been reported to be associated with endothelial dysfunction.¹⁰ Low adropin concentrations correlate with endothelial dysfunction in diabetes mellitus type 2¹¹ and the protective role of adropin has been ascribed to the upregulation of endothelial NO synthase.¹⁰ However, whether adropin can mediate progression of pathophysiological events by regulating ET-1 is still unclear.

In studies using obese pediatric patients, adropin was found to have no relationship with blood pressure, whether similar results would be found in adult hypertensives is still open to debate.^{12,13} However, another study indicated that adropin likely has ability to regulate blood pressure.¹⁴ Therefore, our study was designed to investigate plasma adropin levels in essential hypertension, and to investigate the correlation between adropin and ET-1 in these patients.

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METHODS

Subjects

A total of 123 participants, in total, were diagnosed with primary hypertension in accordance with the World Health Organization criteria (SBP \geq 140 mmHg and/or diastolic blood pressure (DBP) \geq 90 mmHg), and were enrolled in the cross-sectional study. These patients were assessed, either, in the clinic or the in-patient department of the Second Affiliated Hospital of Soochow University (Suzhou, China) from October 2011 to December 2013. Exclusion criteria were established on the presence of any one of the following: secondary hypertension or antihypertensive medication; diabetes; hyperlipidemia; kidney dysfunction; liver disease; lung disease; and cancer. Secondary hypertension was barred from the study on the basis of clinical and biochemical assessments. In parallel, 58 normotensive subjects were assessed in the same hospital and enrolled as a control group, using the same exclusion criteria. All study participants were older than 18 years.

Ethical and Legal Issues

The experimental protocol was in accordance with the Declaration of Helsinki (2008) of the World Medical Association, was approved by the ethics committee of the Second Affiliated Hospital of Soochow University. All subjects provided written informed consent before participating in the study.

Clinical and Biochemical Assessment

The electronic medical records were reviewed to obtain demographic and clinical data. The patients' body mass index (BMI) was calculated by dividing their weight in kilograms by their height in meters squared. Blood pressure was measured, using an automatic BP monitor, in the sitting position, using the right upper arm and an appropriately sized cuff, measurements were performed three times in the participant's right arm with a 2-minute interval, after a rest period of at least 5 minutes. Hyperlipidemia was categorized as a total cholesterol (TC) concentration $>$ 5.69 mmol/L, triglyceride (TG) concentration $>$ 1.7 mmol/L, low-density lipoprotein (LDL) concentration $>$ 3.1 mmol/L, and/or the presence of cholesterol-lowering medication. All venous blood samples were collected after an overnight fasting routine. Blood biochemical parameters (fasting plasma glucose, total cholesterol, TG, and plasma creatinine [Cr] concentration) were performed using an AU5400 automated chemistry analyzer (Beckman Coulter, Fullerton, CA) on the same day of blood collection. LDL cholesterol was indirectly measured using the Friedewald formula. To separate plasma, other venous blood samples were collected into tubes with EDTA2Na (1 mg/mL), aprotinin (500 U/mL) (Becton Dickinson, Franklin Lakes, NJ), and then centrifuged at 1500g at 4°C for 15 min. The prepared plasma samples stored at -80°C until use. Plasma adropin concentrations were measured using the adropin ELISA kit (catalog no. EK-032-35; Phoenix pharmaceuticals Inc., Burlingame, CA), according to the manufacturer's instructions. The detection range of this kit is 0.01 to 100 ng/mL and the sensitivity is 0.3 ng/mL. Circulating ET-1 concentrations were determined using the ET-1 (human) ELISA kit (catalog no. QET00B; R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The detection range for this kit is 0.34 to 250 pg/mL and its sensitivity is 0.102 pg/mL.

Statistical Analysis

Data were analyzed using SPSS software (version 22.0; SPSS, Inc., Chicago, IL). Continuous data are expressed as the

mean \pm SD, categorical variables are expressed as a percentage, and values of $P < 0.05$ are considered statistically significant. A 2-group student *t* test with a 0.05 2-sided significance level will have 80% power to detect an effect size of 0.45 when the sample sizes in the 2 groups are 58 and 123. The difference between the 2 continuous variables was studied using the Student *t* test, and the difference between categorical variables was applied using the χ^2 test. Correlation relationships were performed using Pearson coefficient of correlation. Multivariable logistic regression analyses were used to access the association of various determinants with hypertension, the final multivariable model was selected using backward selection, all variables in the final model are significant $P < 0.05$.

RESULTS

Clinical and Laboratory Characteristics of the Study Participants

A total of 123 patients with newly established hypertension and 58 health controls were included in the study. The demographic characteristics are described in Table 1. Patients with hypertension had a higher DBP and SBP than healthy controls (DBP: 85.3 ± 15.5 vs 70.8 ± 8.3 mmHg, $p < 0.001$; SBP: 164.2 ± 16.7 vs 112.5 ± 12.1 mmHg, $P < 0.001$). There were no significant differences in terms of age, sex, smoking status, glucose, TG, TC, and LDL between hypertensive subjects and healthy controls. Plasma ET-1 was significantly higher in hypertensive subjects than in controls (2.60 ± 1.14 vs 1.54 ± 0.66 pg/mL, $P < 0.001$), whereas adropin levels were lower in hypertensive subjects compared with controls (3.18 ± 1 vs 4.21 ± 1.14 ng/mL, $P < 0.001$). Even excluding patients with kidney dysfunction, hypertensive subjects had higher Cr than controls (65.98 ± 11.64 vs 61.60 ± 13.43 $\mu\text{mol/L}$, $P < 0.05$).

Correlation Between Adropin and Other Clinical Characteristics in Hypertension

As demonstrated in Table 2, plasma adropin levels were negatively correlated with DBP ($r = -0.40$, $P < 0.001$), SBP

TABLE 1. Clinical and Biochemical Characteristics of the 123 Hypertensive Patients and 58 Healthy Controls

	Healthy Controls (n = 58)	Hypertension (n = 123)	P
Age, y	60.5 \pm 11.4	64.0 \pm 11.4	0.06
Sex (M/F)	34/24	64/59	0.43
Smoke	10(17.2%)	31(25.2%)	0.26
BMI, kg/m ²	22.24 \pm 3.2	23.50 \pm 2.67	0.01
SBP, mmHg	112.5 \pm 12.2	164.2 \pm 16.7	<0.001
DBP, mmHg	70.7 \pm 8.3	85.3 \pm 15.5	<0.001
Glucose, mmol/L	4.58 \pm 0.77	4.69 \pm 0.71	0.34
TC, mmol/L	4.26 \pm 1.11	4.19 \pm 0.94	0.71
LDL, mmol/L	2.41 \pm 0.87	2.36 \pm 0.80	0.73
TG, mmol/L	1.58 \pm 0.68	1.63 \pm 0.78	0.67
Cr, $\mu\text{mol/L}$	61.60 \pm 13.43	65.98 \pm 11.64	0.04
Adropin, ng/mL	4.21 \pm 1.14	3.18 \pm 1.0	<0.001
ET-1, pg/mL	1.54 \pm 0.66	2.60 \pm 1.14	<0.001

$P < 0.05$ was considered to be statistically significant. BMI = body mass index, Cr = creatinine, DBP = diastolic blood pressure, ET-1 = endothelin 1, LDL = low-density lipoprotein, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

TABLE 2. Pearson Analysis of ET-1 and Adropin With Other Parameters in Hypertension

	ET-1		Adropin	
	r	p	r	p
Age, y	0.07	0.36	0.02	0.81
BMI, kg/m ²	0.17	0.02	-0.27	<0.001
SBP, mmHg	0.51	<0.001	-0.49	<0.001
DBP, mmHg	0.39	<0.001	-0.40	<0.001
Glucose, mmol/L	0.07	0.32	0.14	0.06
TC, mmol/L	0.39	0.6	0.08	0.29
LDL, mmol/L	-0.04	0.6	0.10	0.18
TG, mmol/L	0.01	0.92	-0.01	0.90
Cr, μmol/L	0.06	0.42	-0.11	0.13

P < 0.05 was considered to be statistically significant. BMI = body mass index, Cr = Creatinine, DBP = diastolic blood pressure, ET-1 = Endothelin 1, LDL = low-density lipoprotein, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

(*r* = -0.49, *P* < 0.001), and BMI (*r* = -0.27, *P* < 0.001) in 123 hypertensive patients. However, plasma adropin levels did not correlate with glucose (*r* = 0.14, *P* = 0.06) or Cr levels (*r* = -0.11, *P* = 0.13). ET-1 was positively correlated with DBP (*r* = 0.40, *P* < 0.001) and SBP (*r* = 0.51, *P* < 0.001). When adjusted for age, BMI, SBP, DBP, Glucose, TC, TG, LDL, and Cr, there was a negative correlation between ET-1 and adropin (*r* = -0.20, *P* = 0.04) (Figure 1).

Multivariate Regression Analysis

Multivariate logistic regression analysis was run with the variables (age, sex, smoking, glucose, TC, TG, LDL, Cr) in all 181 participants. The final model included only ET-1 and adropin. ET-1 (odds ratio [OR], 3.84; 95% confidence interval [CI], 2.16–6.81; *P* < 0.001) and adropin (OR, 0.99; 95% CI, 0.99–1.0; *P* < 0.001) were independent predictors of hypertension (Table 3). Controlling for adropin, for every 1-pg/mL increase in ET-1, the odds of having hypertension increase by 3.84. Likewise, controlling for ET-1, for every 1ng/ml increase in adropin the odds of having hypertension decrease by 0.99.

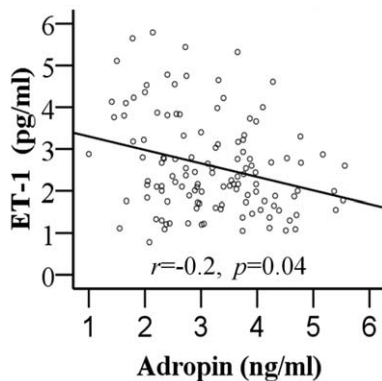


FIGURE 1. The relationship between adropin and endothelin 1 (ET-1) in hypertension subjects. Adropin showed significant correlation with ET-1 (*r* = -0.20, *P* = 0.04).

TABLE 3. Multivariable Logistic Regression Analysis of Factors Correlated With Hypertension in the 58 Healthy Participants and the 123 Hypertensive Patients

Variables	Odds Ratio	95% Confidence Interval	<i>P</i>
ET-1	3.84	2.16–6.81	<0.001
Adropin	0.99	0.99–1.0	<0.001

P < 0.05 was considered to be statistically significant in the multivariate logistic regression analysis. ET-1 = endothelin 1.

DISCUSSION

In this paper, we first show that in the hypertension group, plasma adropin levels are lower than that of healthy controls. Secondly, decreasing adropin is negatively correlated with blood pressure in hypertensive patients. After adjusting for age, BMI, DBP, SBP, glucose, TC, TG, LDL and Cr, decreasing plasma adropin levels continued to be associated with increasing ET-1 levels. Lastly, we report that adropin and ET-1 are independent predictors of hypertension. Thus, the current study suggests an independent link between adropin and endothelial dysfunction in hypertension.

Given the significant impact hypertension has on the global burden of disease, investigating the risk factors and underlying mechanisms of hypertension will shed light on new methods of therapy. ET-1 is a potential vasoconstrictor that is involved not only in the pathogenesis of essential hypertension, but also in progression of chronic kidney disease secondary to hypertension.^{15–17} ET-1 is a peptide originally isolated from the supernatants of cultured endothelial cells and it exerts a wide variety of biological effects on different tissues, including the vascular wall. Hypertensive patients have a higher ET-1 than healthy controls.¹⁸ Circulating levels of ET-1 and endogenous ET(A)-mediated constriction are increased in human aging.¹⁹ ET-1 is also involved in progression of renal hypertension. In CKD, activation of the ET system seems to contribute not only to increased blood pressure but also to loss of nocturnal blood pressure dipping.⁷ Clinical trials have addressed the use of ET receptor antagonists as monotherapy in primary hypertension, and as an add-on therapy in resistant hypertension and CKD.⁶ Our study also shows ET-1 to be elevated in the hypertension group and with ET-1 having a positive relationship with blood pressure. We show that ET-1 is an independent risk factor for hypertension.

Previous studies show that certain energy adipokine regulators such as adiponectin and leptin have an effect on blood pressure by regulating endothelial function and the central nervous system.^{20,21} As a new adipokine energy regulator, whether adropin has the same kind of effect is a question that warrants further investigation. In our study, we find that adropin is negatively correlated with blood pressure and is an independent risk factor for hypertension. Because adropin can be influenced by BMI, glucose, and TGs,²² we adjusted for these parameters, and continued to find a negative correlation between adropin and ET-1. Our results suggest that adropin may influence blood pressure by promoting endothelial dysfunction. Findings from several articles support our results. Lovren et al¹⁰ have reported that one of the endothelial protective actions of adropin is likely mediated via upregulation of endothelial NO synthase and that in patients with obstructive

sleep apnea, a significant risk factor for hypertension, adropin concentration is a reliable indicator of endothelial dysfunction.²³ Lower serum adropin levels are also associated with cardiac syndrome X (CSX), and endothelial dysfunction is involved in the pathophysiology of CSX.²⁴ In individuals with type 2 diabetes, adropin is an independent risk factor for endothelial dysfunction.¹¹ In the context of these studies, we conclude from our results that adropin influences blood pressure by protecting endothelial function.

It is possible that there are other mechanisms by which adropin affects blood pressure. Our study does not show the relationship between adropin and the autonomic nervous system. However, it has been demonstrated that adropin has increased expression in the brain in diabetic rats, and that adropin knockout mice exhibited decreased locomotor activity and impaired motor coordination coupled with defective synapse formation.^{25,26} Thus adropin may be a regulator of nervous system activity. Whether adropin can influence blood pressure by regulating the central automatic nervous system is a question remains to be studied.

In our study, the hypertension group had higher Cr and lower adropin levels compared with the control group. Because adropin has a low molecular weight of about 5 Kda,²⁷ and the normal urine adropin concentration were found to be approximately 4 times higher than that of corresponding serum adropin concentration.¹⁴ Moreover, glomerular perfusion pressure and molecular weight are 2 important determinants for protein to pass through the glomerular filtration barrier. Thus, in hypertensive patients, it is possible that adropin is more easily filtered and may therefore be lower in plasma. In our protocol, we excluded patients with kidney dysfunction, but we continued to observe an appreciable difference in plasma Cr between the hypertensive and control group. It is well known that the kidney has a large functional reserve, with rises in Cr virtually undetectable in early renal dysfunction. Increased protein filtration and decreased protein reabsorption are 2 characteristics of renal dysfunction. Thus, decreased adropin reabsorption may also account for our results. Kuloglu and Aydin²⁸ reported that adropin and iNOS immunoreactivity were co-localized to the glomeruli, peritubular interstitial cells and peritubular capillary endothelium of the cortex. Because adropin is highly expressed in the kidney,²⁵ it may play a role in compensatory mechanisms against renal damage inflicted by diabetes. Whether adropin has a true role in hypertension or is an artifact of renal dysfunction remains to be fully elucidated.

Our study has several limitations. First, our study sample is relatively small, the survey was mainly carried out at a single site, and selection bias might be present, which may restrict the application of the results to broader populations. Second, although our study shows that adropin has a relationship with blood pressure and is an independent risk factor for hypertension, whether the correlation between blood pressure and adropin represents a true cause-and-effect relationship or merely reflects parallel changes because of a common underlying etiology in this population needs to be further clarified. Confirmation that alteration of adropin is a major risk factor for hypertension may require investigation using adropin transgenic overexpression mice models, or systemic treatment using recombinant adropin.

In conclusion, adropin is a risk factor for hypertension; it has a negative relationship with blood pressure and regulates blood pressure by possibly influencing endothelial function.

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