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The Correlation between the Serum Level of Adropin and Blood Pressure: A Case-Control Study

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ABSTRACT

Background: Hypertension is considered a fundamental health issue globally, and adropin is a vascular endothelial protection factor. The increasing prevalence of Hypertension (HTN); i.e., 20 - 50%, among adult populations in developed countries is one of the most common causes of Cardiovascular Diseases (CVDs). HTN is also the major modifiable risk factor for stroke (both ischemic and hemorrhagic). Adropin has the potential to protect the endothelium by increasing the expression of Nitric Oxide (NO) synthesis in the endothelium. Nonetheless, few studies have been conducted on the role of adropin in regulating blood pressure.

Objectives: The present study aimed to assess the adropin level and its relationship with blood pressure.

Methods: The present observational, case-control study was conducted on 40 hypertensive and 40 non-hypertensive patients. The patients' data such as gender, age, years passed since HTN diagnosis, and blood pressure were recorded by the researcher. Then, adropin was measured by the Enzyme-Linked Immunosorbent Assay (ELISA) technique. After all, the significance of the relationship between the variables was statistically analyzed.

Results: The mean level of adropin was 5.44 ± 1.31 pg/mL in the study population. This measure was 4.91 pg/mL in the case group and 5.98 pg/mL in the control group, and the difference was statistically significant ($P < 0.01$). The results of ANCOVA showed that mean level of adropin was 1.19 units (24.5%) lower in the case group than in the control group after adjusting for age. The results also revealed a significant difference in the mean adropin level of the hypertensive patients based on the years passed since diagnosis ($P < 0.01$). Moreover, a negative correlation was observed between the adropin level and systolic blood pressure ($rs = -0.273$, $n = 80$, $P = 0.014$) and diastolic blood pressure ($rs = -0.273$, $n = 80$, $P = 0.008$). However, no significant correlation was found between age and adropin level ($rs = -0.173$, $n = 80$, $P = 0.124$).

Conclusions: Hypertensive patients had lower adropin levels in comparison to non-hypertensive ones. In addition, increase in the number of years passed since diagnosis was associated with decreased adropin levels.

1. Background

Cardiovascular Diseases (CVDs) are among the most prevalent non-communicable diseases and the fourth leading cause of death worldwide. In Iran, 40% of deaths have been reported to occur due to CVDs, and a large portion of the health system resources are dedicated to treating these diseases (1, 2). The increasing prevalence of Hypertension (HTN); i.e., 20 - 50%, among adult populations in developed countries is one of the most common causes of CVDs. HTN is also the major modifiable risk factor for stroke (both ischemic and hemorrhagic) (3). Yet, managing HTN and preventing the resulting mortality are possible. This highlights the necessity to prioritize screening, early diagnosis, and management of HTN in the world through community-based programs.

Adropin is a peptide hormone with 76 amino acids. It is encoded by ENHO, a homeostasis-associated gene expressed in the liver and brain. Therefore, it is probably

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involved in reducing obesity and insulin resistance, improving endothelial function, and modulating the Central Nervous System (CNS) functions (4, 5). Recently, adropine deficiency has been reported to be associated with endothelial dysfunction in type II diabetes. The protective role of adropin depends on the regulation of endothelial Nitric Oxide (NO) synthesis (6). Additionally, few studies have shown that the serum level of this compound decreases with age. However, it has not been well established that aging is an independent risk factor for decreased serum levels of adropine or is an influential factor on adropine serum levels (6). A 2010 study by Fina Lovren et al. examined the effect of adropine as a regulatory factor on endothelial function. At the laboratory level, endothelial cells treated with adropine showed increased proliferation, migration, and capillary tube formation. Thus, the researchers suggested the role of adropine as a vascular protective factor through releasing NO from the vascular endothelial wall (7). Adropin has the potential to protect the endothelium by increasing the expression of NO synthesis in the endothelium. NO is an endogenous vasodilator, which can regulate blood pressure through decreasing vascular resistance (8). Moreover, plasma levels of adropin were increased in patients with heart failure, indicating the association between this compound and CVDs (9). Gu et al. also studied 123 patients with HTN and reported a negative correlation between adropin and HTN and Endothelin 1 (ET-1) levels (10). Considering the limited research in this field, further studies are required to determine whether the relationship between HTN and adropin is causative or incidental.

As mentioned earlier, HTN is considered a fundamental health issue in the world and adropin has been recognized a vascular endothelial protection factor. However, few studies have been conducted on the role of adropin in regulating blood pressure.

2. Objectives

The present study aims to assess the adropin level and its relationship with blood pressure.

3. Materials and Methods

This observational, case-control study was conducted on 40 hypertensive people as the patient group and 40 family members of the patient group as the control group who had referred to Vali-e-Asr Heart Clinic in Birjand from November 2017 to June 2018. The participants were selected via non-probability sampling based on the inclusion and exclusion criteria. The inclusion criteria of the study were aging 25 - 85 years, being willing to cooperate, not suffering from other diseases, being diagnosed with HTN (at least two systolic blood pressure readings of more than 130 mmHg or diastolic blood pressure of 90 mmHg recorded by an expert according to the American Heart Association guidelines) (11), controlling HTN by consuming medications, completing the treatment course, and visiting the heart clinic on a regular basis. The exclusion criteria were lack of cooperation, history of neoplasms, diabetes, dyslipidemia, Coronary Artery Disease (CAD), inflammatory diseases, and other diseases. The patients' families were selected as the control group. In this group, the inclusion criteria were being willing to participate in the research and not suffering from other diseases. The exclusion criteria were unwillingness to cooperate and having diseases.

According to the study performed by Xiaosong Gu et al. (12) reporting the mean level of adropin as 3.18 ± 1 in the hypertensive group and 4.21 ± 1.14 in the control group, considering the confidence level of 95% and power of 80%, and using the following formula, a 33-subject sample size was estimated for each study group. However, considering the probability of loss, this value was increased to 40. Thus, 40 hypertensive patients referred to Vali-e-Asr Heart Clinic who met the inclusion criteria were entered into the case group by the clinic's cardiologist using the non-probability method. Additionally, 40 healthy individuals were selected from the family members of the patients referred to the clinic as the control group using the non-probability method.

The data were collected using a goal-based checklist including gender, age, years passed since the diagnosis of HTN (one year or more), blood pressure (recorded by an expert according to the American Heart Association guidelines), and adropin serum level. Moreover, 5 mL samples were taken from the individuals referred to the clinic using median cubital and cephalic veins. If the sampling was unsuccessful, hand or ankle veins were used. In doing so, standard and adult needles with butterfly set (scalp vein) were used. The serum level of adropin was measured by the Enzyme-Linked Immunosorbent Assay (ELISA) technique using adropin kits (ZellBio Company, Germany).

Data analysis was done using the SPSS software, version 18. Kolmogorov–Smirnov test was used to assess the normal distribution of adropin, systolic blood pressure, diastolic blood pressure, and age. Then, Mann–Whitney U test was used to compare the two groups with respect to the means of adropin level, systolic blood pressure, and diastolic blood pressure. Additionally, independent t-test was used to compare the mean age between the two groups as well as between the hypertensive patients diagnosed within less than a year and those diagnosed more than a year ago. Fisher's exact test was also employed to compare the two groups concerning sex distribution. Furthermore, Spearman's correlation was run to determine the relationship between the serum level of adropin and systolic blood pressure, diastolic blood pressure, and age. Considering the mismatch effect of age in the two groups (since HTN is more prevalent among elderly individuals) and since data matching was not possible, Analysis of Covariance (ANCOVA) was used to adjust the effect of age. $P < 0.05$ was considered statistically significant.

3.1. Limitations of Study

One of the study limitations was non-probability sampling and the number of available patients. Other study limitations included the mismatch effect of age in the two groups and the high cost of adropin ELISA kits.

4. Results

The descriptive statistics of age, blood pressure, and

Table 1. Descriptive Statistics of Age, Blood Pressure, and Adropin Serum Levels

Variable	Total		Control Group		Case Group	
	Mean	SD	Mean	SD	Mean	SD
Age	48.91	13.11	41.12	9.21	56.70	11.79
Systolic blood pressure	122.14	87.87	132.37	12.80	113.37	9.96
Diastolic blood pressure	75.18	9.39	80.00	5.99	70.37	9.76
Adropin	5.44	1.33	4.91	1.43	5.98	0.92

Table 2. Comparing the Two Groups Regarding the Raw and Adjusted Mean Levels of Adropin Using Analysis of Covariance

Adropin Level / Group	Raw and Adjusted Means	Adjusted Mean*	Effect (%)
Case	4.91 ± 1.431	4.85 ± 1.18	24.5
Control	5.98 ± 0.92	6.04 ± 1.19	
Significance level	< 0.001	0.001	

*Age and gender were adjusted.

serum levels of adropin have been presented in Table 1. Considering the normal distribution of age (Kolmogorov-Smirnov, P = 0.20, statistic = 0.05), independent t-test showed a significant difference between the two groups in terms of mean age (P < 0.01). In this study, nine patients (22.5%) in the case group and 34 ones (85%) in the control group were below 50 years of age.

Given the non-normal distribution of systolic blood pressure (Kolmogorov-Smirnov test, P < 0.01, statistic = 0.20) and diastolic blood pressure (Kolmogorov-Smirnov, P < 0.01, statistic = 0.29), Mann–Whitney test was used for comparison. The results revealed a significant difference between the two groups regarding the means of systolic and diastolic blood pressure (P < 0.01 for both groups).

In this study, nine participants (11.3%) were male and 71 (88.8%) were female. Besides, three patients (7.5%) in the case group and six participants (15%) in the control group were male. The results indicated no significant difference between the two groups in terms of gender distribution.

Given the non-normal distribution of adropin level (Kolmogorov-Smirnov, P = 0.04, statistic:0.10), Mann–Whitney U test was used for comparison. The results showed a significant difference between the case and control groups concerning the mean adropin level (P < 0.01). Accordingly, the level of adropin was significantly higher in the control group than in the case group. The mean level of adropin was 1.13 ± 4.84 pg/mL in the hypertensive patients younger than 55 years and 4.97 ± 1.72 in those aged 55 years and above, but the difference was not statistically significant (P = 0.47). Moreover, the mean level of adropin was 4.46 ± 2.70 pg/mL in male hypertensive patients and 4.94±1.34 pg/mL in female ones, and the difference was not statistically significant (P = 0.91). Furthermore, the mean adropin level was 6.10 ± 0.74 pg/mL in the hypertensive patients diagnosed within less than a year and 4.19 ± 1.27 pg/mL in those diagnosed more than a year ago. The results showed a significant difference in the hypertensive patients' mean adropin level regarding the number of years passed since diagnosis (P < 0.01). The results of ANCOVA indicated that the mean level of adropin was 1.19 units (24.5%) lower in the case group than in the control group after adjusting for age (Table 2).

Spearman's correlation was run to determine the relationship between the serum level of adropin and systolic blood pressure, diastolic blood pressure, and age. The results revealed a negative correlation between the adropin level and systolic blood pressure (rs = -0.273, n = 80, P = 0.014) and diastolic blood pressure (rs = -0.273, n = 80, P = 0.008). However, no significant correlation was observed between age and adropin level (rs = -0.173, n = 80, P = 0.124).

5. Discussion

The present study findings demonstrated a significant difference between the case and control groups regarding the mean adropin level (P < 0.01). Accordingly, the control group had significantly higher adropin levels compared to the case group even after adjusting for the effect of age. Gu et al. conducted a cross-sectional study on 123 patients with primary HTN as the case group and 58 non-hypertensive patients as the control group in 2015. The results showed that adropin levels were significantly lower in the hypertensive group than in the control group (12), which was in line with the findings of the present study. In another study performed by Altinicik et al. in 2015, adropin serum levels were significantly lower in obese patients than in the control group. However, no significant association was observed between the serum level of adropin and blood pressure (4). Moreover, Gulen et al. conducted a research in 2016 and measured adropin level in patients with critical organ damage secondary to high blood pressure. The results demonstrated that the serum level of adropin was significantly higher in hypertensive patients (13). Furthermore, Yu et al. disclosed that low adropin levels could be perceived as a biomarker for the severity of coronary artery atherosclerosis (14). The results of the present study were in agreement with those of the studies mentioned above. However, the study groups were not age-matched in the present study, which was one of the study limitations. Nevertheless, a limited number of studies have shown decreased adropin levels with increase in age (5). It has been suggested that adropin may be involved in regulating blood pressure by affecting the endothelial function (5). This positive impact increases NO and improves endothelial function (8). However, given the limited number of studies in this field, further research is necessary for correct decision-making.

The current study findings indicated no significant difference in the mean adropin levels of hypertensive patients based on age and gender. Altincik et al. also found no significant association between the serum level of adropin and gender (4). However, Nergiz et al. conducted a study on 74 patients with endometrial cancer and showed a negative correlation between the adropin level and age (6). In the study performed by Hu et al. on patients with diabetic nephropathy, a negative correlation was observed between adropin level and age, while there was no association between gender and adropin level (7). In another study by Butler et al., the serum level of adropin had a negative correlation with age, while no association was observed between the serum level of adropin and gender (15). The discrepancy among the results might result from the fact that in addition to age, other factors including underlying diseases such as diabetes, increased resistance to insulin, Non-Alcoholic Fatty Liver Disease (NAFLD), and endothelial dysfunction affect the serum level of adropin (16, 17).

5.1. Conclusion

The present study findings indicated a significant difference in the hypertensive patients' mean adropin levels regarding the number of years passed since diagnosis. Accordingly, the level of adropin was significantly higher among the hypertensive patients diagnosed within less than a year. As mentioned earlier, endothelial dysfunction has been mentioned as one of the most important factors in decreasing adropin levels (16, 17). Besides, Yang et al. emphasized that increased oxidative stress was accompanied by a decrease in the serum level of adropin (16). On the other hand, various studies revealed endothelial dysfunction and oxidative stress amongst hypertensive patients, which deteriorated with increased number of years since diagnosis (18, 19). It seems that increased number of years since diagnosis is accompanied by endothelial dysfunction. Therefore, a lower level of adropin is predictable in patients who are diagnosed in less than a year than in those diagnosed within more than a year.

5.2. Ethical Statement

After gaining the approval of the Research Committee and Ethics Committee (IR.BUMS.REC.1397.350), the present study was conducted in line with ethical principles. Accordingly, the participants were assured about the confidentiality of their information and their written informed consent forms were obtained.

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Authors' Contribution

Conceptualization: M.V., M.H., and A.T. Experiments design: M.H. and A.T. Data analysis: M.V. and A.T. Provision of the study materials and equipment: M.V., A.T., and M.H. Supervision: M.H. Draft preparation: M.V. and A.T. Writing and reviewing: M.V. and A.T. Project administration: M.V. and A.T.

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References

1. Haghdoost AA, Sadeghirad B, Rezazadehkermani M. Epidemiology and heterogeneity of hypertension in Iran: a systematic review. *Arch Iran Med*. 2008;**11**(4):444-52.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;**365**(9455):217-23.
3. Cifkova R, Wohlfahrt P. Epidemiology of Hypertension and Brain Disease. *Hypertension and Brain Damage*: Springer; 2016. p. 1-11.
4. Altincik A, Sayin O. Evaluation of the relationship between serum adropin levels and blood pressure in obese children. *J Pediatr Endocrinol Metab*. 2015;**28**(9-10):1095-100.
5. Chen M, Ouyang F, Zhou S. Adropin as a novel energy factor likely has the ability to regulate blood pressure. *Medical hypotheses*. 2015;**85**(2):234.
6. Hu W, Chen L. Association of Serum Adropin Concentrations with Diabetic Nephropathy. *Mediators Inflamm*. 2016;**2016**:6038261.
7. Butler AA, Tam CS, Stanhope KL, Wolfe BM, Ali MR, O'Keeffe M*, et al.* Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. *J Clin Endocrinol Metab*. 2012;**97**(10):3783-91.
8. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M*, et al.* Adropin is a novel regulator of endothelial function. *Circulation*. 2010;**122**(11 Suppl):S185-92.
9. Lian W, Gu X, Qin Y, Zheng X. Elevated plasma levels of adropin in heart failure patients. *Intern Med*. 2011;**50**(15):1523-7.
10. Li L, Xie W, Zheng XL, Yin WD, Tang CK. A novel peptide adropin in cardiovascular diseases. *Clin Chim Acta*. 2016;**453**:107-13.
11. Gu X, Li H, Zhu X, Gu H, Chen J, Wang L*, et al.* Inverse Correlation Between Plasma Adropin and ET-1 Levels in Essential Hypertension: A Cross-Sectional Study. *Medicine (Baltimore)*. 2015;**94**(40):e1712.
12. Gulen B, Eken C, Kucukdagli OT, Serinken M, Kocyigit A, Kilic E*, et al.* Adropin levels and target organ damage secondary to high blood pressure in the ED. *Am J Emerg Med*. 2016;**34**(11):2061-4.
13. Yu HY, Zhao P, Wu MC, Liu J, Yin W. Serum adropin levels are decreased in patients with acute myocardial infarction. *Regul Pept*. 2014;**190-191**:46-9.
14. Nergiz S, Altinkaya SO, Kurt Omurlu I, Yuksel H, Kucuk M, Demircan Sezer S. Circulating adropin levels in patients with endometrium cancer. *Gynecol Endocrinol*. 2015;**31**(9):730-5.
15. Yang C, DeMars KM, Candelario-Jalil E. Age-Dependent Decrease in Adropin is Associated with Reduced Levels of Endothelial Nitric Oxide Synthase and Increased Oxidative Stress in the Rat Brain. *Aging Dis*. 2018;**9**(2):322-30.
16. Marczuk N, Cecerska-Heryc E, Jesionowska A, Dolegowska B. Adropin - physiological and pathophysiological role. *Postepy Hig Med Dosw (Online)*. 2016;**70**(0):981-8.
17. Puddu P, Puddu GM, Zaca F, Muscari A. Endothelial dysfunction in hypertension. *Acta Cardiol*. 2000;**55**(4):221-32.
18. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. 2000;**87**(10):840-4.
19. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C*, et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;**71**(6):e13-e115.