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Original Article

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The Role of Some Adipokines in The Pathophysiology of Hypertension

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Abstract

Objective: Hypertension is defined as an average systolic blood pressure (SBP) of 140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg. Adipokines play regulatory roles in many functions in the body through various intermediary mediators. There is a growing interest in adipokines in recent years. Adipokines are currently being investigated as potential drug targets for many systemic diseases. The aim of this study is to elucidate the effects of adipokines, which play important regulatory roles in metabolic pathways, in the pathophysiology of hypertension and to investigate their relationships with various biological parameters in patient and control blood samples.

Material and Methods: Blood samples were obtained from patients aged 18 and over who presented to the Family Medicine and Cardiology outpatient clinics of Dicle University Faculty of Medicine Hospital. Serum levels of leptin, visceral, intelectin, chemerin, retinol binding protein (RBP1), adiponectin, resistin, visfatin, and C-reactive protein (CRP) were measured using ELISA kits.

Results: A total of 180 individuals participated in our study, including 96 patients and 84 controls, of whom 105 were female and 75 were male. In the patient and control groups, systolic and diastolic blood pressure values were 149.07±15.689 and 112.53±10.064, respectively. There were significant differences in median (min-max) values of leptin, intelectin, RBP1, resistin, and visfatin between normotensive and hypertensive individuals. All these adipokine levels were higher in hypertensive patients compared to normotensive ones. There was no significant difference in CRP.

Conclusion: Adipokines correlating with systolic and diastolic blood pressure are leptin, intelectin (omentin), RBP1, resistin, and visfatin. Leptin was found to be correlated with body mass index (BMI). A slight negative correlation between chemerin levels and blood pressure was observed. Adiponectins correlating with age are leptin, intelectin, RBP1, resistin, and visfatin. However, the roles of adipokines in the cardiovascular system still need to be clarified. Our study highlights the need for both in vivo and in vitro studies to be conducted more extensively.

Keywords: Mediterranean Diet, Phase Angle, Healthy Eating Attitude, Bioelectrical Impedance Analysis

Introduction

Hypertension is defined as an average systolic blood pressure (SBP) of 140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg. According to office blood pressure measurements, it is estimated that the worldwide prevalence of hypertension was approximately 1.3 billion in 2015, with a prevalence of 150 million in Europe. The general prevalence in adults is about 30-45%, and it is predicted that the prevalence of hypertension will increase by 15-20% by 2025, reaching 1.5 billion (1).

According to the American Hypertension Association, the normal limit for systolic blood pressure is <135 and for diastolic blood pressure is <85 in outpatient measurements, but according to PAMELA, the daily average is determined to be 129-132 / 80-85 in men and 125-129 / 80-82 in women. These values correspond to the 40/90 limit in office measurements (2).

Hypertension is a progressive problem with increasing prevalence and complications. It is one of the most common chronic diseases, with multiple complications including heart disease, stroke, kidney disease, and premature death. However, it is a preventable and treatable condition.

Adipokines have been known for over 20 years as cells that secrete proteins called adipokines. They are considered one of the main endocrine organs with soluble mediators called adipokines. Adipokines are mediators that are mainly secreted from adipocytes and perform biological functions either locally (autocrine/paracrine) or systemically. They can also be secreted from active macrophages and immune system cells (3). In patients with hypertension, levels of pro-inflammatory and anti-inflammatory adipokines vary.

Increased adiponectin in hypertension may be a protective method aimed at improving endothelial function, reducing oxidative stress, and increasing nitric oxide synthase. Academic studies have facilitated comprehensive research on adipokines in diseases. Additionally, in this emerging world of adipokines, we believe that elucidating their interaction with hypertension will provide a foundation for studies on the control and treatment of hypertension and related diseases.

Some of these adipokines include adiponectin, visfatin, leptin, resistin, RBP1, chemerin, intelectin, visceral, and CRP. They play significant roles in various aspects of metabolism such as insulin resistance, glucose and lipid metabolism, fatty acid oxidation, weight control, eating behavior, energy balance, inflammation, vascular tone, coagulation, the complement system, angiogenesis, immunity, and even reproduction. Recent studies have begun to reveal significant connections between metabolism and the immune system. These connections emerge when a complex network of mediators arises from immune cells and adipocytes (4).

From this perspective the aim of this study is elucidate the effects of adipokines, which play important regulatory roles in metabolic pathways, in the pathophysiology of hypertension and to investigate their relationships with various biological parameters in patient and control blood samples.

Material and Method

Our study was conducted at Dicle University Faculty of Medicine Hospital in Diyarbakır, Turkey. The population of this case-control study consisted of patients aged 18 and over who presented to the Family Medicine and Cardiology outpatient clinics of Dicle University Faculty of Medicine Hospital between March 1, 2019, and September 1, 2019.

Sample

For the sample calculation, the "Sample Size Calculator Software" prepared by The Survey System, which operates at a 95% confidence interval and $p \leq 0.05$ significance level, was used, determining a minimum of 83 patients to be included in the study (https://www.surveysystem.com/sscalc.htm). We reached 96 patients, and additionally, 84 healthy volunteers were included as the control group. In total, 180 individuals were included in the study.

Inclusion Criteria

Inclusion criteria for the study were as follows: the patient's willingness to participate in the study, having the mental competence to understand and make decisions, having a pre-diagnosis of hypertension, not having previously received a diagnosis of hypertension, not receiving any antihypertensive treatment, and not having diagnoses such as renal failure or heart failure.

Ethical Approval

Ethical approval for our study was obtained from the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine on February 14, 2019, with approval number 78.

Measurement Procedure

Informed consent was obtained from all participating patients. Written consent forms containing detailed information prepared by the researcher were signed by the patient or their caregiver. Subsequently, a socio-demographic data form was completed. For patients who were illiterate, the consent form and socio-demographic data form were read aloud, and any unclear points were explained and completed. Patients were seated in a calm environment and allowed to rest for 5 minutes. After sufficient rest, the cuff was placed on the upper arm, approximately 2 cm above the elbow. The cuff was manually inflated by the researcher to approximately 200 mmHg, then slowly released to measure blood pressure. This process was repeated three times, and the average was recorded.

Laboratory Measurements

Serum leptin, visceral, intelectin, chemerin, RBP1, adiponectin, resistin, visfatin, and CRP measurements were collected using blood samples collected into gel tubes between 09:00-12:00. After collection, samples were left at room temperature for 15 minutes to facilitate clotting. Blood samples were centrifuged at 5000 rpm for 5 minutes. Serum was transferred to 1.5 ml

polypropylene tubes and stored at -80°C for further analysis. Serum levels were measured using ELISA kits from YLA BİONT (Shangai YL Biotech Co ELISA Kit, China). Analysis was performed on a Biotek micro ELISA device. To minimize test variance, all measurements were performed on the same day following the manufacturer's instructions.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) for Windows version 21.0 (IBM Corp., Armonk, USA). Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics (mean ± standard deviation, median, number, and percentage) were used to evaluate the data Mann Whitney U test, and Kruskal Wallis test were used for the intergroup comparison of the data. Results were considered significant at $p<0.05$ with a confidence interval of 95%.

RESULTS

Out of the 180 participants in our study, 96 (53.3%) were patients, and 84 (46.6%) were from the control group. Of these participants, 105 (58.3%) were female, and 75 (41.7%) were male. Regarding marital status, 129 (71.7%) were married, and 51 (28.3%) were single. Among the participants, 44 (24.4%) were illiterate, 40 (22.2%) had completed primary school, 17 (9.4%) had completed secondary school, and 54 (30%) had completed high school.

Table 1. Comparison of Patients and Control Groups in Terms of Blood Pressure, Adipokines, and Some Parameters

	Group	n	Median(min-max)	p
Systole	Study	96	150 (110-190)	
	Control	84	112.53 (90-140)	**<0.001***
	Total	180		
Diastole	Study	96	90.00 (60-120)	
	Control	84	72.56 (60-85)	**<0.001***
	Total	180		
Leptin	Study	96	7.84 (1.13-980.88)	
	Control	84	2.40 (1.15- 46.92)	**<0.001***
	Total	180		
Visceral	Study	96	1.01 (0.23-5.14)	
	Control	84	0.79 (0.1-2.65)	0.41
	Total	180		
Intelectin	Study	96	74.18 (10.3-1438.78)	
	Control	84	37.53 (10.1-131.54)	**<0.001***
	Total	180		
Chemerin	Study	96	198.57 (91.72-1380.13)	
	Control	84	177.57 (131.46-852.25)	0.347
	Total	180		
RBP1	Study	96	109.64 (44.97-5314.66)	
	Control	84	48.53 (12.56-377.05)	**<0.001***
	Total	180		
Adinopectin	Study	96	5.21 (1.08-23.90)	
	Control	84	4.07 (1.01-10.19)	**0.016***
	Total	180		

Rezistin	Study	96	529.32 (119.97-3071.44)	
	Control	84	276.18 (109.24-1078.04)	**<0.001***
	Total	180		
Visfatin	Study	96	10.6134 (1.25-93.92)	
	Control	84	5.77 (1.77-27.04)	**<0.001***
	Total	180		
Crp	Study	96	2.19 (0.04-6.56)	
	Control	84	2.19 (0.72-5.22)	0.113
	Total	180		
BMI	Study	96	28.72 (18.43- 41.62)	
	Control	84	25.13 (16.22-47.38)	**<0.001***
	Total	180		

P<0.05 statistical significance, Mann Whitney U Test

The systolic blood pressure measurements were observed as 150 (110-90) in the patient group and 112.53 (90-140) in the control group (P < 0.001). Similarly, for diastolic blood pressure, measurements for patients and controls were 90 (60-120) and 72.56 (60-85), respectively (P < 0.001). All adipokine level measurements for both patient and control groups are provided in Table 1 as median (min-max) values.

Table 2. Comparison of Adipokine Levels Between Hypertension Groups

	Normotensive	Pre-Hypertensive	Hypertensive	
		Median(min-max)	Median(min-max)	p
Leptin	2.60 (1.15-65.5)	3.59 (2.14-614.65)	7.4 (1.13-980.88)	**<0.001***
Visceral	0.80(0.1-3.5)	0.91 (0.42-5.06)	0.95 (0.13-5.14)	0.285
Intelectin	38.06 (10-336)	41.49 (10.3-956.49)	63.32 (14.31-1438.78	**0.02***
Chemerin	180.60 (111-852)	175.74 (98.861086.41)	189.55 (91.72-1380.13)	0.406
RBP1	49.2 (12.56-810.48)	61.36 (45.87-3744.76)	100.93 (19.17-5314.66)	**<0.001***
Adiponectin	4.1 (1.01-10.19)	4.78 (1.08-21.12)	5.37 (1.90-23.90)	0.075
Rezistin	277.71 (109.24-1078.04)	574.3 (234.63-2682.53)	477.79 (119.97-3071.44)	**<0.001***
Visfatin	5.95 (1.77-29.63)	6.34 (1.25-88.74)	9.1479 (1.52-93.92)	**<0.001***
CRP	2.19 (0.72-6.56)	2.19 (0.04-5.49)	2.19 (0.5-6.24)	0.574

p<0.05 statistical significance, Kruskal Wallis Test

Among the total patients enrolled in the study, the levels of adipokines, including leptin, RBP1, resistin, and visfatin, were found to be lower in normotensive and prehypertensive individuals compared to those with hypertension, and this difference was statistically significant (P < 0.001). The results for other adipokine levels are provided in Table 2.

Table 3. Intergroup Comparison of Some Adipokine Levels Between Normal and High Blood Pressure Groups

	Normotensive	Hypertensive	p
	Median (min-max)	Median (min-max)	**<0.001***
Leptin	2.60 (1.15-65.59)	7.40 (1.13-980.88)	**<0.001***
Intellectin	38.06 (10-33)	63.32 (14.31-1438.78)	**<0.001***
RBP1	49.2 (12.56-810.48)	100.93 (19.17-5314.66)	**<0.001***
Rezistin	277.71 (109.24-1078.04)	477.79 (119.97-3071.44)	**<0.001***
Visfatin	5.95 (1.77-29.63)	9.1479 (1.52-93.92)	**<0.001***

p< 0.05 statistical significance, Mann Whitney U Test

DISCUSSION

Adipose tissue secretes various bioactive factors known as adipokines, which include enzymes, hormones, growth factors, chemokines, and cytokines. Under healthy conditions, white adipose tissue primarily produces anti-inflammatory adipokines such as adiponectin. However, it has been observed that diseased adipose tissue, as seen in obesity, can transition to a pro-inflammatory state with increased expression of factors like leptin, CCL2, interleukin-6, and TNFα.

Approximately 50% of obese individuals have hypertension, making obesity one of the most common causes of hypertension. Various mechanisms contribute to the relationship between obesity and hypertension, including activation of the sympathetic nervous system, abnormal renal sodium handling, insulin resistance, and physical compression of the kidneys.

Leptin levels decrease during fasting to regulate energy balance in humans and increase after several days of overfeeding. Leptin resistance is observed in obesity, leading to increased levels of leptin. It is believed that leptin resistance occurs only in mechanisms related to satiety and weight gain, and not in mechanisms leading to sympathetic activation and hypertension.

In our study, the serum leptin level was found to be 7.84 on average in the patient group and 2.40 in the non-patient group, with this difference being statistically significant. When patients were clustered according to blood pressure, the average leptin level was found to be 2.60 in normotensive individuals, 3.59 in prehypertensive individuals, and 7.4 in hypertensive individuals. Consistent with the literature, our study also found an association between the development of hypertension and leptin levels.

According to the Framingham study, half of patients aged 65 and older with blood pressure in the prehypertension range develop hypertension within 4 years. A study examining the effects of blood pressure levels in the prehypertension range on cardiovascular events and stroke found that these levels increase cardiovascular events and stroke.

Omentin (intelectin) is released from the epicardial perivascular adipose tissue and protects against atherosclerosis by activating the eNOS system. In a study by Liu et al., individuals with

atherosclerosis were found to have lower omentin levels than those without. Omentin also prevents arterial calcification. According to a study by Yamawaki et al., omentin causes endothelial-derived vascular dilatation, which occurs through NO. This indicates the effect of omentin levels on the pathogenesis of hypertension. In our study, omentin levels were significantly different between the patient and control groups, contrary to literature findings.

While some adipokines (omentin, apelin, adiponectin) play anti-inflammatory roles, others (leptin, visfatin) play pro-inflammatory roles. The amount of plasma and tissue adipokines is proportional to the body's adipose tissue mass.

Resistin can cause insulin resistance and glucose intolerance. Insulin resistance is associated with various diseases such as diabetes and hypertension. Serum resistin concentration is higher in patients with diabetes than in normal individuals and those with prediabetes. Studies on serum resistin levels have shown that it is present in low concentrations in adipose tissue and is not associated with parameters such as body weight and BMI.

In our study, we investigated the relationship between serum resistin levels and hypertension, another component of the metabolic disease profile. The difference in serum resistin levels between the patient group and the control group was found to be statistically significant. However, interestingly, resistin did not show a consistent increase with the stage of hypertension, reaching its highest level in the prehypertensive group.

Chemerin is a newly discovered protein in the adipokine family. It is initially synthesized as pre-prochemerin and acts on a receptor called Chemerin. It is mostly released from tissues such as the placenta, liver, and white adipose tissue. Chemerin has both autocrine and paracrine effects and plays a role in adipogenesis, osteoclastogenesis, angiogenesis, and the inflammation process.

In our study, there was no statistically significant difference in chemerin levels between the patient group and the control group, and no relationship was found between chemerin levels and hypertension. Ademoğlu et al. found chemerin to be correlated with BMI and triglycerides, while Kort et al. found a positive correlation between chemerin and BMI and HOMA-IR. However, in our study, chemerin did not show a correlation with BMI.

Apelin has been found to be associated with insulin resistance in some studies. Apelin was isolated by Tatemoto et al. in 1998 and is released from various tissues such as the central nervous system, heart, lungs, breasts, and possibly from the endothelium.

In our study, the RBP1 levels were found to be an average of 109.57 in the patient group and 48.53 in the control group, and this difference was found to be statistically significant.

While some studies have not found a relationship between visfatin and blood lipids, others have found a strong relationship. In a study, the use of ARBs, ACE inhibitors, and rosiglitazone in type 2 diabetes patients was found to increase visfatin levels. Telmisartan was found to decrease visfatin in metabolic syndrome hypertensive individuals, while valsartan was found to increase it, but the difference was not statistically significant. In our study, visfatin levels were found to be statistically significantly different between the patient group and the control group.

In conclusion, adipokines correlating with systolic and diastolic blood pressure are leptin, intelectin (omentin), RBP1, resistin, and visfatin. Leptin was found to be correlated with body mass index (BMI). A slight negative correlation between chemerin levels and blood pressure was observed. Adiponectins correlating with age are leptin, intelectin, RBP1, resistin, and visfatin. However, the roles of adipokines in the cardiovascular system still need to be clarified. Our study highlights the need for both in vivo and in vitro studies to be conducted more extensively.

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Conflict of Interest

The authors report that there is no conflict of interest.

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