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Natriuretic peptides and their association with renin, aldosterone, and electrolytes in hypertension: A cross-sectional study

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Abstract. *Despite the extensive prevalence of hypertension and its established role as a leading risk factor for various heart diseases, there remains a significant gap in understanding the intricate mechanisms and physiological markers involved in the condition. Although natriuretic peptides are known to regulate numerous physiological processes, their precise relationship with other physiological variables such as resistin, renin, aldosterone, and electrolytes in individuals with hypertension has not been thoroughly investigated. The present study aimed to evaluate the levels of natriuretic peptides and their correlation with some physiological variables, such as resistin, renin, aldosterone, sodium, potassium, and chloride in hypertensive patients.*

Methods. This cross-sectional study recruited 90 participants (50 hypertensive patients and 40 healthy volunteers as controls) between the ages of 30 and 50. The blood samples were collected from all the participants between December 2023 and April 2024 at Al-Ramadi Teaching Hospital. Serum levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), renin, resistin, aldosterone, potassium, sodium, and chloride were measured.

Results. The results showed that the concentration of ANP, BNP, and CNP was significantly higher ($p < 0.001$) in the hypertensive group compared with the control group. Renin, resistin, sodium, and chloride concentrations in the hypertensive group were significantly higher ($p < 0.001$) than in the control group. Conversely, potassium levels were significantly lower ($p < 0.001$) in the hypertensive patient group compared with the control group. There was a positive correlation between ANP with resistin and renin r=0.500, 0.505 respectively, while there is a negative correlation between ANP wilt sodium and chloride r= -0.321, r= -0.297 respectively, a positive correlation was observed between BNP and renin (r= 0.316), and aldosterone (r=0.395).

Conclusions. The present study discovered that patients with hypertension experienced increased levels of natriuretic peptides, resistin, renin, and aldosterone, as well as a decline in the concentration of electrolytes. The observed associations between natriuretic peptides and certain physiological variables, such as resistin and renin, sodium, and chloride, highlight interconnected pathways involved in hypertension. This suggests that natriuretic peptides may be used as a treatment for hypertensive patients.

Keywords: *aldosterone, atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, hypertension, resistin, renin, electrolytes.*

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Натрійуретичні пептиди та їх зв'язок з реніном, альдостероном та електролітами крові хворих з гіпертонічною хворобою: одномоментне перехресне дослідження

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Резюме. *Незважаючи на широку поширеність артеріальної гіпертензії та її роль як провідного фактора ризику різних серцево-судинних захворювань, залишається значна прогалина в розумінні складних механізмів і фізіологічних маркерів, залучених до її патогенезу. Хоча натрійуретичні пептиди, як відомо, регулюють численні фізіологічні процеси, їх точний зв'язок з іншими фізіологічними змінними, такими як резистин, ренін, альдостерон і електроліти у пацієнтів з гіпертонією, не був ретельно досліджений. Метою цього дослідження було оцінити рівні натрійуретичних пептидів та їх кореляцію з резистином, реніном, альдостероном й електролітами у пацієнтів з гіпертензією.*

Методи. До цього одномоментного, перехресного дослідження було залучено 90 учасників (50 пацієнтів з гіпертонією та 40 здорових добровольців у якості контрольної групи) віком від 30 до 50 років. Зразки крові були зібрані у всіх учасників у період з грудня 2023 року по квітень 2024 року в навчальній лікарні Аль-Рамаді. Визначали сироваткові рівні передсердного натрійуретичного пептиду (ANP), мозкового натрійуретичного пептиду (BNP), натрійуретичного пептиду С-типу (CNP), реніну, резистину, альдостерону, калію, натрію та хлориду.

Результати. Результати продемонстрували, що концентрація ANP, BNP і CNP була значно вищою ($p < 0,001$) у пацієнтів з гіпертонією порівняно з контрольною групою. Концентрації реніну, резистину, натрію та хлориду в групі гіпертоніків були вищими ($p < 0,001$) ніж в контрольній групі, тоді як рівень калію був значно нижчими ($p < 0,001$) у групі пацієнтів з гіпертензією порівняно з контрольною групою. Встановлено позитивний кореляційний зв язок між ANP та резистином і реніном ($r = 0,500$ та $r = 0,505$, відповідно), між BNP та реніном ($r = 0,316$) й альдостероном ($r = 0,395$); негативна кореляція визначена між ANP та натрієм і хлоридом ($r = -0,321$ та $r = -0,297$, відповідно).

Висновки. У пацієнтів з гіпертензією спостерігається підвищення концентрації натрійуретичних пептидів, резистину, реніну та альдостерону, а також зниження концентрації електролітів. Визначений взаємозв язок між натрійуретичними пептидами та певними фізіологічними маркерами, такими як резистин і ренін, натрій і хлорид, підкреслюють взаємопов'язані шляхи, залучені до гіпертензії та свідчить на користь можливого застосування натрійуретичних пептидів в лікуванні гіпертонії.

Ключові слова: *гіпертензія, альдостерон, передсердний натрійуретичний пептид, мозковий натрійуретичний пептид, натрійуретичний пептид С-типу, резистин, ренін, електроліти.*

Introduction. Hypertension ranks third among the six primary risk factors for cardiovascular disease globally. It is a primary risk factor for heart disease, stroke, and renal failure [1]. Hypertension is a prolonged increase in systolic blood pressure of at least 140 mmHg and/ or diastolic blood pressure of at least 90 mmHg, as well as the use of blood pressure drugs [2]. The term "natriuretic peptides" (NPs) refers to a group of structurally related hormones and paracrine substances that control several physiological processes, such as cell division, vascular tone, inflammation, neurohumoral pathways, fluid balance, and electrolyte levels, through the action of the natriuretic peptide system [3]. Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) are the three peptides that have been investigated the most [3]. The first member of the natriuretic peptide family, ANP, was discovered as a peptide hormone in 1983 and 1984 [4]. Atrial natriuretic peptide plays a vital role in blood pressure regulation by raising the glomerular filtration rate (GFR) and preventing the kidneys from reabsorbing salt and water [5]. By preventing the kidneys from releasing renin and producing aldosterone, ANP inhibits the renin-angiotensin-aldosterone pathway [5].

Brain natriuretic peptide, a peptide that shares characteristics with ANP, such as natriuretic-diuretic, hypotensive, and smooth muscle relaxant effects, was initially identified in pig brain tissue [4]. The most recently identified member of the natriuretic peptide family is the C-type natriuretic peptide (CNP), which

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is mostly synthesized in the endothelium [6]. Scientists discovered C-type natriuretic peptide (CNP) in pig brains in 1990 and cloned humans, rats, and pigs to replicate it [7]. According to a recent study, naturally occurring CNP in endothelial cells plays a critical role in regulating the blood pressure of living things over the long term [8]. Suppression of vasopressin, sympathetic outflow, and adrenocorticotropic hormone (ACTH) is a key strategy for maintaining long-term blood pressure management [9]. Blood pressure is significantly increased by the mineralocorticoid steroid hormone aldosterone, which was first discovered and purified in 1954. Aldosterone is the primary component and mediator of the renin-angiotensin-aldosterone system (RAAS). This steroid is essential to understanding abnormal physiological processes, especially those connected to cardiovascular disease [10]. Aldosterone has been extensively studied for its important role in fluid balance extracellular potassium concentration, and the renin-angiotensin system [11].

Recent research has elucidated new processes that contribute to understanding the immediate and long-lasting effects of resistance in cardiovascular diseases. Resistin has a significant impact on cardiovascular disease progression. It stimulates inflammation, impairs the function of vascular endothelial cells, and causes the death of smooth muscle cells [12]. Resistin is a well-known cytokine that is secreted by human inflammatory blood cells and has also been discovered to be secreted by adipocytes. It is thought to be important for neurodegenerative and autoimmune diseases, as well as for inflammatory and autoimmune disorders [13]. Resistin stimulates inflammatory processes in the heart and blood vessels, which leads to the development of hypertension and coronary artery disease. This is supported by the association between circulating resistin levels and inflammatory markers [14]. Many researchers have investigated the relationship between resistin levels in circulation and heart disorders, and they discovered a role in vascular remodeling and renin-angiotensin pathway modification, both of which lead to hypertension [13]. Hypertension is considered a hidden killer due to its silent symptoms and causes the death of many people all over the world, so studying some of the physiological changes associated with the disease is one of the necessities. The present study was therefore conducted to evaluate the levels of natriuretic peptides (ANP, BNP, and CNP) and their correlation with some physiological variables, such as resistin, renin, aldosterone, sodium, potassium, and chloride in hypertensive patients.

Materials and Methods. ***Study design and participants.*** This cross-sectional study was conducted from December 2023 to April 2024, with ethical approval obtained from the Ethical Approval Committee of the University of Anbar in Ramadi, Iraq, under approval number 33. The study included ninety participants, comprising fifty patients with hypertension and forty healthy donors, both male and female, aged 30 to 50 years. Hypertension was defined as having a diastolic blood pressure (DBP) of ≥90 mm Hg and/or a systolic blood pressure (SBP) of ≥140 mm Hg [15]. Exclusion criteria for the study included individuals with diabetes mellitus, cardiac conditions, smokers, pregnant women, and those with vascular illnesses.

Collection and preparation of blood samples. The blood specimens were obtained from the participants by venipuncture, which involved draining 5 mL of blood using a disposable syringe, after a 10-hour overnight fast. After the blood was drained, it was placed in a gel tube and allowed to coagulate at room temperature (18 to 25°C). Then, it was centrifuged for 5 minutes at 3,500 rpm to isolate the serum. The serum was then split into white tubes and stored in a deep freezer at −18°C until it was needed. Each participant's blood pressure was also measured with a sphygmomanometer.

The body mass index (BMI) was calculated using the equation: BMI = Weight (kg) / Height (m^2).

Biochemical and physiological analyses. Biochemical analyses of serum ANP, BNP, CNP, resistin, renin, and aldosterone were carried out. The sandwich enzyme-linked immunosorbent assay (ELISA) technology kits (Melsin Medical Co., Limited) were employed with CAT numbers: EKHU-0190 for ANP, EKHU-0216 for BNP, EKHU-0211 for CNP, EKHU-0845 for resistin, EKHU-0663 for renin, and EKHU-1169 for aldosterone. The electrolyte measuring device was used to measure the serum potassium, sodium, and chloride according to the manufacturer's recommendations.

Statistical analysis. Data were analyzed using Genstat software. Simple measures such as frequency, percentage, mean, and standard error were used to present the results. Additionally, data were analyzed and presented as histograms using the Statistical Package for the Social Sciences (SPSS, version 29, IBM, NY, USA). The Student's t-test was used to test the difference between two independent means (quantitative data), with p-values of <0.05 considered statistically significant. Pearson correlation was calculated to assess the relationship between two quantitative variables [16].

Results. As expected, systolic blood pressure (SBP) at 166.00±11.909 mmHg and diastolic blood pressure (DBP) at 102.10±5.810 mmHg in hypertensive patients were significantly higher compared to the control group, which had SBP of 119.75±8.161 mmHg and DBP of 79.75±6.299 mmHg (Table 1).

Table 1

Sex, age, BMI, and electrolyte levels in hypertensive patients and normotensive controls

Parameter	Hypertensive group (n = 50)	Control group (n = 40)	p-value
Gender (M/F)	25/25	20/20	-
SBP (mmHg)	166.00 ± 11.909	119.75 ± 8.161	0.001
DBP (mmHg)	102.10 ± 5.810	79.75 ± 6.299	0.001
BMI (kg/m^2)	28.260 ± 1.806	23.145 ± 2.925	0.001
Age	43.58 ± 0.80	41.92 ± 0.82	0.05
Potassium (mmol/ L)	3.769 ± 0.3194	4.141 ± 0.3413	0.001
Sodium (mmol/ L)	131.12 ± 9.966	117.96 ± 3.632	0.001
Chloride (mmol/ L)	96.40 ± 5.610	91.62 ± 13.949	0.001

Abbreviations: SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index

However, there was no significant difference in age between the two groups. The hypertension group had a significantly higher BMI, sodium and chloride levels while potassium concentration was significantly lower compared to the control group.

Table 2 shows significantly higher levels of natriuretic peptides, resistin, renin, and aldosterone in hypertensive patients compared to the normotensive control group.

Table 2

Levels of natriuretic peptides, resistin, renin, and aldosterone in hypertensive patients and normotensive controls

Parameter	Hypertensive group (n = 50)	Control group (n = 40)	p-value
ANP (pg/mL)	560.22 ± 146.875	472.53 ± 76.265	0.001
BNP (pg/mL)	692.60 ± 84.250	538.50 ± 538.50	0.001
CNP (pg/mL)	3320.00 ± 1174.192	2939.82 ± 1644.56	0.001
Resistin (ng/mL)	42.75 ± 9.430	36.39 ± 4.537	0.001
Renin (pg/mL)	91.70 ± 24.714	75.65 ± 8.928	0.001
Aldosterone (pg/mL)	543.180 ± 48.0159	490.164 ± 46.9116	0.05

Abbreviations: ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide

As indicated in Table 3, correlations between natriuretic peptides and various studied variables were observed. Specifically, ANP showed a moderately positive correlation with resistin and renin. Additionally, ANP was negatively correlated with sodium and chloride. BNP also demonstrated positive correlations with renin, aldosterone, and BMI.

Table 3

Correlation between natriuretic peptides and studied variables in hypertensive patients

Variables	r	p-value
ANP - Resistin	0.500	0.01
ANP - Renin	0.505	0.01
ANP - Na	-0.328	0.05
ANP - Cl	-0.297	0.05
BNP - Renin	0.316	0.05
BNP - ALD	0.395	0.01
BNP - BMI	0.291	0.05

Abbreviations: ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; ALD: Aldosterone; BMI: Body mass index

Discussion. Body mass index is a significant measure of body fat that accounts for the influence of high body mass. Research has demonstrated that BMI is the most responsive physical measurement for predicting high blood pressure compared to other prevalent indicators of obesity [17]. The results of the present study showed that the hypertensive patients had excess weight compared to normotensive individuals. The Framingham study revealed that those who are overweight have greater systolic and diastolic blood pressures compared to those with a normal BMI. Conversely, reducing body weight leads to a decrease in blood pressure, both systolic and diastolic [18, 19]. A study involving 1,145 participants from a survey conducted in the general population revealed that weight gain was identified as a significant risk factor for hypertension [20]. According to the investigation by Xu (2020), the incidence of hypertension decreased in overweight people who made weight loss efforts. The study's findings demonstrated a statistically significant rise in natriuretic peptide levels compared with normotensive individuals. The study's findings were consistent with many previous investigations, which found an increase in the concentration of ANP in hypertensive patients [22-24].

Atrial natriuretic peptide (ANP) is secreted by the heart. It attaches to its receptor in the kidney and blood vessels, stimulating salt excretion, reducing blood volume, and causing vessel relaxation. The endocrine system connects the heart and the kidney to maintain an optimal equilibrium between electrolytes and bodily fluids [5]. In a canine model of acute hypertension with elevated cardiac filling pressures, infusion of ANP significantly lowered pulmonary wedge pressure, artery pressure, and right atrial pressure, and reduced aldosterone levels [25]. The elevated levels of ANP in individuals with hypertension may be associated with a predisposition for decreased excretion of sodium by the kidney. This can occur due to a hereditary renal abnormality or high blood pressure. Consequently, sodium retention may occur, leading to the activation of compensatory mechanisms to eliminate the excess sodium [5]. Many other investigations, including the present study, also found that hypertension patients had higher BNP concentrations [26, 27]. According to the study, the distal portion of the kidney experiences a decrease in sodium reabsorption and an increase in sodium filtration due to BNP's natriuretic effect. The second finding in the present study is consistent with previous investigations on rats that found BNP activates particulate guanylate cyclase, inhibits conductive sodium absorption, and reduces sodium transport in the medullary collecting duct [28]. Brain natriuretic peptide enhances the pace at which blood is filtered by the kidneys by increasing the constriction of the blood vessels that carry blood away from the kidneys in circumstances where there is an excess of fluid content. Additionally, they hinder the reabsorption of sodium in the kidneys [29]. Essential hypertension is characterized by the hardening of artery walls due to hypertrophy and fibrosis, which leads to a decrease in elasticity and the maintenance of high blood pressure. Natriuretic peptides are well recognized for their ability to function as antifibrotic and antihypertrophic agents in cardiac and vascular tissues. However, the exact processes behind these effects are not yet completely understood [30].

The current findings, along with those of a previous study [30], point to a significant increase in CNP levels in hypertensive patients. Also, the administration of CNP inhibits the accumulation of collagen in the spaces between cells and around blood vessels in the heart tissue. Additionally, it decreases the amount of collagen in the aorta and reduces the thickness of the middle layer of the aortic wall [30]. Spiranec et al. discovered that endothelial paracrine CNP increases GC-B/cGMP signaling in microcirculatory pericytes, which lowers arterial blood pressure and peripheral vascular resistance. The interaction between CNP/GC-B and cGMP in pericytes has a beneficial effect on the long-term control of blood pressure [31]. The finding demonstrated an increase in the levels of serum resistin in hypertensive patients compared to normal participants. This finding agrees with the outcome of analytical research, which revealed an increased level of resistance in hypertensive patients compared to the normotensive group [32]. Resistin is thought to increase blood pressure by vascular remodeling and altering the renin-angiotensin pathway. In another study, a strong association between increased resistin levels and an increased future risk of developing hypertension was observed [33]. The impact of resistin on blood pressure may be elucidated by an elevation in mRNA levels of fatty acid-binding protein in human coronary artery endothelial cells produced by resistin. Another possible way that resistin is connected to hypertension is through its capacity to stimulate the growth of smooth muscle cells [34]. Potential mechanisms linking resistin to hypertension include its vasoconstrictor property, which promotes smooth muscle cell proliferation, and its effects on the renin-angiotensin system [35].

The study's findings indicated a significant increase in the concentration of aldosterone and renin, and this is consistent with the results of previous research [36-38]. Aldosterone plays a pivotal role in the development of hypertension. It binds to the mineralocorticoid receptor, which triggers the activation of the amiloride-sensitive sodium channel, also referred to as the epithelial sodium channel (ENaC). This triggers renal sodium reabsorption in the cortical collecting duct [39]. Aldosterone also exerts numerous non-epithelial actions that contribute to endothelial dysfunction, vasoconstriction, and hypertension. These factors encompass the proliferation of vascular smooth muscle cells, deposition of extracellular matrix in blood vessels, remodeling of blood vessels, fibrosis, and heightened oxidative stress [29]. Aldosterone enhances ionic transport in the main cells by augmenting the quantity of active sodium and potassium channels in the luminal membrane and the function of the Na/K-ATPase pump

in the basolateral membrane. Therefore, aldosterone stimulates the reabsorption of sodium chloride and the release of potassium in the main cells of the cortical collecting tubular section of the nephron. It also enhances the production of hydrogen ions in the intercalated cells of the cortex and tubular cells in the outer medulla [40]. The regulation of fluid and electrolyte balance is a very precise physiological mechanism known as homeostasis. One of the hallmarks of hypertension is the failure of this process to occur [41]. The present study found a significant decrease in potassium concentration compared to normotensive control. This finding is consistent with previous studies [42, 43], suggesting that lower amounts of potassium in the blood may contribute to high blood pressure. Other studies also showed a significant increase in sodium and chloride concentrations in hypertensive patients compared to controls [43-45]. Sodium plays a vital role in regulating blood volume. When the concentration of sodium in the blood is high, it promotes fluid retention, leading to an increase in blood volume and blood pressure. Also, when dietary salt consumption rises in normotensive individuals, the body undergoes compensatory hemodynamic modifications to keep blood pressure stable [40]. The changes involve a decrease in resistance in the kidneys and blood vessels, as well as an increase in the synthesis of nitric oxide (NO), which is a substance that dilates blood vessels, by the endothelium. Nevertheless, blood pressure rises when the effects of NO are absent or diminished. Endothelial dysfunction is a contributing factor to the development of salt sensitivity and eventual hypertension [29]. A growing body of empirical research suggests that chloride plays a crucial role in regulating vascular tone by depolarizing vascular smooth muscle cells. It appears that the development and progression of hypertension are associated with the increased role of chloride in artery constriction [43]. In the present study, the small sample size and time constraints are the most prominent.

The present study has several limitations that should be acknowledged. First, the study did not assess the potential impact of antihypertensive medications and dietary sodium and potassium intake on the levels of natriuretic peptides, resistin, renin, and aldosterone. Second, potential interactions or synergistic effects between the different natriuretic peptides, hormones, and electrolytes were not explored. Such interactions could influence the correlations observed and may impact the overall understanding of their roles in hypertension. Third, the study's cross-sectional design and the relatively small sample size limit the ability to draw conclusions about causality or relationships between studied markers. Finally, the absence of longitudinal data means that changes in biomarker levels over time, as well as their effects on the progression of hypertension, were not assessed.

Conclusion. The study demonstrated that hypertensive patients exhibit significantly higher levels of ANP, BNP, and CNP compared to healthy individuals, suggesting these peptides could serve as reliable indicators of hypertension severity. Additionally, hypertensive patients showed marked dysregulation in hormonal and electrolyte balances, with elevated levels of renin, resistin, and aldosterone, and altered sodium, chloride, and potassium concentrations. The positive correlations between natriuretic peptides and certain physiological variables, such as resistin and renin, alongside negative correlations with sodium and chloride, highlight interconnected pathways involved in hypertension. Further studies with larger sample sizes and longer time on natriuretic peptides in hypertension are greatly recommended.

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Competing Interest. The authors declare no competing interests.

Author's contributions.

Amna Adil Mohammed: Sample collection, sample analysis, data collection, statistical analysis, and manuscript writing.

Maryam I. Salman: Conceptualization of the research, research design, and manuscript proofreading.

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