Academia Open
Vol 9 No 2 (2024): December
DOI: DOI 10.21070/acopen.9.2024.8961 . Article type: (Medicine)

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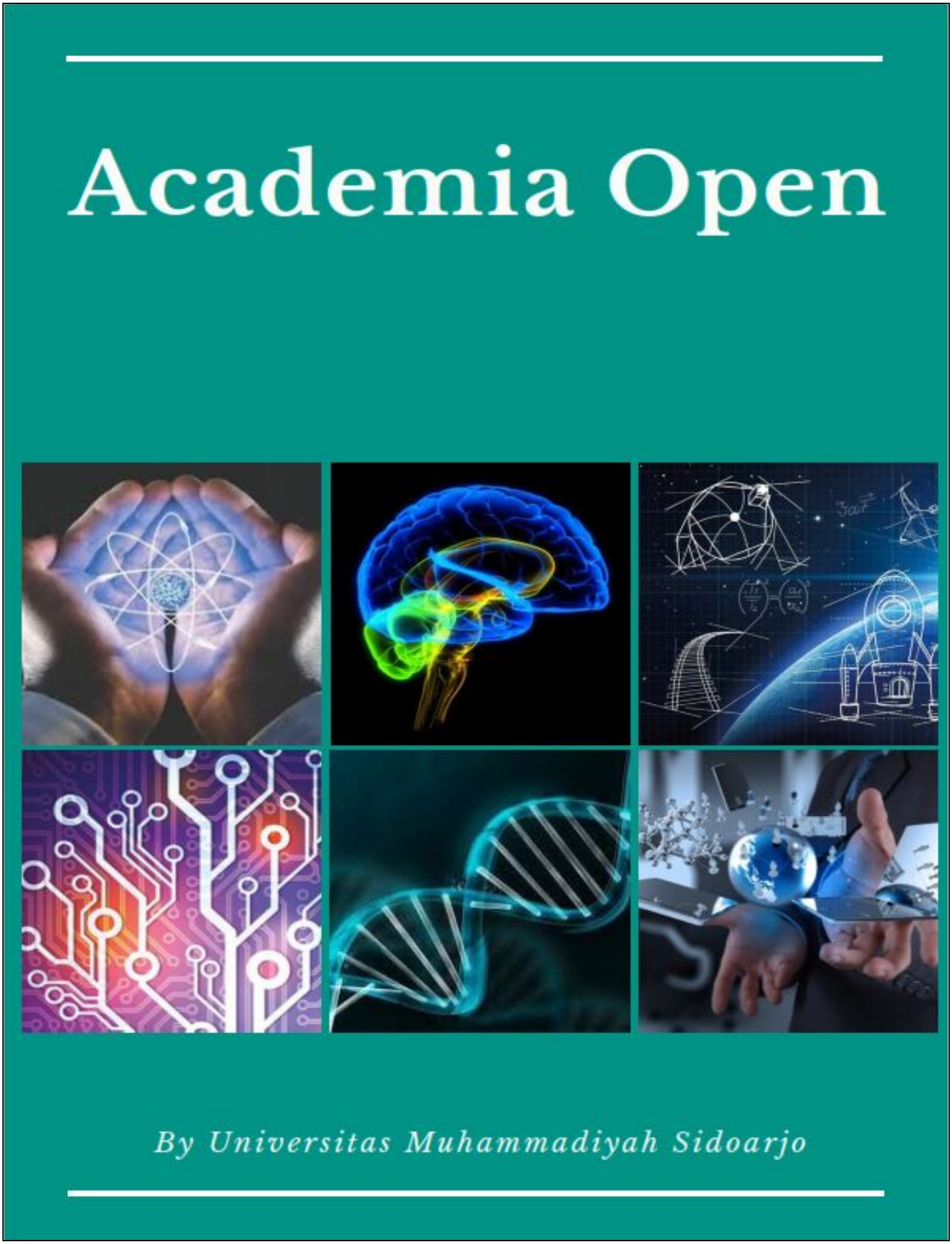
ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 9 No 2 (2024): December
DOI: DOI 10.21070/acopen.9.2024.8961 . Article type: (Medicine)



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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DOI: DOI 10.21070/acopen.9.2024.8961 . Article type: (Medicine)

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Vol 9 No 2 (2024): December
DOI: DOI 10.21070/acopen.9.2024.8961 . Article type: (Medicine)

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Adipokines Identify Crucial Biomarkers for Hypertension in Iraq

Adipokin Mengidentifikasi Biomarker Penting untuk Hipertensi di Irak

Zainab F. Salbookhh, zainab@gmail.com, (1)
Department of Clinical Laboratory Sciences, College of Pharmacy, University of Basrah, Basrah, Iraq

Usama H. Ramadhan, usama@gmail.com, (0)
Department of Pathological Analyses, College of Science, University of Basrah, Iraq

Gibran K. Hassan, gibran@gmail.com, (0)
Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Iraq

(1) Corresponding author

Abstract

Adipokines, which are generated by adipose tissue, are biologically active compounds that function similarly to traditional hormones. These proteins are involved in cellular signaling and control or modify several biological processes in target organs such as the brain, liver, muscles, heart, blood vessels, pancreas, and immune system. Adipokines can be incorporated into new diagnostic approaches as biological indicators of different metabolic, inflammatory, and cardiovascular conditions. The study was conducted at Al-Basrah Teaching Hospital on hypertensive patients between December 2022 and March 2023. This study included a sample of fifty-three patients with hypertension, whose ages ranged from 30 to 60 years. The features of these patients were compared to the same variables in a group of fifty-three healthy volunteers aged 30 to 40 years. This study aimed to identify the most significant alterations in serum apelin, spexin, and serum electrolyte levels (sodium, potassium, calcium, magnesium, and chloride) in patients solely diagnosed with hypertension. The analysis involved a statistical examination of the variables. The hypertension group had lower apelin and higher spexin levels than the control group. Additionally, each group had normal electrolyte levels (sodium, potassium, calcium, magnesium, chloride). The control group had somewhat higher potassium, calcium, and chloride levels than the hypertension group. The concentration of apelin does not influence sodium, calcium, magnesium, or chloride. Negative potassium correlation for apelin. However, spexin concentration does not impact sodium, potassium, calcium, or magnesium. Spexin concentrations are negatively correlated with apelin and chloride concentrations.

Highlight:

1. Adipokines Role: Adipokines are key in cellular signaling affecting multiple organs.
2. Study Findings: Hypertensive patients showed lower apelin and higher spexin levels.
3. Serum Electrolyte Levels: normal in both groups, with minor differences in potassium, calcium, and chloride.

Keyword: Adipokines, Hypertension, Apelin, Spexin, Electrolytes

Published date: 2024-12-15 00:00:00

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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INTRODUCTION

Adipokines, secreted by white adipose tissue, act as "molecular messengers" that govern several activities, including the body's energy balance. They can function in an autocrine, paracrine, or endocrine manner and communicate with different organs such as the brain, vasculature, muscle, pancreas, and liver (1). Adipokines influence reproduction, adipogenesis, appetite regulation, insulin secretion, cardiovascular function, inflammation, and immunity. Adipokines and obesity are associated, and research into adipokines has generated new insights regarding the pathogenesis and treatment of obesity (2). Ascertaining whether an individual is overweight or obese, body mass index is calculated by dividing their weight in pounds by the square of their height in square meters. Overweight and obesity, denoted by body mass index values exceeding 25 and 30, respectively, are associated with an increased susceptibility to developing numerous chronic ailments, such as type 2 diabetes, coronary artery disease, and carcinoma (3). Adipokines are categorized as either pro-inflammatory or anti-inflammatory adipokines based on their impact on inflammatory reactions in adipose tissues. Most adipokines, such as chemerin, exhibit pro-inflammatory properties. However, there are a few exceptions, including adiponectin, apelin, secreted frizzled-related protein 5 (SFRP5), visceral adipose tissue-derived serine protease inhibitor (Vaspin), and omentin-1. In obese rodents and humans with insulin resistance, there is an increase in pro-inflammatory adipokines and a reduction in anti-inflammatory adipokines (4).

Apelin, a bioactive peptide, was initially identified in an extract of bovine stomach tissue. Apelin and its receptors are also found in a variety of organs, adipocytes, and the placenta, in addition to the central nervous system. Apelin is an adipocytokine that functions as a ligand for the APJ, which is a G protein-coupled receptor (5). Apelin has various biological effects, such as nitric oxide-induced hypotension, angiogenesis, cardiac contractility stimulation, water intake, diuretic action, angiotensin II antagonistic effects, endothelium-dependent vasodilation, smooth muscle vasoconstriction, positive inotropes, and other cardiovascular activities of the apelin-receptor system. These findings have prompted a study on apelin as an endogenous mediator, crucial for cardiovascular diseases (6).

Spexin is adipokine detected by a hidden Markov model (7). Spexin has a significant impact on obesity as it regulates energy and appetite, controls feeding behaviours, reduces O2 consumption and CO2 production, affects the respiratory exchange ratio, and increases physical activity. It also inhibits the uptake of long-chain fatty acids into adipocytes. These findings suggest that spexin may play a crucial role in the development of metabolic syndrome (8). Administering spexin intracerebroventricularly to rats leads to a decrease in arterial pressure, sodium reabsorption, and cardiac output while maintaining normal urine output. These data indicate that spexin may be involved in the stimulation of renal functions and the development of cardiovascular disease (9).

Hypertension can be defined by an increase in systolic blood pressure (BP), an increase in diastolic BP, or both. The 2017 BP guideline, published by the American College of Cardiology (ACC)/American Heart Association (AHA), revised the definition of hypertension. The previous threshold of 140/90 mm Hg, established by the Joint National Committee (JNC) 7 guideline in 2003, was lowered to a new threshold of 130/80 mm Hg (10). Hypertension impacts approximately 26.4% of the adult population worldwide, making it the primary avoidable risk factor for premature mortality and disability globally. In addition to the majority of patients who have primary (essential) hypertension, around 10% of individuals are also affected by secondary hypertension (11). More than fifty million people have died from blood pressure-related diseases, many more have been rendered disabled, and these conditions wreak havoc on economies that are already precarious, according to the Global Burden of Disease. The majority of individuals with hypertension are asymptomatic, which is why it is commonly referred to as the "silent killer". While hypertension can occasionally lead to symptoms such as headache, dizziness, dyspnea, angina, palpitations, and epistaxis (12). Hypertension is the primary cause of disease worldwide, responsible for 66% of strokes, 50% of instances of coronary heart disease, and a total of 9.4 million deaths annually. Multiple cohort studies have been reported about the correlation between hypertension and the risk of sudden cardiac death (13).

Population studies show that high-sodium diets increase stroke and hypertension. Conversely, low-sodium diets reduce hypertension. In some patients with increased BP, dietary salt restriction has been demonstrated to lower blood pressure in clinical investigations. The processes by which high salt causes hypertension are unknown (14).

Alterations in calcium and potassium may also cause hypertension. Insufficient dietary calcium may disrupt the balance between intracellular and extracellular calcium, leading to increased intracellular calcium concentration and changes in vascular smooth muscle function. Dietary potassium is inversely associated with blood pressure and may mitigate sodium's effect (15). Calcium impacts various physiological processes such as blood coagulation, neurotransmitter release, blood pressure regulation, cardiac electrophysiology, and contraction. Calcium and magnesium regulate blood pressure by facilitating the opening and closing of calcium channels, which control the contraction and relaxation of smooth muscles at various locations in the body (16). In the current study, the serum concentrations of two adipokines, apelin, and spexin, as well as the electrolytes sodium, potassium, calcium, magnesium, and chloride were studied. In addition to that, the purpose of the study was to investigate the possible connections that exist between these variables. We conducted a targeted study on persons with hypertension and compared them to a control group of healthy individuals, focusing on the notable impact that electrolytes and adipokines have on hypertension.

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METHOD

Place and time of data collection

A study was carried out at the Internal Medicine Division of Al-Basrah Teaching Hospital between December 2022 and March 2023. As the primary referral hub for private, direct, and secondary healthcare providers, the hospital is a significant healthcare facility in this region. Twenty contributors were not included in the investigation, which involved 126 participants. Two groups were created out of the remaining participants. Regarding characteristic data, the 53 hypertensive patients who made up the first group were compared to the 53 healthy adults who made up the second group.

Inclusion and exclusion samples

The study included everyone who had been given a diagnosis of hypertension and was receiving care from internal medicine specialists. People with hypertension who also had diabetes, kidney disease, or thyroid disorders were not eligible for the study and were excluded.

Measurements

Babyly company's device evaluated blood pressure for all participants. After 5 minutes of rest, the individual sat with their right arm on the desk. Also, body mass index has been calculated following weight and height measurements for all individuals. A 5ml blood sample was taken from all participants and then collected in a sterile disposable syringe. Then, blood was transferred to a gel tube that did not have an anticoagulant. To assess the fasting serum electrolyte levels, including sodium, potassium, calcium, magnesium, and chloride, as well as the levels of adipokines (apelin and spexin) and the ability for clot retraction, the tubes were allowed to stand at room temperature for 30 minutes. The serum was extracted from the blood samples using a Kokusan centrifuge H-F and centrifuged at 3000 rpm for 15 minutes. The serum was then transferred to polyethene Eppendorf tubes and stored at -20°C for electrolytes and adipokines analysis. The electrolytes were analyzed using an ARCHITECTplus c4000. Enzyme-linked immunosorbent assay (ELISA) kits from the Wuhan, China-based company Elabscience were used to measure the serum levels of apelin and spexin.

Statistical Analysis

The data were initially entered into Microsoft Excel files. The IBM Corporation in Armonk, New York, the United States, provided SPSS version 22, which was used for all statistical studies. The Shapiro-Wilk test was used to determine whether each variable's distribution was normal. The independent Student's t-test was used for the analysis of the data. The analyzed data were represented by mean ± standard deviation. P-value equal to 0.05 or less, which represents Statistical significance. A Pearson correlation analysis was also used to determine the correlation between the serum apelin level, serum spexin level, and serum electrolyte levels in the hypertensive and normotensive groups. Also, many variables were analyzed in this study, such as body mass index (BMI) and systolic and diastolic blood pressure for both groups.

RESULT AND DISCUSSION

Result

The characteristics of the individuals, like their biochemistry and anthropometrics, are delineated in Table (1). A significant difference was found in the mean age of both groups (p=0.00). A significant difference was shown in BMI between the control group (25.108+2.711) and the hypertensive group (27.947+2.781). All participants in both groups were considered non-obese individuals due to a BMI under 30. The control group and hypertensive patients had significant differences in systolic BP (p=0.000, $p < 0.001$) and diastolic BP (p=0.000, $p < 0.001$), respectively. The control had significantly higher levels of apelin ($p = 0.00$) than the hypertensive group. While the serum spexin level of the hypertensive patients (481.59+562.836) was considerably more than that of the control group (261.02+584.909). A descriptive analysis of the electrolyte study variables is represented in Table (1). There is no significant difference in serum electrolyte levels between the control group and hypertensive groups for Na (p=0.581), Mg (p=0.145), and K (p=0.196). At the same time, there were statistically significant differences between patients and controls for Ca (p=0.003) and Cl (p=0.020).

The correlation between the serum level of apelin for both the control and hypertensive groups with serum electrolytes is represented in Table (2). There was no significant relationship observed between apelin level and Na (p=0.782), K (p=0.910), Mg (p=0.082), Ca (p=0.212), and Cl (p=0.145) in the control group. Moreover, the hypertensive group did not show a significant relationship between apelin with Na (p=0.294), Mg (p=0.602), Ca (p=0.426), and Cl (p=0.950) except K (p=0.033), which exhibits a negative relationship. Apelin has no significant association with systolic BP, diastolic BP, and BMI. Apelin relationship with spexin shows significance in the hypertensive group (p=0.039), while in the control group no significant relationship (p=0.135).

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The correlation between serum level of spexin for both the control and hypertensive groups with serum electrolytes was represented in Table (3). There was no significant relationship detected between spexin level and Na (p=0.229), K (p=0.062), Mg (p=0.355), Ca (p=0.156) and Cl (p=0.686) in the control group. Additionally, the hypertensive group did not display a significant relationship between spexin with Na (p=0.373), K (p=0.095), Mg (p=0.290), and Ca (p=0.126) except Cl (p=0.018) which exhibits a negative relationship. There is no significant relationship between spexin with diastolic BP, systolic BP, and BMI for each group. The spexin relationship with apelin displays significance in the hypertensive group (p=0.039), while in the control group no significant relationship (p=0.135).

Group	No.	%No.	M/F	%M/F
Control	53	50	24/29	45.28/54.72
Patients	53	50	24/29	45.28/54.72
BMI (Kg/m2)	Age (years)	Systolic (mm Hg)	Diastolic (mm Hg)	
Control	25.108+2.711**	35.962+4.612**	72.377+5.368**	111.584+6.428**
Patients	27.947+2.781**	41.056+6.726**	89.886+10.053**	141.47+16.82**
Apelin (pg./ml)	spexin(pg./ml)	Na (mmol/L)	K (mmol/L)	
Control	1660.605+1404.66	261.02+584.909	139.26±3.97	4.08±0.41
Patients	598.903+552.937**	481.59+562.836	138.86±3.37	3.97±0.38
Mg (mg/dL)	Ca (mg/dL)	Cl (mmol/L)		
Control	1.933+0.173**	9.147+0.9214**	106.188+3.138**	
Patients	1.98±0.18	9.611+0.607**	104.698+3.343**	

Table 1. ***Anthropometric and clinical characteristics of the study groups*.**

Values are expressed as mean ± standard deviation in each group. * = significant at p< 0.05; ** = significant at p<0.01.

Apelin		Na	K	Mg	Ca	Cl
Control	R	-0.039	-0.016	0.241	0.174	-0.203
	P	0.782	0.910	0.082	0.212	0.145
	Patients	R	-0.147	-0.293*	0.073	0.112
		P	0.294	0.033	0.602	0.426
		Spexin	BMI	Systolic	Diastolic	
Control	R	0.21	0.184	-0.048	0.015	
	P	0.135	0.186	0.732	0.917	
	Patient	R	-.284*	-0.070	0.101	0.041
		P	0.039	0.620	0.471	0.773

Table 2. ***The relationship of apelin with other parameters of patients and control in terms of probability and correlation.***

Spexin		Na	K	Mg	Ca	Cl
Control	R	0.170	0.261	-0.131	0.200	0.057
	P	0.229	0.062	0.355	0.156	0.686
	Patients	R	-0.125	-0.232	-0.148	-0.213
		P	0.373	0.095	0.290	0.126

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		Apelin	BMI	Systolic	Diastolic	
Control	R	0.21	0.102	0.070	0.105	
	P	0.135	0.472	0.620	0.461	
	Patient	R	-0.284*	-0.157	0.047	-0.121
		P	0.039	0.262	0.738	0.389

Table 3. ***The relationship of spexin with other parameters of patients and control in terms of probability and correlation***

Discussion

The hypertensive group's serum apelin level has decreased compared to the control group. Several studies concurred with the findings of the current investigation. The concentration of apelin in normotensive and hypertensive populations has been the subject of extensive research in numerous studies. Consistently, research has demonstrated that individuals with hypertension demonstrate considerably reduced concentrations of apelin in comparison to those with normal blood pressure (17,18). In addition, apelin concentrations in the blood samples of patients with cardiovascular diseases, including hypertension, were substantially lower than those of the control group, according to a meta-analysis (19). It is noteworthy that in hypertensive animals, apelin administration resulted in an immediate decrease in mean arterial pressure, systolic blood pressure, and diastolic blood pressure (20). This suggests that apelin may play a function in the regulation of blood pressure. Furthermore, an investigation that contrasted the effects of various medications on apelin levels in hypertensive patients discovered that losartan and amlodipine produced a more pronounced surge in apelin levels; this finding may indicate that losartan and amlodipine have a preventative effect against hypertension (21). In the present study, apelin does not correlate with body mass index (BMI) or systolic and diastolic blood pressure. This result disagreed with Hemmati M et al. Apelin level was significantly associated with mean systolic and diastolic blood pressure; that is, individuals with a low Apelin level had significantly higher mean systolic and diastolic blood pressures than those with a normal Apelin level (21). In addition, this result contradicted the finding of Zaki M et al., which suggested a positive correlation between serum plasma apelin levels and BMI (22).

In the present study, elevated levels of spexin in plasma have been observed in individuals with hypertension. Studies have demonstrated a negative relationship between spexin levels and blood pressure. Furthermore, multiple regression analysis has revealed blood pressure as a significant predictor of plasma spexin levels (23). In this study, there is no correlation observed between spexin and BMI or systolic and diastolic blood pressure. This outcome conflicted with Liu Y et al. that there was a negative correlation between blood pressure (systolic blood pressure and diastolic blood pressure) and spexin, regardless of BMI. Blood pressure was also found to be an independent factor affecting spexin levels in both the entire population and the group of individuals with normal weight. This suggests that spexin may have a role in the initial stages of cardiovascular disease in persons who appear to be healthy, as seen by lower levels of spexin when cardiovascular disease risk variables such as BMI, blood pressure, hyperlipidemia, and hyperglycemia are elevated (24).

The electrolyte concentrations may vary among individuals due to geographical location and lifestyle factors such as diet and exercise (25). Serum sodium levels were all within the normal range for all groups in this study. A non-linear correlation between serum potassium and sodium levels and hypertension was also identified by Wu et al. (26). The findings are in opposition to the hypothesis that the patients with hypertension exhibited elevated levels of Na+ (25). On the contrary, the findings corroborated those of Abdul-Razak et al. that there was no significant difference in sodium levels between the control and hypertensive groups (27).

A study involving hypertension and a healthy group showed that total body potassium was linked inversely with blood pressure (28) According to study data, the control and hypertension groups' potassium levels were within the normal range. However, the potassium levels in the hypertensive group were lower than in the control group. While the mechanisms through which potassium disruptions impact patient life are comprehended, there is limited knowledge regarding the optimal range of serum potassium in disease and the levels that are linked to increased risk (29). In comparison to the control group, the hypertension group exhibited elevated levels of serum calcium concentration. It is crucial to note that both groups had normal calcium levels. Epidemiological studies have established a correlation between elevated serum Ca levels and an increased susceptibility to hypertension (30). Lower serum Ca levels, on the other hand, were associated with an increased risk of hypertension. Plasma calcium levels are primarily regulated by parathyroid hormone (PTH) and 1,25(OH)2 D. Despite the absence of a clearly defined physiological role in humans, calcitonin may also be classified as a calcitropic hormone (31). Serum calcium levels in hypertensive individuals were significantly diminished and negatively correlated with both systolic and diastolic blood pressure (32).

The magnesium level is assessed in control people and patients with hypertension. The results were determined to be indistinguishable, and the magnesium concentration was within the normal range. The result disagreed with a study that showed lower magnesium levels in hypertensive patients compared to the control group (25).

The magnesium level has a direct impact on the capacity of vascular smooth muscle cells to relax and regulate

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

other essential cations involved in blood pressure, such as intracellular calcium and the sodium-to-potassium ratio in cells. The presence of magnesium in one's diet has a direct and indirect impact on blood pressure regulation and, as a result, the occurrence of hypertension. In the year 2021, a deficiency of magnesium may have an impact on blood pressure levels and lead to the development of hypertension (33). The study conducted by E. Koulouridis and I. Koulouridis has demonstrated that consuming excessive amounts of sodium chloride can increase blood pressure. However, replacing sodium chloride with sodium bicarbonate does not produce the same impact on blood pressure.

In this study, chloride levels were normal, however they were greater in the control group compared to the hypertensive group. There is a positive correlation between hyperchloremia and in-hospital mortality in hospitalised patients (34). Many studies suggest that hyperchloremia may increase blood pressure and negatively impact prognosis. In outpatients with hypertension or chronic heart failure, hypochloremia predicts death, whereas Cl^- levels are not linked to blood pressure (35)(36).

In the present study, there is no correlation between the concentration of apelin and the levels of sodium, calcium, magnesium, and chloride. Apelin exhibits a negative correlation with potassium levels. A study conducted by AL-Samarraie AM et.al aimed to investigate the impact of Apelin peptide deficiency on coronary atherosclerosis and acute myocardial infarction. The study reached a result regarding this matter. There was a positive association between the concentration of Apelin and the levels of sodium, potassium, magnesium, and chloride ions (37). Chloride levels increase in patients with cardiac disease due to the use of drugs that decrease blood volume and alter the concentration of ions in the blood serum. Additionally, hypoxia and changes in the permeability of the ion membrane of muscle cells contribute to this elevation. Myocardium perfusion can restore the necessary balance of ions in bodily fluid by utilizing apelin. Hypoxia modulates the expression and secretion of the apelin gene to the myocardial cells (38).

On the other hand, there is no correlation between spexin concentration and the levels of sodium, potassium, calcium, and magnesium. There is a negative correlation between the level of spexin and the levels of apelin and chloride. There is a lack of research on the comparison between spexin and electrolytes in cardiovascular disease. According to numerous studies, each of these plays a function in hypertension. Spexin is involved in the control of arterial blood pressure and the management of sodium and water balance through the central nervous system (CNS). As a result, it can potentially contribute to the development and advancement of metabolic disorders (8). The result of Said MA et.al demonstrates that spexin can safeguard against metabolic syndrome by effectively reducing the comorbidities associated with it, such as hypertension, hyperuricemia, obesity, hyperglycemia, and dyslipidemia. These effects can be ascribed, at least partially, to the activation of PPAR-Ç and AMPK, as well as the inhibition of inflammation (IL-6 and TNF-a). This suggests that spexin could be a new and potential medication for treating metabolic syndrome (38).

CONCLUSION

Conclusively, this study measured the levels of apeline and spexin, which are produced by adipose tissue and classified as adipokines, in the study groups. The hypertensive group exhibited a decrease in apelin level and an increase in spexin level in comparison to the control group. Simultaneously, the electrolyte levels (sodium, potassium, calcium, magnesium, chloride) of each group are within the normal range. The control group exhibited a small rise in potassium, calcium, and chloride levels in comparison to the hypertension group. Apelin concentration does not affect sodium, calcium, magnesium, or chloride levels. Apelin has a negative potassium correlation. However, spexin concentration does not affect sodium, potassium, calcium, or magnesium levels. A negative correlation exists between the concentration of spexin and the concentrations of apelin and chloride.

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